Palladium- and Copper-Catalysed Heterocycle Synthesis

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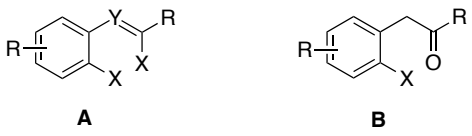
Abstract

A number of privileged starting materials based on aryl halide frameworks have emerged that allow access to a variety of different heterocyclic scaffolds through judicious choice of reaction conditions. This work describes efforts to develop and extend the utility of two of these general heterocycle precursors - *ortho*-(haloalkenyl)aryl halides **A** and α-(*ortho*-haloaryl) ketones **B** - in conjunction with cascade reactions involving the construction of key carbon-heteroatom bonds *via* palladium or copper catalysis (Scheme 1).

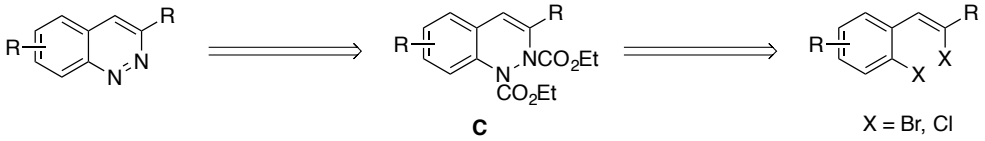


X = I, Br, Cl, OTf, OMe
Y = CH, N

Scheme 1

Chapter 1 entails an overview of the development of palladium- and copper-catalysed carbon-heteroatom bond forming processes. The application of these processes in heterocycle synthesis using *ortho*-(haloalkenyl)aryl halide and *ortho*-haloacetanilides/α-(*ortho*-haloaryl) ketone precursors is also described.

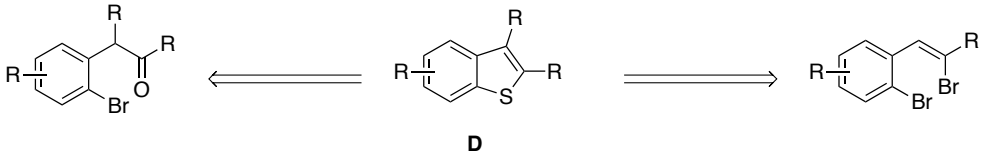
Chapter 2 focuses on the development of a two-step synthesis of cinnolines using *ortho*-(haloalkenyl)aryl halides *via* intermediate protected dihydrocinnoline derivatives **C** (Scheme 2).



Scheme 2

Chapter 3 demonstrates how the inherent reactivity of protected dihydrocinnoline derivatives **C** can be harnessed to provide access to functionalised products. A brief target synthesis of a pharmaceutically-relevent cinnoline is also described.

Chapter 4 details attempts to develop a novel synthesis of benzothiophenes **D** from both *ortho*-(haloalkenyl)aryl halide and α-(*ortho*-haloaryl) ketone precursors.



Scheme 3

Acknowledgements

Firstly, I would like to thank Dr Michael Willis for his support, insight and input into my research project, and for having a door that was always open. It's been a pleasure to be part of the Willis group for the past three-and-a-bit years. I'd also like to thank my supervisor at Eli Lilly, Dr. Jeremy Gilmore, for his advice and patience while I completed my industrial placement.

Big thanks are also due to the MCWs past and present who have shaped my time in Oxford and made working in F2 such a fun experience. Rob, Paul, SJ, Jessie, Radleigh, Charlie, Ed, Alex, Matt and the various part IIs along the way made the lab a good place to be even when my chemistry didn't! Thanks go to the F4 folk too: Carlos, Joel, Fiona and Maria. Particular thanks go to Ed for his support and sharing my obsessions with stirring, TV cookery programmes and pretentious food shops. Thank you to Jessie for representing the end of Team Heterocycles with me and answering a lot of inane questions. Thanks to Radleigh for being a constant source of entertainment and advice, and SJ for the fumehood chat and keeping me sane at points! For proof-reading I am indebted to Ed, Joel, Radleigh, Charlie and Alex – thanks again.

Thanks also to the NMR, mass spec and CRL staff.

I'd also like to say thanks to my Oxford housemates past and present for sharing the pain, the rants (who might that be referring to?!) and the fun times: Charley, Laura (my computing hero), Matt, Kylie (hands off!), Becky and Ruby.

Massive thanks are due to my friends who have put up with three-and-a-bit years of DPhil chat. Thanks to Marion for always trying to understand and for introducing me to Ladurée. Thank you to Ingrid for giving such good, grounded advice and for providing me with the excellent distraction of being your maid of honour during my final year. Thank you to Claire for listening to endless DPhil trauma chat and being generally inspirational. Thanks go to Mark for sharing the doctoral experience with me through many evenings with wine and our various 'bunker chats' at key points in our lives. Thanks also to Sam for being such a shining example of the light at the end of the tunnel.

My final and biggest thanks go to my family - my Mum, Dad (B-Dawg) and Sa - for their unwavering and endless support. I really couldn't have done it without you.

Contents

Abbreviations and Acronyms

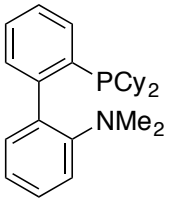
δ	chemical shift
Å	angstrom
Ac	acetyl
Ad	adamantyl
AIBN	azobis*iso*butyronitrile
ap.	apparent
aq.	aqueous
Ar	aryl
atm	atomosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
Bu	butyl
BTF	α,α,α-trifluorotoluene, also known as benzotrifluoride
°C	degrees celsius
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
cm	centimetre(s)
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane

DIPA	di*iso*propylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
E	entgegen
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
fur	furyl
g	gram(s)
h	hour(s)
Hex	hexyl
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
L_n	ligand(s)
LRMS	low resolution mass spectrometry
M	molar/molarity

m	multiplet
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
mL	millilitres(s)
mol	mole(s)
mmol	millimole(s)
mp.	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
MW	microwave irradiation
m/*z*	mass to charge ratio
n	normal
NBS	*N*-bromosuccinimide
NBSH	2-nitrobenzenesulfonylhydrazide
NCS	*N*-chloroosuccinimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NMP	1-methyl-2-pyrrolidinone
Oct	octyl
PCC	pyridinium chlorochromate
Pent	pentyl
Ph	phenyl
PPA	polyphosphoric acid

ppm	parts per million
Pr	propyl
*p*TSA	*p*-toluenesulfonic acid monohydrate
q	quartet
quant.	quantitative
R	generic group/substituent
rac	racemic
RSM	returned starting material
RT	room temperature
s	singlet
t	triplet
TEA	triethylamine
Temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
X	generic halide or pseudo halide (unless defined)
Z	zusammen

Ligands for Palladium Catalysis



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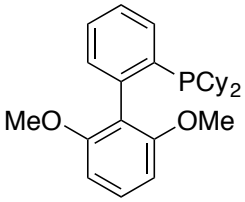

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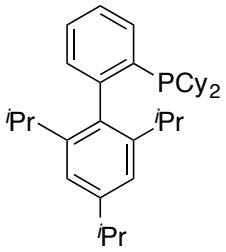

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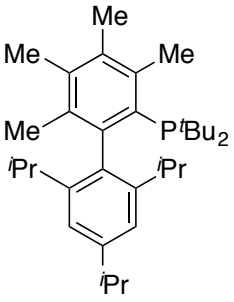

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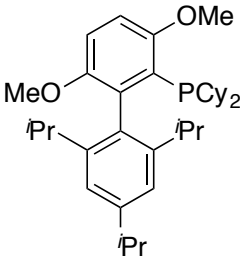

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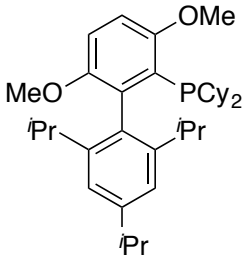

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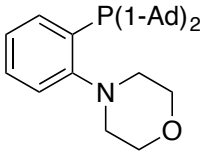

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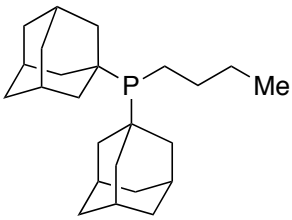

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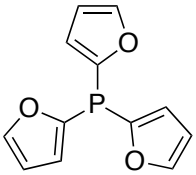

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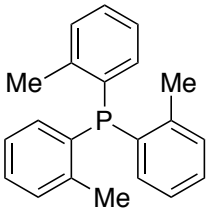

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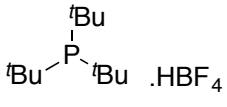

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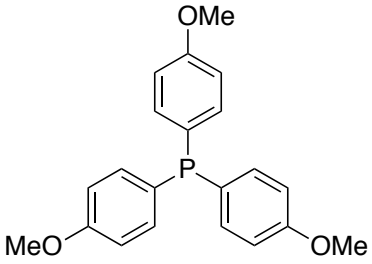

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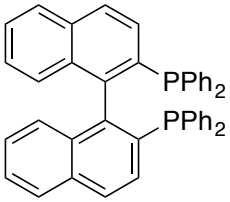

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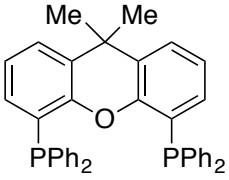

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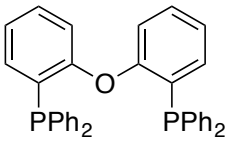

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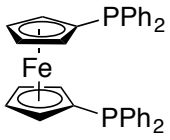

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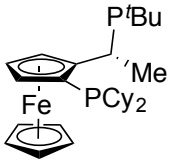

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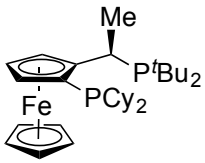
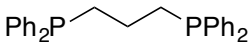


JosiPhos



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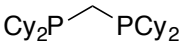

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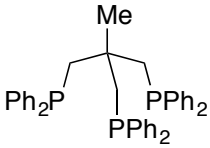
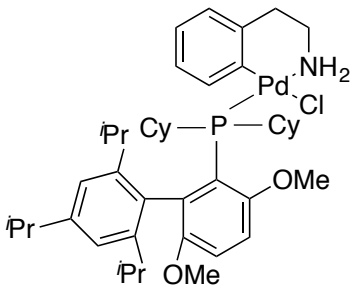


TriPhos

Pre-catalysts



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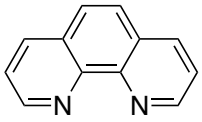
Ligands for Copper Catalysis



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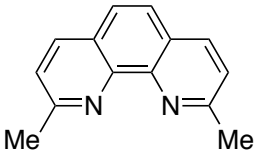

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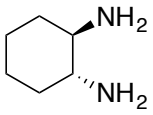

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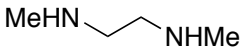

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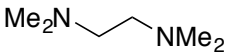

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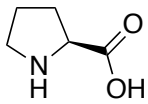

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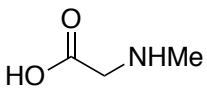

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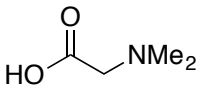

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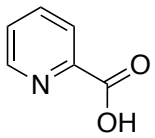

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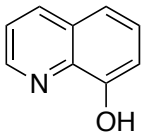

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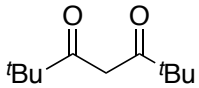

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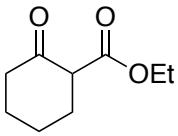


ketoester A

Chapter 1. Palladium- and Copper-Catalysed Carbon-Heteroatom Bond Forming Reactions and their Application in Aromatic Heterocycle Synthesis Using General Precursors

Aromatic heterocycles are ubiquitous throughout nature and both the pharmaceutical and agrochemical industries.[1] Thus, the development of efficient, rapid and versatile routes towards their synthesis has become a key area of research. To this end, methods involving transition metal catalysis have gained prominence.[2, 3] Employing such a tactic presents a departure from traditional approaches that often rely on condensation reactions or pericyclic processes,[4] and where harsh conditions, long reaction times and limited substrate scopes are common. In particular, strategies incorporating the palladium- or copper-catalysed construction of carbon-nitrogen, carbon-oxygen and carbon-sulfur bonds have become prevalent.[5]

1.1 Palladium-Catalysed Carbon-Heteroatom Bond Formation

As well as being crucial tools in aromatic heterocycle synthesis, palladium-catalysed carbon-heteroatom bond forming reactions (Figure 1.1) have found application in the synthesis of pharmaceuticals, natural products and novel materials.[6, 7] Indeed they have become a vital component of the modern-day organic chemist's repertoire.

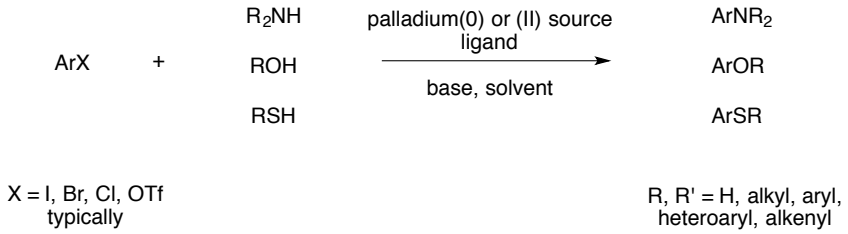
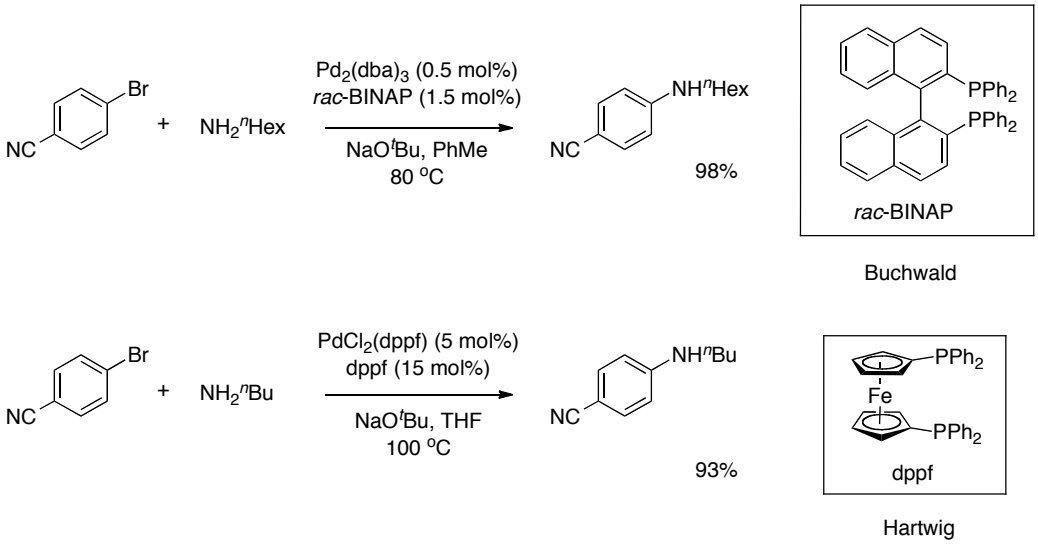


Figure 1.1

Early development of such processes focused on C-N bond formation, and it was pioneering work by Migita[8] using tin amides which provided the inspiration for initial investigations by both Buchwald[9] and Hartwig.[10] Simultaneous work in both these laboratories led to the development of tin-free protocols and the first general palladium-catalysed amination reactions (Scheme 1.1). Both research teams explored aryl bromide substrates and primary amines and found the nature of the ligand employed to be crucial. Initial reports utilised monophosphine ligands, however the bidentate ligands *rac*-BINAP (Buchwald)[11] and dppf (Hartwig)[12] were found to affect a more general reaction.



Scheme 1.1

Key to further investigations was a fundamental understanding of the mechanism involved. Numerous studies have been undertaken,[13] and as a result a generalised catalytic cycle for palladium-catalysed amination can be postulated (Figure 1.2).

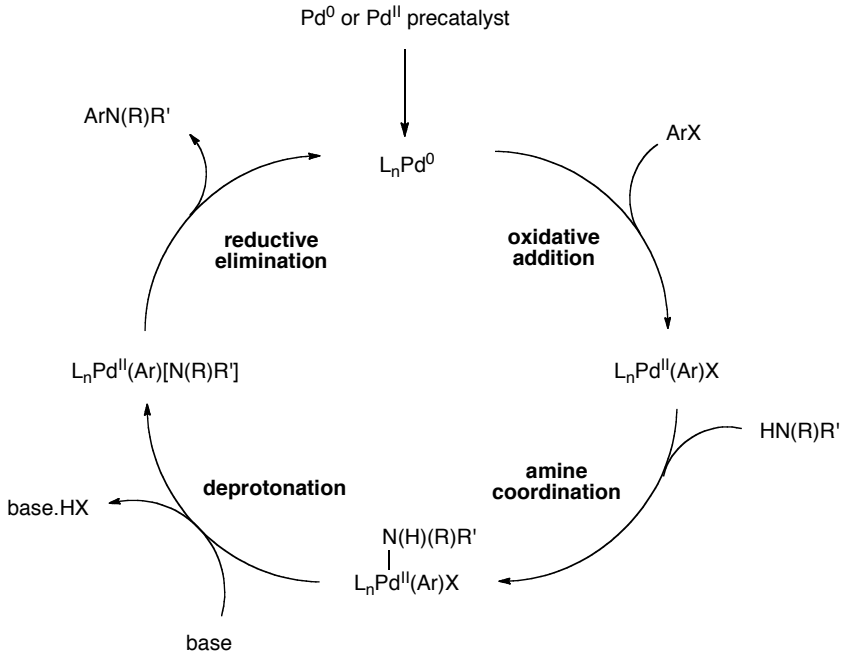


Figure 1.2

Such a mechanism can be considered to proceed through four main processes. Firstly, oxidative addition occurs *via* the interaction of a nucleophilic monoligated palladium(0) species – itself generated from a palladium(0) precursor or from *in situ* reduction of a palladium(II) precatalyst – and the aryl halide (or pseudo-halide) to generate an aryl palladium(II) complex. Amine coordination, deprotonation and halide displacement then occur to afford an aryl palladium(II) amide species. The order of the co-ordination/deprotonation processes is dependent on factors such as pK_a and bond strength, though for most amines co-ordination precedes deprotonation.

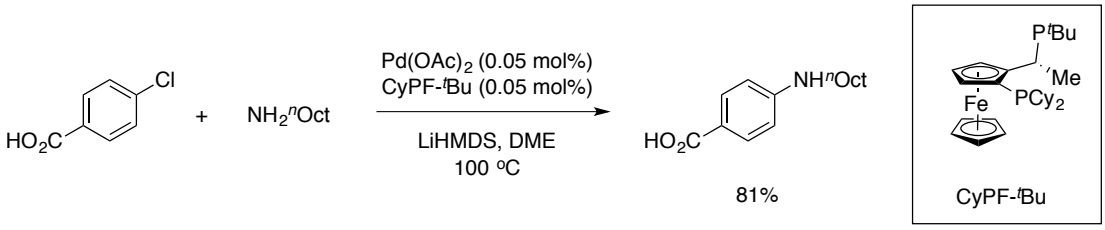
Finally, reductive elimination creates the desired C-N bond within the product and regenerates the active palladium(0) complex.

Key to the manipulation of these steps is the nature of the ligand. Oxidative addition can be facilitated by the use of electron-rich phosphine ligands. Conversely, electron-poor ligands can aid reductive elimination. Use of particularly sterically encumbered ligands can also aid this process. Favouring reductive elimination can be especially important since the aryl palladium(II) amide species can undergo several other non-productive processes. β-Hydride elimination, protonolysis or ligand displacement can occur resulting in reduced product yields.

The key influence of the nature of the ligand is reflected by the fact that the major advances in palladium-catalysed amination chemistry have been driven by the implementation of new types of ligand. Notable classes include chelating diphenylphosphino ligands such as XantPhos,[14] more electron-rich chelating phosphines such as JosiPhos,[15, 16] dialkylbiaryl phosphines,[17] *N*-heterocyclic carbenes,[18] and particularly bulky trialkylphosphines.[19] These ligands have served to render reactions more efficient in several ways. For example, low catalyst loadings can now be used and reactions can proceed at lower temperatures.

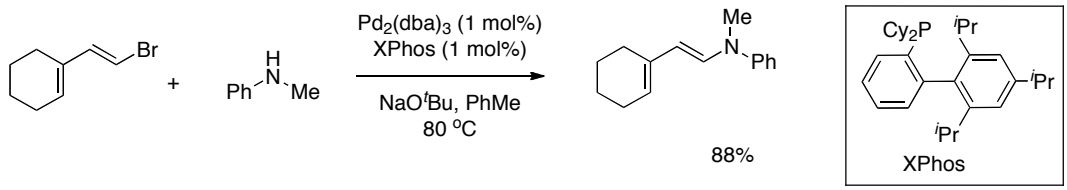
Another advance heralded by specialist ligand design, and one that is particularly important in the context of aromatic heterocycle synthesis, is the wide expansion of the substrate scope encompassed by the amination reaction.

Aryl iodide, bromides and triflates were initially explored, and now aryl chlorides can also be utilised. Their comparative recalcitrance can be attributed to the high C-Cl bond strength. However, breakthroughs in ligand design have meant that oxidative addition into such a bond can be facile. This is illustrated by Hartwig's JosiPhos series of ligands, particularly CyPF-^{t}Bu, used in very low loadings (Scheme 1.2).[15] This example is particularly notable as protic functionality, in this case a carboxylic acid, can be readily tolerated.



Scheme 1.2

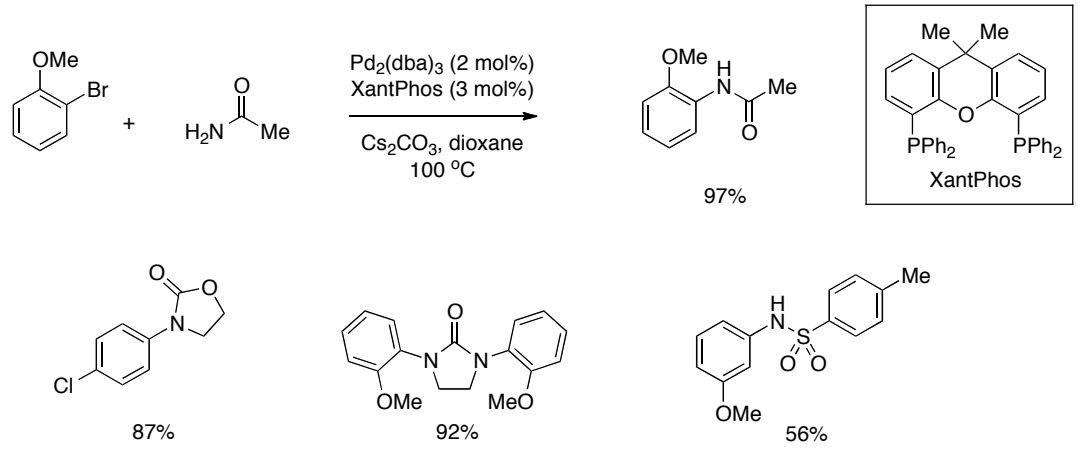
Another advancement in the expansion of the substrate scope was the discovery that alkenyl halides could also be exploited. Barluenga and co-workers were one of the first to demonstrate this using alkenyl bromides and invoking the bulky dialkylbiaryl phosphine ligand XPhos in a synthesis of amino dienes (Scheme 1.3).[20]



Scheme 1.3

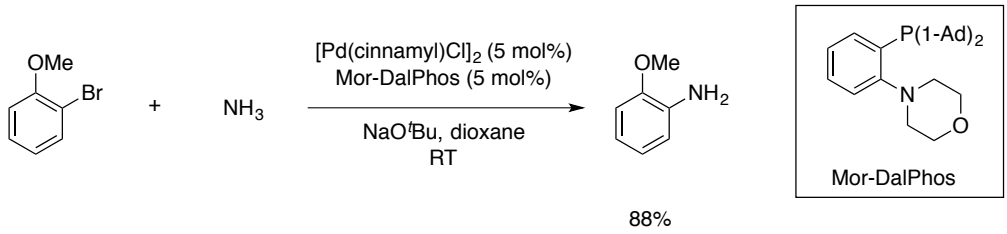
It is not only the aryl halide component that has benefitted from the advent of increasingly sophisticated ligand systems. Primary and secondary aryl and alkyl

amines were initially focused on as the *N*-based coupling partners, while their poorly nucleophilic and more acidic amide counterparts were more challenging. However, Buchwald reported that the use of a rigid bidentate ligand such as XantPhos could overcome these problems (Scheme 1.4).[21] Arylation of a carbamate, a urea and a sulfonamide could also be performed using these conditions. Buchwald has also established several specialised dialkylbiaryl phosphine ligands specifically for amide couplings.[22] Advances in ligand design have meant that incorporation of almost any *N*-based nucleophile is now possible.



Scheme 1.4

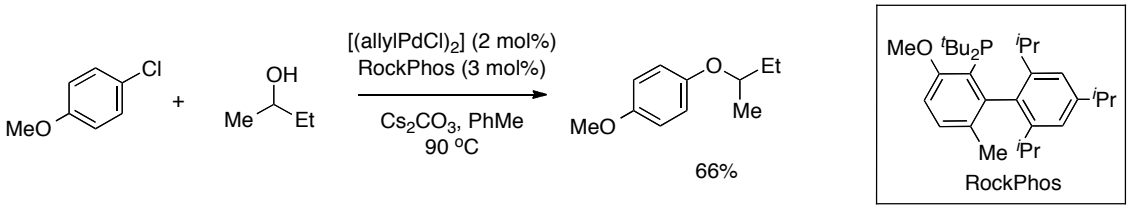
Another key advance was the development of protocols that allowed the direct use of ammonia as a coupling partner. While Buchwald and Hartwig have both demonstrated such a process - using their dialkylbiaryl monophosphine[23] and JosiPhos[24] classes of ligands respectively - Stradiotto and co-workers have developed a specific ligand to facilitate the process. The sterically encumbered monophosphine ligand Mor-DalPhos allows the coupling of ammonia at room temperature (Scheme 1.5).[25]



Scheme 1.5

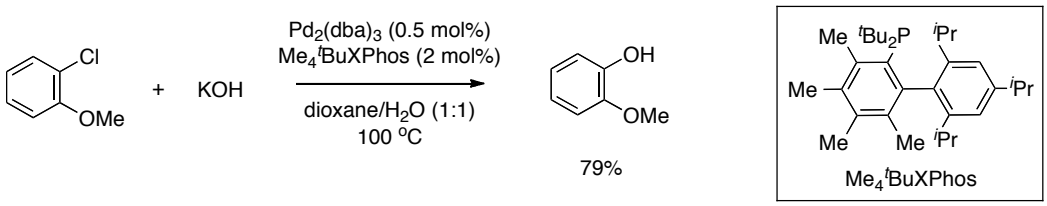
In the quest for a truly general carbon-heteroatom bond forming reaction, the synthesis of C-O bonds has also been investigated. This chemistry has been developed in analogy to the corresponding C-N forming processes, and as such can largely be considered as an extension to the range of amenable coupling partners. However, the substrate scope was initially far more limited as slow reductive elimination from the $[L_nPd^{II}(Ar)(alkoxide)]$ intermediates, generated in the catalytic cycle, led to competitive β-hydride elimination and/or protonolysis pathways.

Once again, the development of specialised ligand systems provided a solution. One of the most recent involves another of Buchwald's specifically designed dialkylbiaryl monophosphine ligands, RockPhos.[26] Using this ligand, a variety of primary and secondary alcohols, which had previously proven challenging, could be successfully coupled. An illustrative example is shown in Scheme 1.6.



Scheme 1.6

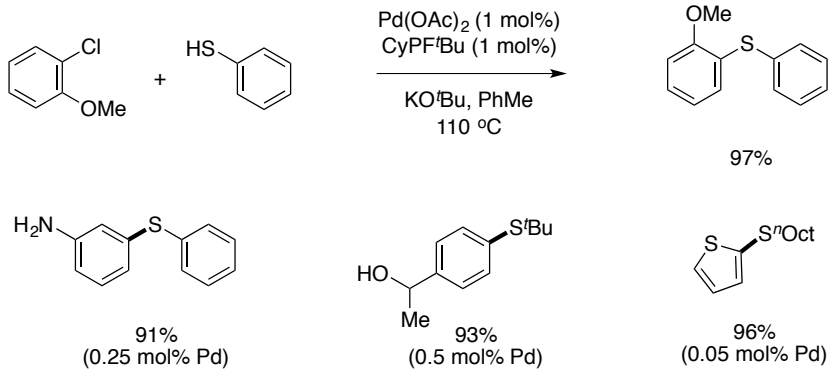
Another breakthrough in palladium-catalysed etherification chemistry came with the advent of hydroxide couplings. Again, Buchwald and his dialkylbiaryl monophosphine series of ligands led the way; a modified version of XPhos allowed access to a range of phenols in good yields, as illustrated in Scheme 1.7.[27]



Scheme 1.7

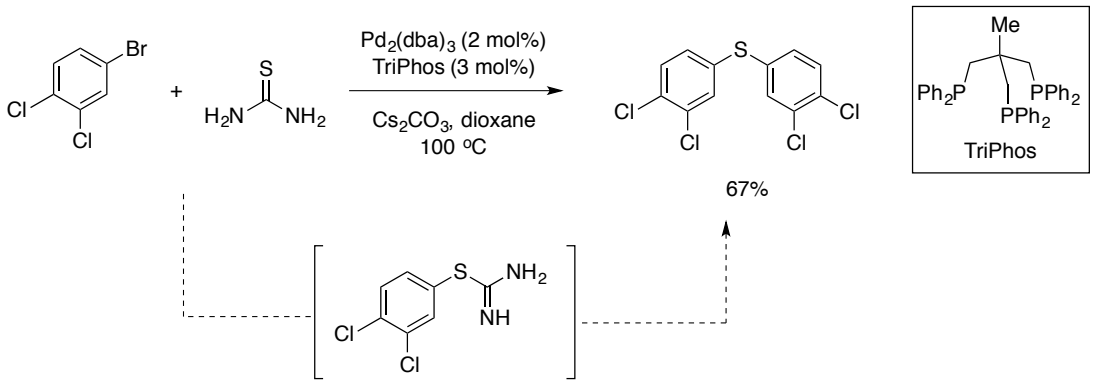
With the establishment of C-N and C-O bond forming processes came a simultaneous investigation into C-S bond formation. Though somewhat under-developed by comparison, such couplings are generally efficient. However, the strong coordinating ability of many sulfur-containing compounds can result in catalyst poisoning and low turnover. Judicious ligand choice has, once again, resulted in the generation of efficient protocols.

Hartwig's bulky JosiPhos bisphosphine series of ligands are particularly effective catalysts for coupling reactions with thiophenol derivatives. Extremely high catalyst turnovers could be achieved using CyPF-^{t}Bu (Scheme 1.8).[28]



Scheme 1.8

Palladium-catalysed thioetherification methodology has also relied on the development of so-called 'hydrogen sulfide surrogates'. Use of these compounds as coupling partners allows access to thiophenols and diaryl thioethers *via* single and double C-S bond forming processes respectively. Potassium thioacetate,[29] sodium thiosulfate[30] and thiourea have all found application in such procedures. A selected example of the synthesis of a symmetrical diaryl thioether using thiourea, invoking the unusual ligand TriPhos, is shown in Scheme 1.9.[31] Such a reaction presumably proceeds *via* the degradation of a thiouronium-type species formed upon *S*-arylation of thiourea.



Scheme 1.9

1.2 Copper-Catalysed Carbon-Heteroatom Bond Formation

Copper-catalysed carbon-heteroatom bond formation (Figure 1.3) is an important tool in aromatic heterocycle synthesis as well as in modern-day organic chemistry.[32]

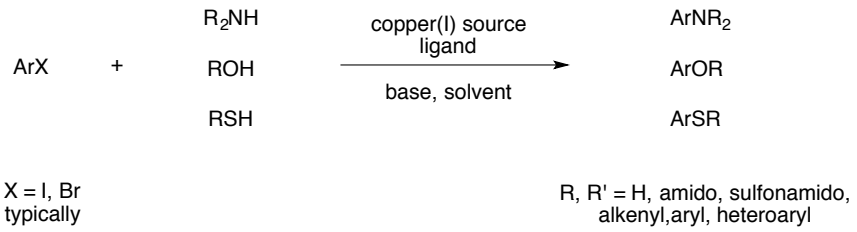


Figure 1.3

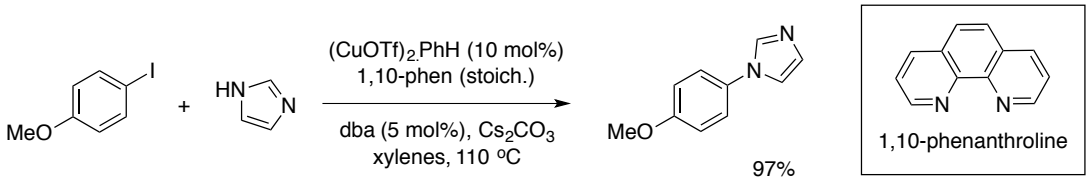
The roots of copper-catalysed coupling chemistry delve deep into the history of chemistry. Ullmann[33] and Goldberg[34] discovered that copper salts could affect both C-N and C-O bond formation around the turn of the twentieth century. Their seminal discovery changed the way chemists thought about constructing carbon-heteroatom bonds and laid the foundations for modern transition metal-catalysed coupling chemistry.

The Ullmann condensation reaction, as it has come to be known, involves the arylation of aniline- or phenol-derived nucleophiles, while the Goldberg reaction involves the arylation of amides and related nucleophiles. Due to their relevance in aromatic heterocycle synthesis, Goldberg-type reactions will be predominantly discussed here. Ullmann-type etherifications and thioetherifications will also be briefly considered.

Though copper-catalysed carbon-heteroatom bond-forming reactions were discovered over 100 years ago, they have lain dormant in the literature for much of this time. The use of harsh reaction conditions, stoichiometric quantites of copper and long reaction times made such processes unattractive to modern organic chemists. However, with the advent of palladium-catalysed protocols came renewed interest; copper is a cheaper, more abundant and comparatively less toxic metal.

The necessary breakthrough arose with the employment of bidentate chelating ligands. Improved catalyst solubility, reduced aggregation, inhibition of catalyst decomposition and prevention of multiple ligation of the copper centre by the nucleophile are all possible advantageous effects that ligation confers.[35]

Thus, reactions can be performed using mild conditions and, crucially, using catalytic quantities of copper. One of the first reports employing this breakthrough strategy focused on the use of 1,10-phenanthroline in an Ullmann condensation (Scheme 1.10).[36] Used in stoichiometric quantites, along with a dibenzylidenediacetone additive, it allowed the coupling of aryl iodides and imidazoles in excellent yields. Without the influence of the chelating ligand no such reaction was possible.



Scheme 1.10

Since this discovery a variety of different bidentate chelators have been identified as suitable ligands, which can be used in catalytic quantites. Common ligand types are based around either '*N*,*N*', '*N*,*O*' or '*O*,*O*' chelation and include bipyridines and phenanthrolines,[37] 1,2-diamines,[38] bis-pyridylamines,[39] α-amino acids[40] and 1,3-diketones.[41]

In contrast to the corresponding palladium-mediated methodology, the nature of the ligand is much less influential in copper catalysis; subtle modulations of ligand electronic and steric properties have not been exploited. This can perhaps be attributed to the fact that a general mechanism of copper-catalysed aryl halide amidation has remained elusive, though a variety of pathways have been postulated.[35, 42, 43]

It is generally agreed that the mechanism involves two stages. Firstly, formation of a (mono)ligated Cu(I) nucleophile complex *via* a simple metathesis reaction - a Cu(I) species is widely believed to be the true catalyst even though Cu(0) and Cu(II) catalysts have been shown to be active - followed by a process of aryl halide activation (Figure 1.4).

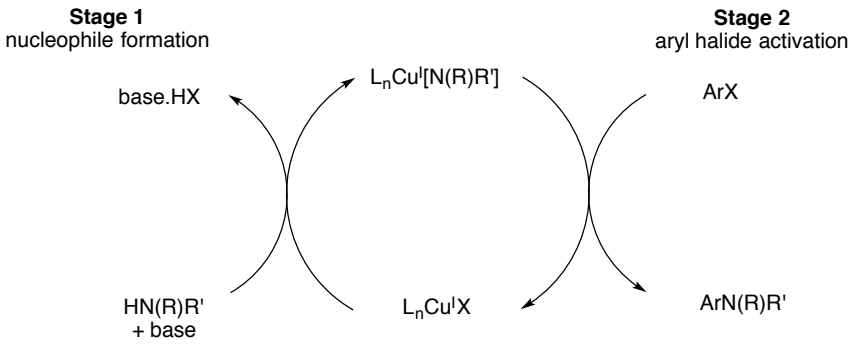


Figure 1.4

The mode of aryl halide activation has been the subject of several mechanistic studies and a number of putative pathways have been suggested. These are summarised in Figure 1.5.

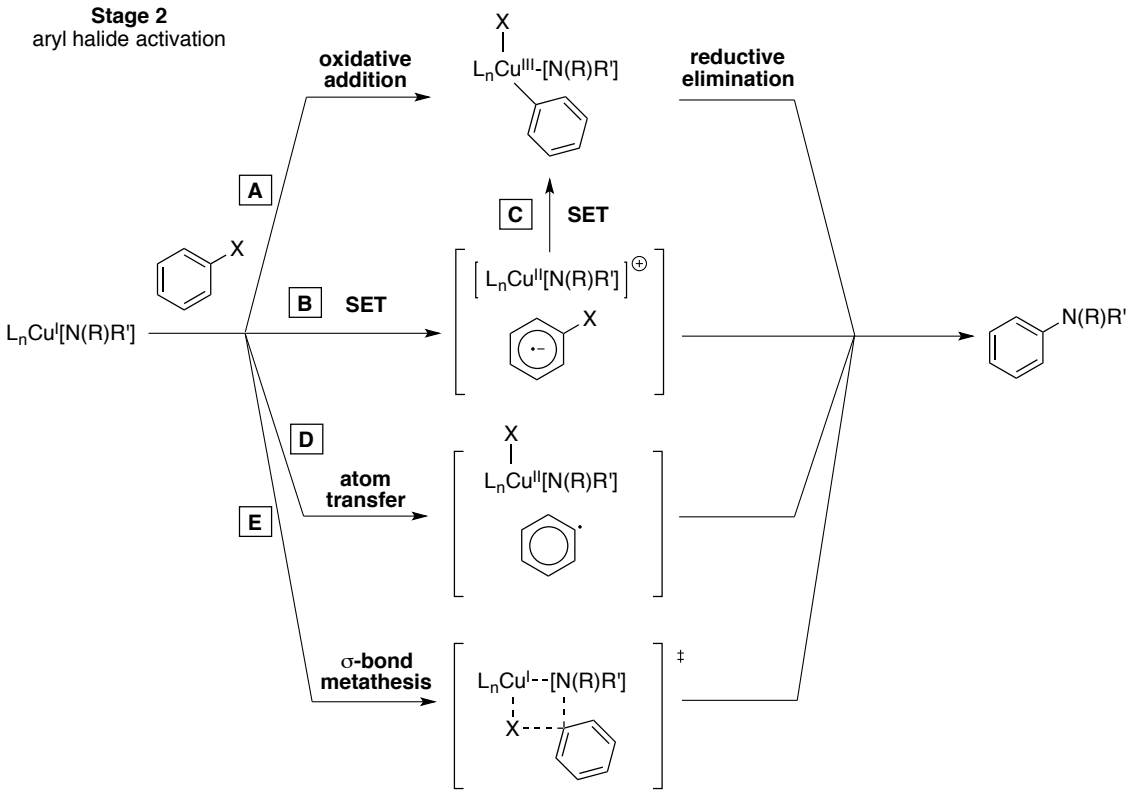


Figure 1.5

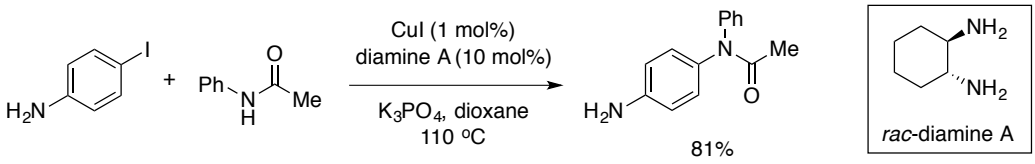
Pathway A follows a mechanism analogous to that postulated for palladium-catalysed aryl halide amination, *via* a Cu(III) intermediate. Alternatively, pathways B and C involve a single electron transfer (SET) process from the Cu(I) nucleophile complex to the aryl halide resulting in the formation of a radical pair. This pair comprises of the radical anion of the aryl halide and a Cu(II) species and could either result in direct product formation (pathway B) or undergo a second SET process to form the same Cu(III) intermediate implicated in pathway A (pathway C). Pathway D also involves a Cu(I)/Cu(II) process, in this case *via* transfer of the halide atom from the

aryl halide. Finally, a four-centred σ-bond metathesis mechanism, pathway E, has also been postulated.

The most widely accepted mechanism follows that of pathway A, although several recent studies have argued that a SET process is more likely.[43] However, the rich redox chemistry of copper combined with influences such as solvent/ligand co-ordination and the potential for aggregation and disproportionation mean that it may be possible for more than one mechanism to be in operation. The favoured pathway could be highly dependent on the conditions and components involved in a particular reaction. Unlike the analogous palladium-catalysed processes, a general mechanism may not be agreed upon.

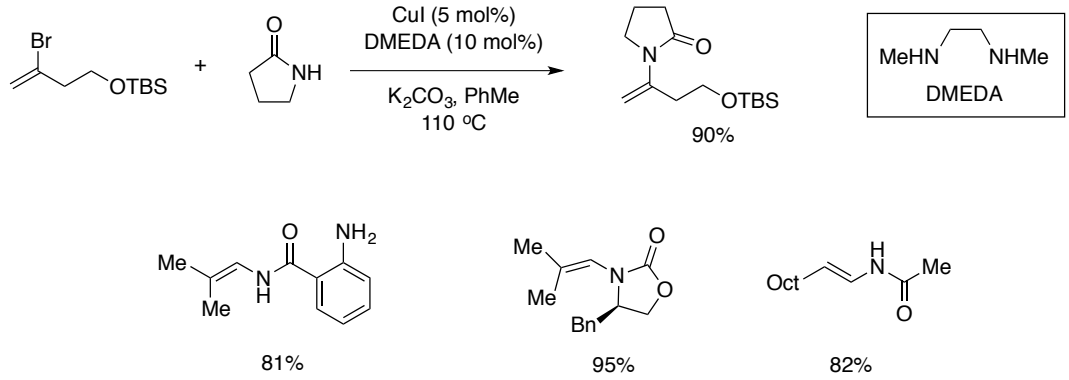
Although copper-catalysed C-N bond formation has been largely focused on for mechanistic study, protocols for C-N, C-O and C-S bond formation have been developed in parallel. Again no specialist ligands are required, and many catalyst systems can invoke all three processes.

Arguably one of the most general ligand types are 1,2-diamines,[7] pioneered by Buchwald. He discovered that very low loadings of copper could be used when combined with the inexpensive ligand *rac*-*trans*-cyclohexanediamine, diamine A (Scheme 1.11).[44] High functional group tolerance was observed; for example, arylation of the amide was selective even in the presence of an aniline motif.



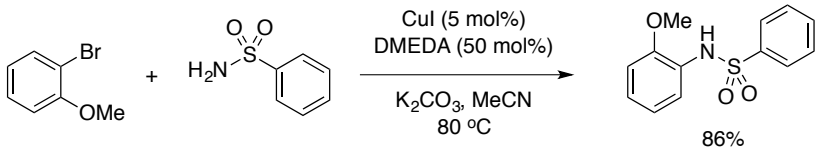
Scheme 1.11

One of the most ubiquitous of the diamine ligands is dimethylethylenediaime (DMEDA). Buchwald introduced the use of this ligand in an efficient synthesis of enamides, which also demonstrated that alkenyl halide substrates can be used. A variety of nucleophiles could be alkenylated, including carbamates (Scheme 1.12).[45]



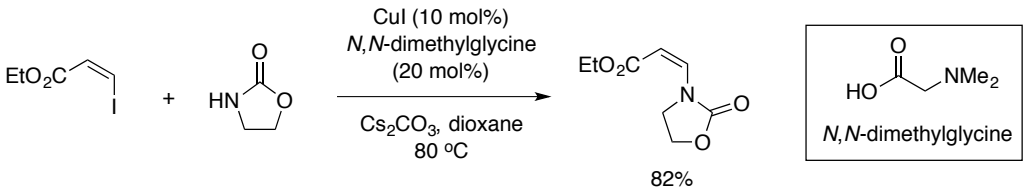
Scheme 1.12

As well as amides and carbamates, a variety of other nucleophiles can partake in the Goldberg-type reaction. Copper catalysis can be particularly effective when combined with more acidic and less nucleophilic coupling partners. Thus ureas, amidines and sulfonamides can all be readily employed. Again, use of DMEDA is prevalent, as is illustrated in a recent synthesis of secondary sulfonamides (Scheme 1.13).[46]



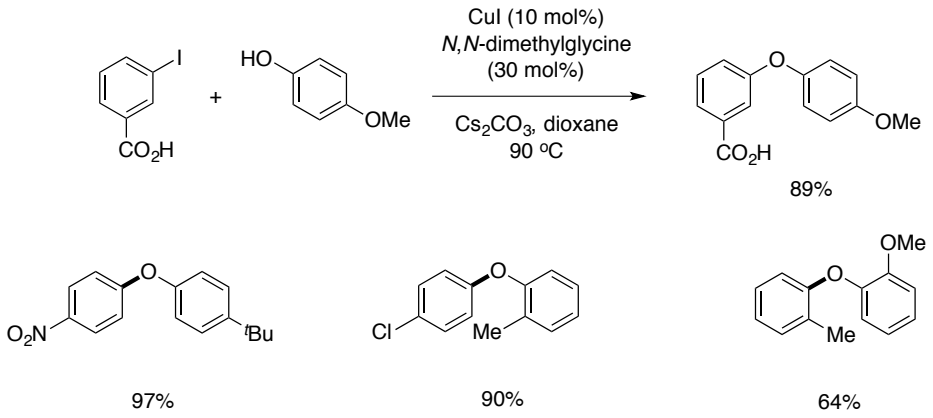
Scheme 1.13

Although ligands based on '*N*,*N*' chelation tend to be the most general and most frequently employed, '*N*,*O*' ligands have also been used to great effect. Ligands based on amino acid frameworks are common, as is exemplified by the use of *N*,*N*-dimethylglycine in a particularly effective alkenylation of cyclic carbamates (Scheme 1.14).[47]



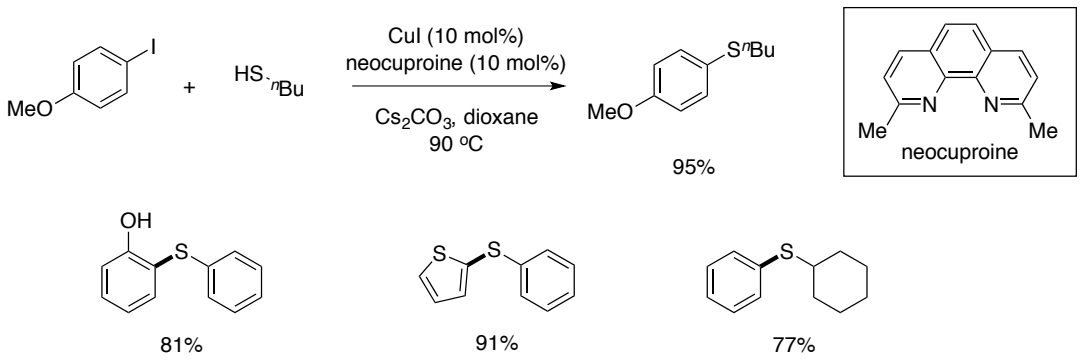
Scheme 1.14

A particularly appealing aspect of modern copper-catalysed carbon-heteroatom bond-forming chemistry is that remarkably similar catalytic systems can be used to affect a wide variety of transformations. For example, nearly identical conditions to those reported for the alkenylation of cyclic carbamates (Scheme 1.14) can be used to synthesize a range of diaryl ethers *via* copper-catalysed etherification (Scheme 1.15).[48]



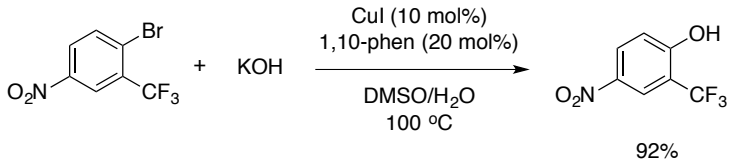
Scheme 1.15

The emergence of these general catalytic systems is in sharp contrast to the reliance of palladium-catalysed methodologies on process-specific, highly tailored, ligands. Indeed, even alkyl thiols, traditionally challenging substrates with palladium catalysis, can be coupled using a variation of these general conditions. One of the first examples of the use of '*N*,*N*' chelation in a copper-catalysed thioetherification employed the phenanthroline-derived ligand neocuproine (Scheme 1.16).[49]



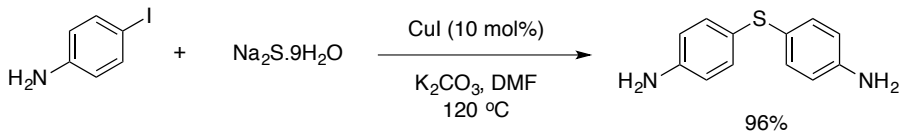
Scheme 1.16

Ligands based on diamine chelation are also amenable to the use of hydroxide-based coupling partners. For example, phenol derivatives can be readily accessed with the use of 1,10-phenanthroline (Scheme 1.17).[50]



Scheme 1.17

In a somewhat analogous manner, sodium sulfide salts can be utilised with the action of a copper catalyst. Another member of the 'hydrogen sulfide surrogates' family, these salts can be readily reacted with aryl halides, without the need for additional ligand, to generate diaryl thioethers (Scheme 1.18).[51]



Scheme 1.18

When copper-catalysed carbon-heteroatom bond formation is considered as a whole, a level of orthogonality, and indeed complementarity, can be observed when compared to the corresponding palladium-catalysed strategies. Hence, both processes have been thoroughly investigated in the context of aromatic heterocycle synthesis. Often both palladium- and copper-catalysed strategies have been developed for a single process so that as full a substrate scope as possible can be amassed and thus a truly general procedure can be created.

1.3 The Emergence of General Heterocycle Precursors

The numerous advances that both palladium and copper catalysis have undergone has allowed the development of new classes of starting materials, particularly those applicable for heterocycle synthesis. Of these, several privileged structures have emerged which can allow access to more than one heterocycle class *via* a cascade process. Thus, with judicious choice of reaction conditions a variety of different heterocyclic scaffolds can be rapidly assembled from the same functionalised framework.

The four most exploited general heterocycle precursors are *ortho*-alkynylhaloarenes **A**, *gem*-dihaloalkenylarenes **B**, (*ortho*-haloalkenyl)aryl halides **C** and *ortho*-haloacetanilides/α-(*ortho*-haloaryl) ketones **D** (Figure 1.6).[52]

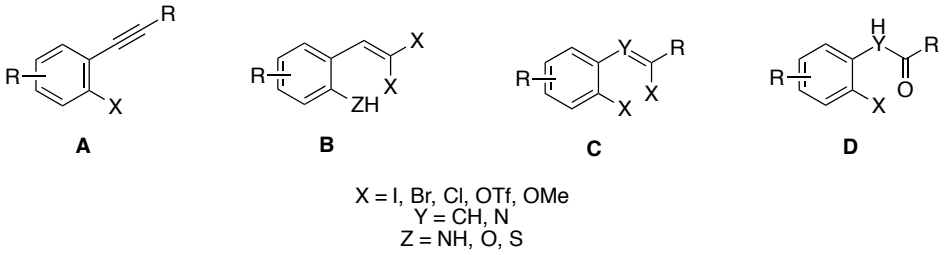


Figure 1.6

Of these, (*ortho*-haloalkenyl)aryl halides **C** and *ortho*-haloacetanilides/α-(*ortho*-haloaryl) ketones **D** are most relevant in this context. The synthesis of these substrate types and their use in aromatic heterocycle synthesis using palladium- and/or copper-catalysed C-N, C-O and C-S bond-forming processes will be discussed.

1.3.1 (*ortho*-Haloalkenyl)aryl halide precursors and pseudo-haloalkenyl variants

A wide variety of heterocyclic scaffolds can be accessed *via* cascade palladium- or copper-catalysed intermolecular and intramolecular carbon-heteroatom bond forming processes using (*ortho*-haloalkenyl)aryl halide-type precursors (Figure 1.9).

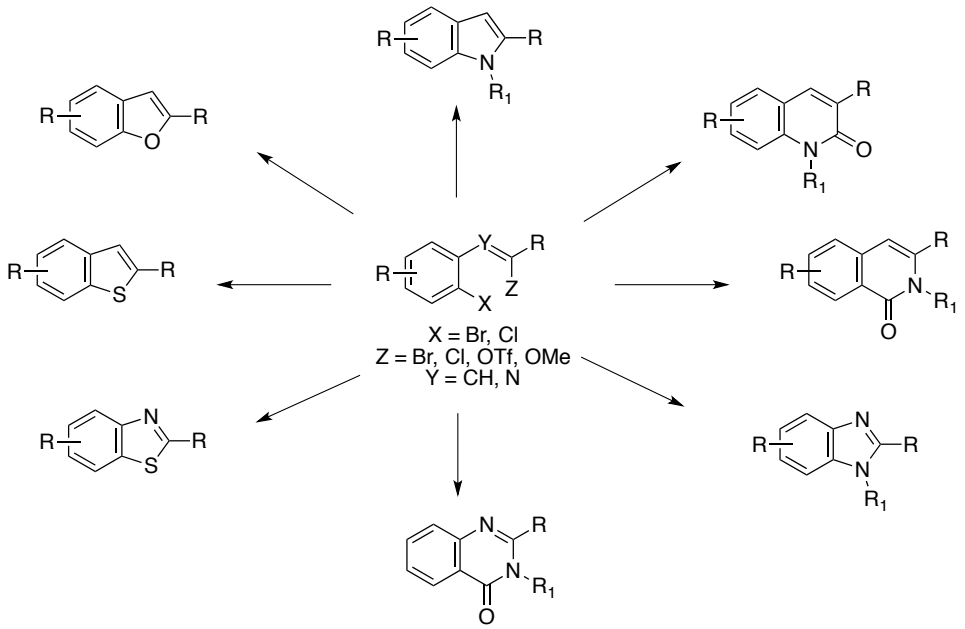
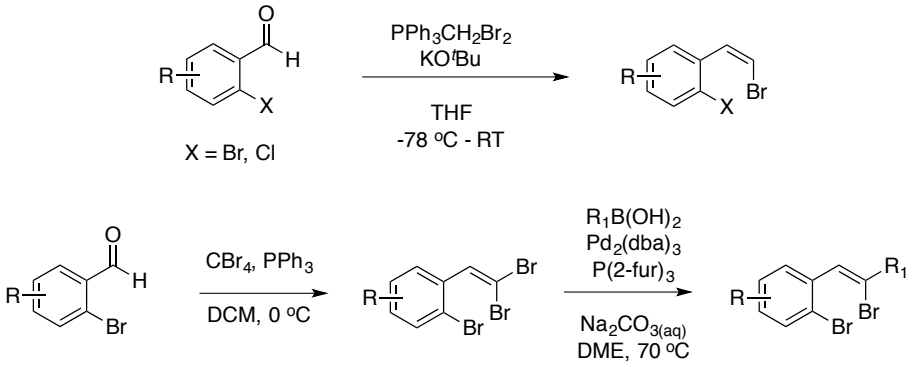


Figure 1.7

1.3.1.1 Precursor Synthesis

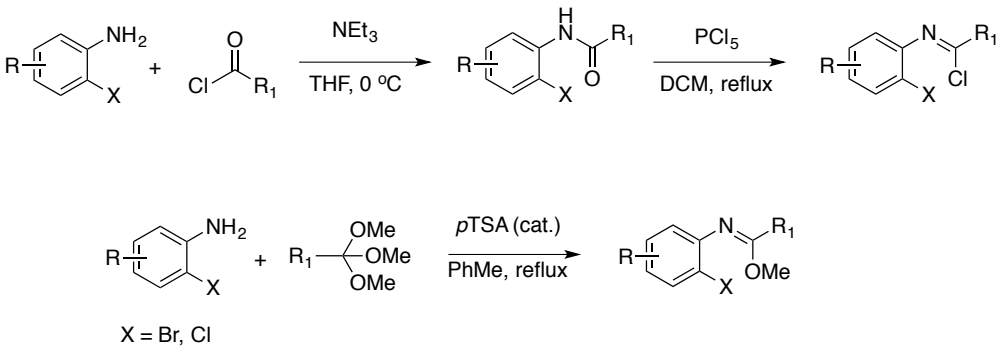
A simple Wittig olefination provides ready access to (*ortho*-haloalkenyl)aryl halides from commercially available 2-halobenzaldehydes (Scheme 1.33).[53] Products obtained typically display high levels of *Z*-selectivity. Substrates bearing aryl or alkenyl substituents on the alkene moiety can be obtained *via* a two-step process. Commencing from 2-bromobenzaldehyde, a Ramirez olefination delivers *gem*-dibromoalkenyl intermediates, which can then be subjected to Suzuki conditions

whereupon the least hindered *E*-alkenyl halide selectively reacts to generate 2-substituted products (Scheme 1.19).



Scheme 1.19

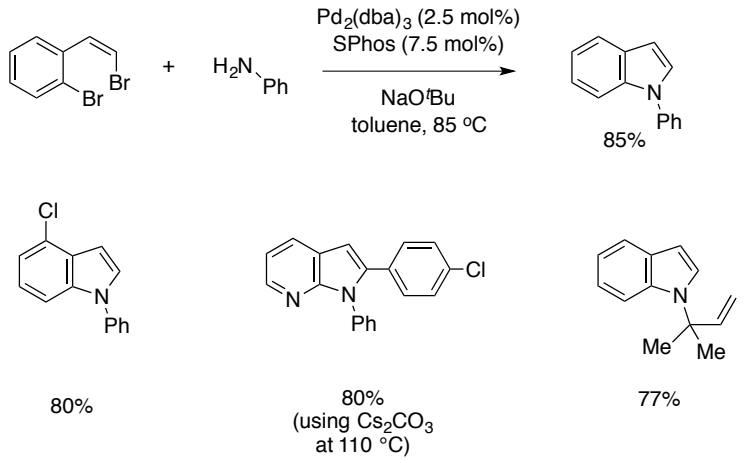
The analogous substrates bearing a *N*-atom in the 'alkenyl' moiety can be used in both imidoyl chloride and imidate forms. Either are readily accessible from the same commercially available 2-haloaniline starting materials (Scheme 1.20).[54]



Scheme 1.20

1.3.1.2 C-N Bond Formation

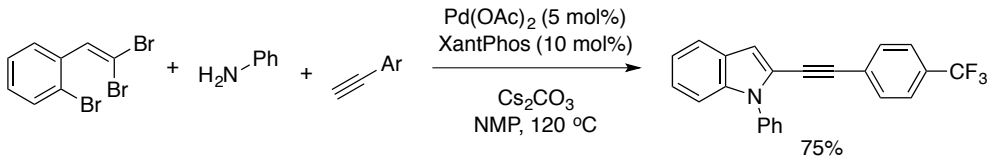
Use of (*ortho*-haloalkenyl)aryl halide substrates in conjunction with palladium- or copper-catalysed carbon-heteroatom bond-forming processes originally focused on the synthesis of indoles. After initially exploring the corresponding alkenyl triflate substrates,[55] Willis and co-workers demonstrated that these dihalides could undergo tandem intermolecular *N*-alkenylation and intramolecular *N*-arylation processes to yield indoles. A palladium-based catalytic system was first invoked which allowed access to *N*-substituted products in excellent yields (Scheme 1.21).[53, 56, 57] Notably, both the *Z*- and *E*-isomers of the starting alkenyl halides could be employed. A complementary synthetic route employing copper-catalysis was also developed.[58]



Scheme 1.21

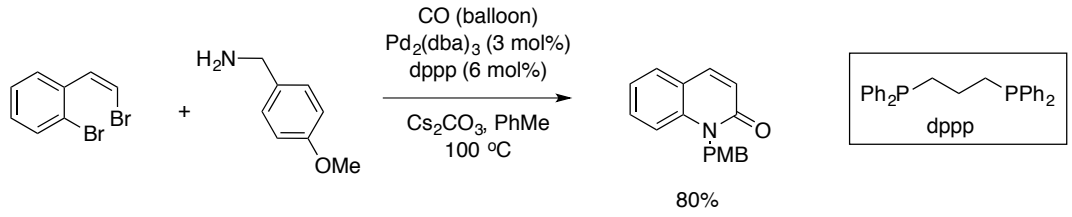
Several variations of this procedure have been developed.[59] Work described by Liang and Xi sought to include an additional tandem process by employing a geminal dibromoalkenyl aryl bromide substrate. In a highly selective three-component process using a palladium catalyst derived from bidentate ligand XantPhos, they were able to

demonstrate that 2-alkynyl indoles such could be obtained in good yields (Scheme 1.22).[60] Though full mechanistic studies were not performed, a putative mechanism suggested that reaction of the *E*-alkenyl bromide with the alkyne preceeded interaction with the aniline.



Scheme 1.22

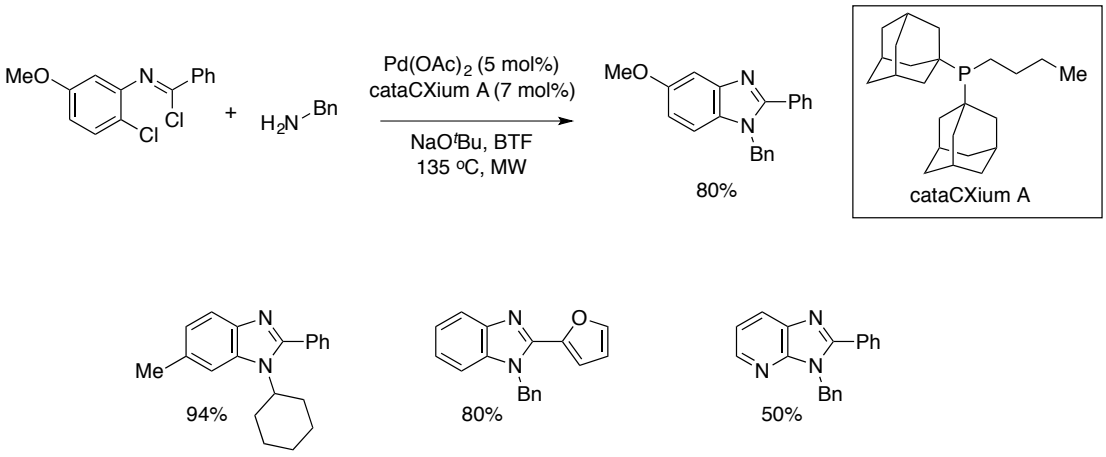
In an extension of their palladium-catalysed methodology, Willis and co-workers demonstrated that a carbonylation process could be incorporated to deliver quinolone products. Use of a catalytic system incorporating bidentate ligand dppp facilitated the alkenyl aminocarbonylation/intramolecular aryl amidation processes (Scheme 1.23).[61]



Scheme 1.23

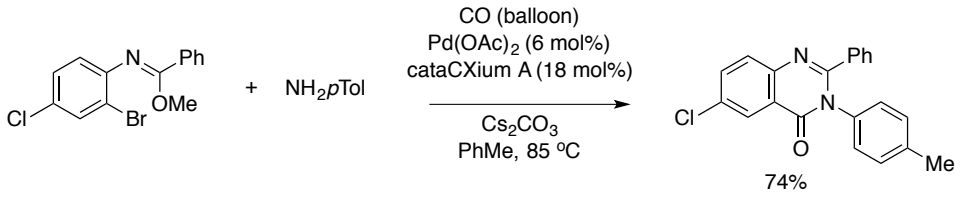
By delaying the introduction of the carbon monoxide and performing the reaction as a two-stage process, it was possible to access the regioisomeric isoquinolone products. Florent and co-workers have also reported a related synthesis of 3-subsitiuted isoquinolones.[62]

To provide access to an even wider range of heterocycles, the analogous *N*-containing substrates can also be employed. Use of a palladium-based catalytic system and *N*-(*ortho*-halophenyl)imidoyl chlorides allowed Willis and co-workers access to a broad range of 2-substituted benzimidazole products (Scheme 1.24).[54] Bulky adamantyl-substituted trialkylphosphine ligand cataCXium A proved to be optimal for the protocol involving a microwave irradiation strategy.



Scheme 1.24

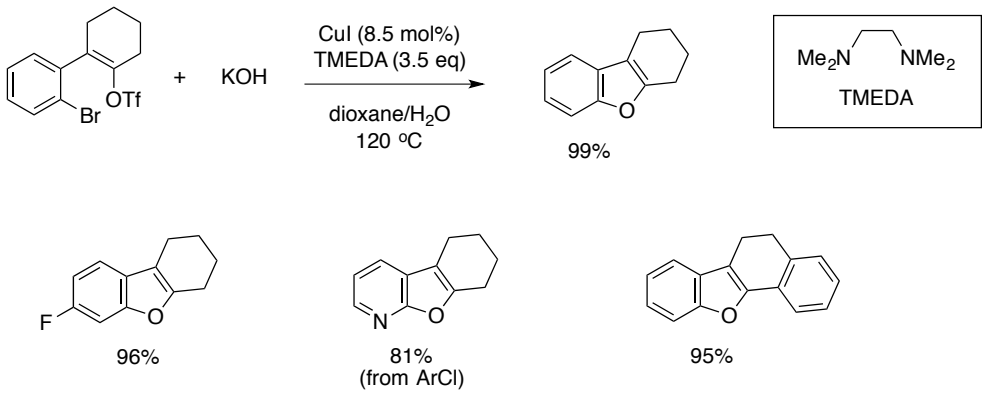
Willis and co-workers showed that the corresponding *N*-(*ortho*-halophenyl)imidate substrates could also act as benzimidazole precursors when subjected to the same catalyst system. Furthermore, they were able to demonstrate that these starting materials could be used in the synthesis of unusual quinazolinone structures *via* the incorporation of a carbonylation step (Scheme 1.25).[54]



Scheme 1.25

1.3.1.3 C-O Bond Formation

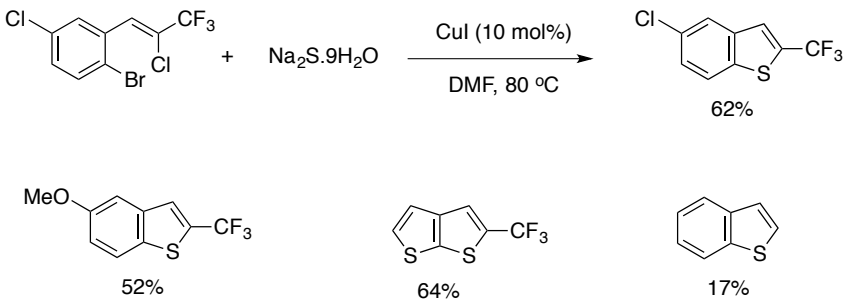
C-O bond formation has not proved to be a popular strategy when combined with (*ortho*-haloalkenyl)aryl halide precursors. Indeed, the only example involves the use of the corresponding alkenyl triflate precursors. Willis and co-workers reported that these substrates, when reacted with potassium hydroxide and a copper catalyst, allowed access to the corresponding benzofurans *via* presumed enolate intermediates (Scheme 1.26).[63]



Scheme 1.26

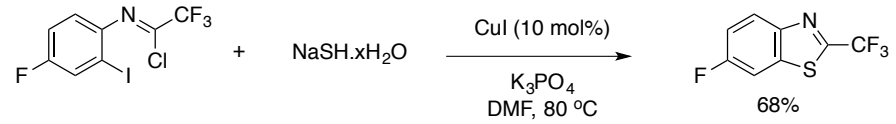
1.3.1.4 C-S Bond Formation

(*ortho*-Haloalkenyl)aryl halide precursors and the corresponding pseudo-haloalkenyl variants have been used in conjunction with C-S bond forming processes to extend the range of heterocycles accessible from these general substrates. Li and co-workers demonstrated that a range of 2-trifluoromethyl benzothiophenes could be generated from (*ortho*-chloroalkenyl)aryl bromide precursors. A simple reaction system comprising of sodium sulfide nonahydrate and copper iodide was found to deliver the desired products in good yields (Scheme 1.27).[64] However, the incorporation of the 2-trifluoromethyl group was found to be crucial to the success of the reaction.



Scheme 1.27

The same authors were able to demonstrate that 2-trifluoromethyl benzothiazoles could be obtained from the corresponding *N*-(2-haloaryl)trifluoroacetimidoyl chlorides under very similar conditions. (Scheme 1.28).[64]



Scheme 1.28

1.3.2 *ortho*-Haloacetanilide and α-(*ortho*-Haloaryl) Ketone Precursors

ortho-Haloacetanilides and their corresponding ketone analogues have proven to act as starting materials in the synthesis of a range of different heterocycles *via* key palladium- or copper-catalysed intermolecular carbon-heteroatom bond forming processes (Figure 1.10).

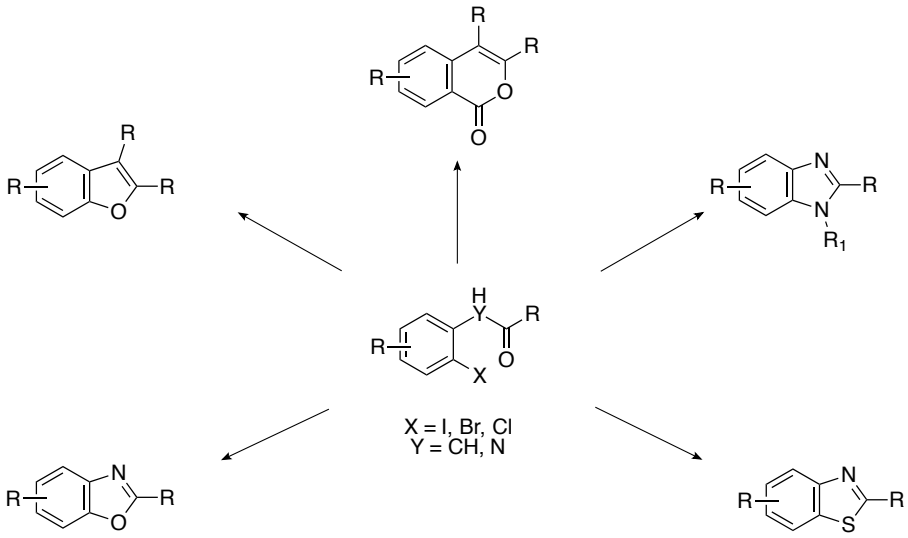
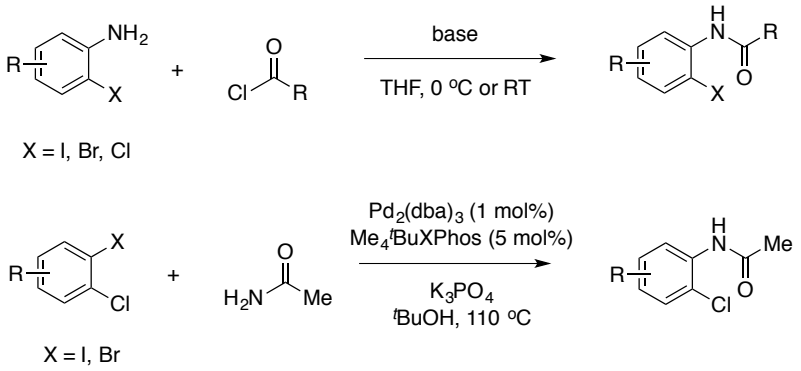


Figure 1.8

1.3.2.1 Precursor Synthesis

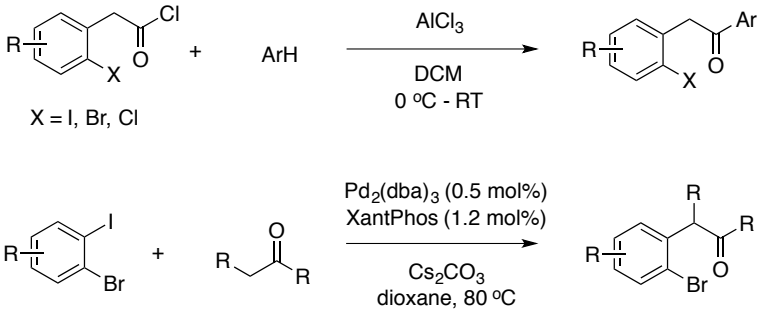
ortho-Haloacetanilides can be readily accessed using a simple one-step synthesis from commercially available starting materials. Both *ortho*-haloanilines and *ortho*-

dihaloarenes can be utilised (Scheme 1.29). A simple base-promoted reaction of the former with acid chlorides allows access to a range of diversely substituted *ortho*-haloacetanilide products.[65] Alternatively, *ortho*-halochloroarenes can be used in a palladium-catalysed *N*-arylation of acetamide.[66]



Scheme 1.29

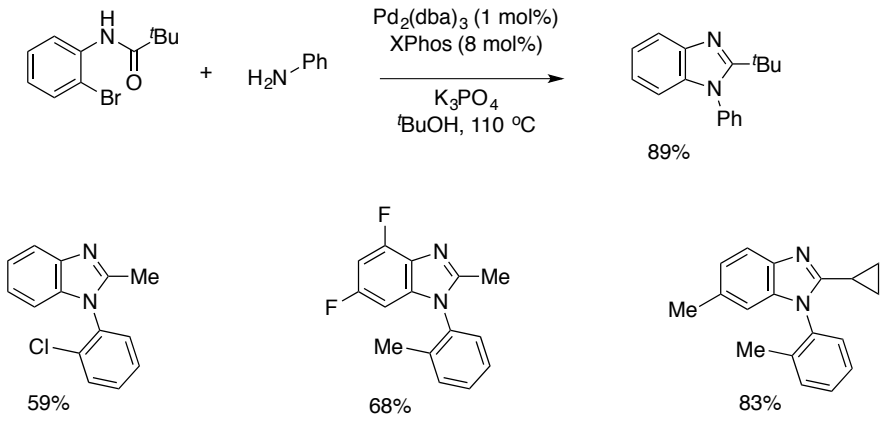
To access the ketone-based counterparts of these heterocycle precursors, two main strategies have been employed (Scheme 1.30). The first invokes a Friedel-Crafts reaction.[67] Alternatively, a palladium-catalysed approach can be utilised. α-Arylation of ketones using *ortho*-bromoiodobenzenes results in the synthesis of α-(*ortho*-bromoaryl) ketones *via* selective reaction of the more labile aryl iodide.[68]



Scheme 1.30

1.3.2.2 C-N Bond Formation

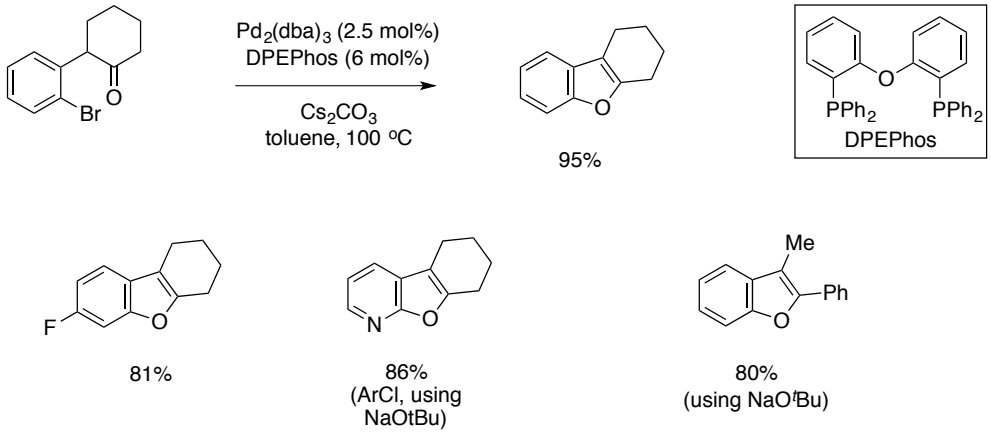
Strategies combining *ortho*-haloacetanilides with C-N bond forming processes have been described resulting in the synthesis of a variety of benzimidazole products. Zheng and Buchwald reported a palladium-catalysed route (Scheme 1.31).[66] Copper-catalysed versions of such a protocol have also been described.[69]



Scheme 1.31

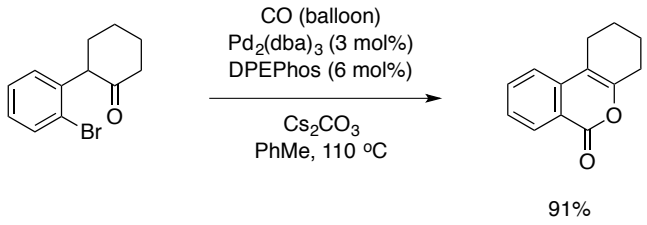
1.3.2.3 C-O Bond Formation

α-(*ortho*-Haloaryl) ketone precursors have been particularly useful in conjunction with C-O bond forming processes. Intramolecular enolate *O*-arylation has proven to be a popular tactic. Willis and co-workers described the implementation of such a strategy. They used a palladium catalyst to synthesize a range of 2,3-substituted benzofurans (Scheme 1.32).[68] An analogous procedure invoking copper catalysis has also been reported.[67]



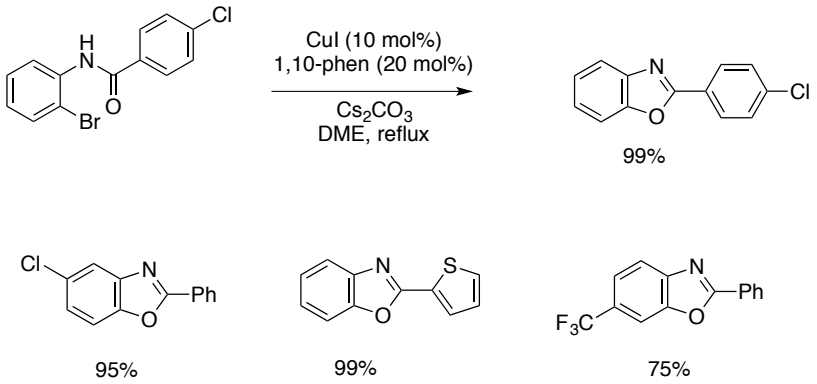
Scheme 1.32

Willis and co-workers were able to extend their methodology to create a synthesis of isocoumarins by incorporating a carbonylation process (Scheme 1.33).[70] A putative mechanism involves palladium-catalysed carbonylation of the aryl bromide followed by intramolecular enolate *O*-acylation.



Scheme 1.33

ortho-Haloacetanilides have also enjoyed considerable success when combined with C-O bond-forming protocols. Intramolecular *O*-arylation provides ready access to benzoxazole products and the use of copper-based catalytic systems has dominated. Evindar and Batey were the first to report such a synthesis and a range of 2-aryl benzoxazole products were obtained in exemplary yields (Scheme 1.34).[65]

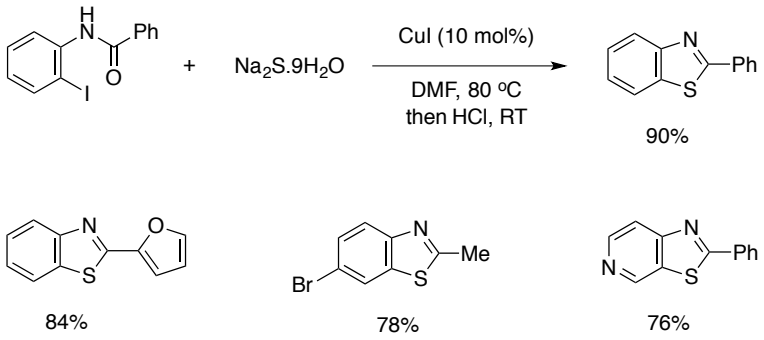


Scheme 1.34

1.3.2.4 C-S Bond Formation

The range of heterocycles accessible from *ortho*-haloacetanilide precursors has been expanded using C-S bond forming strategies. Reaction with a *S*-source, under palladium or copper catalysis, results in the formation of benzothiazoles. An analogous procedure using α-(*ortho*-haloaryl) ketone precursors to access benzothiophene derivatives has not been reported, though should hypothetically be possible.

Ma and co-workers reported a particularly effective synthesis of benzothiazoles from *ortho*-iodoacetanilides. They invoked the use of sodium sulfide nonahydrate as the 'hydrogen sulfide surrogate'. This, combined simply with copper iodide, resulted in the formation of a range of 2-aryl or alkyl benzothiazoles after acid-promoted cyclisation (Scheme 1.35).[71]



Scheme 1.35

Palladium catalysis has also been used to access benzothiazole products using this strategy. Mase and co-workers described the use of an alkyl thiol as the 'hydrogen sulfide surrogate'.[72]

1.4 Concluding Comments

By definition, palladium- and copper-catalysed aryl C-N, C-O and C-S bond forming processes are designed to construct bonds between heteroatoms and aromatic rings. It is thus not surprising that these reactions have been used with considerable success in the synthesis of aromatic heterocycles. The enormous development these processes have undergone, in terms of the range of coupling partners which can be employed and the substrates which can be utilised, has resulted in the emergence of a set of privileged starting materials which can act as precursors to a wide variety of different heterocycles *via* judicious choice of reaction conditions. The reactions presented above have demonstrated how, from four key substrates, a plethora of diverse heterocyclic frameworks can be accessed. As advances in the underpinning transformations continue to develop, the number of heterocycles accessible – and the ease with which they can be synthesised – will undoubtedly continue to grow.

Chapter 2. Synthesis of Cinnolines from (*ortho*-Haloalkenyl)aryl Halide Precursors

2.1 Introduction

Previous work performed in the Willis group has demonstrated that a variety of heterocyclic frameworks are accessible from general (*ortho*-haloalkenyl)aryl halide precursors (section 1.3.1). Prompted by this success, it was envisaged that these starting materials could be used to access further, more challenging, heterocyclic products. To this end, the synthesis of cinnolines was targeted (Figure 2.1).

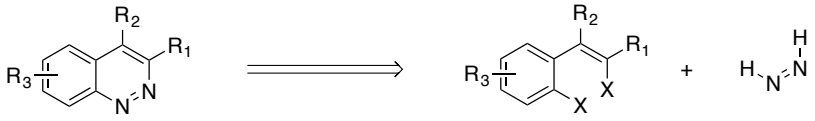


Figure 2.1

It was anticipated that a tandem palladium- or copper-catalysed C-N formation with a hydrazine derivative could provide access, either directly or indirectly *via* a protected dihydrocinnoline intermediate, to cinnoline products.

As well as expanding the range of heterocyclic scaffolds attainable from (*ortho*-haloalkenyl)aryl halides, cinnolines are structures worthy of pursuit in their own right. Compounds containing such a motif have a wide range of biological and pharmaceutical applications as well as interesting physical properties.[73] They are known to exhibit anti-cancer,[74] anti-inflammatory,[75] fungicidal and bactericidal[76] activity as well as luminescent and optical properties.[77] However, these structures

remain unusual and relatively unfamiliar in modern-day organic chemistry; perhaps because a mild and general synthesis has remained elusive.

Methods for the synthesis of cinnolines are currently dominated by routes involving diazotisation.[78] The structure is generally formed *via* the cyclisation of a phenyldiazonium ion onto *ortho* functionality. In the seminal Von Richter synthesis[79] this cyclisation is onto an activated *ortho* alkyne, while in the Borsche and Widman-Stoermer syntheses this is onto an activated alkene or an enolisable ketone respectively (Figure 2.2).[80]

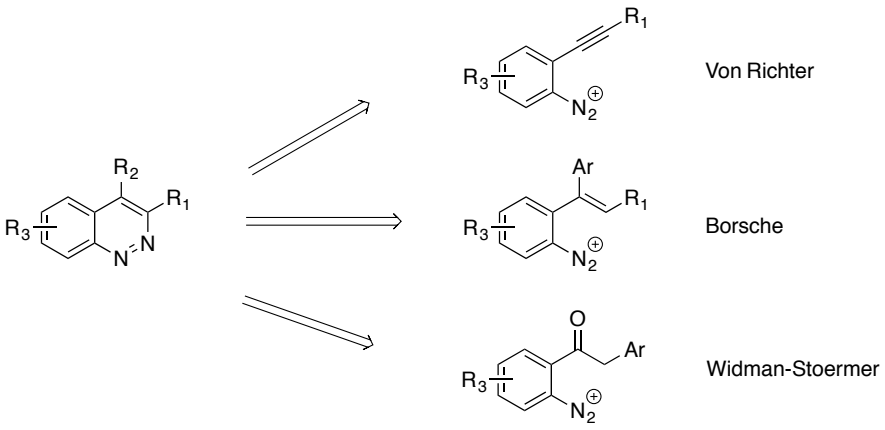
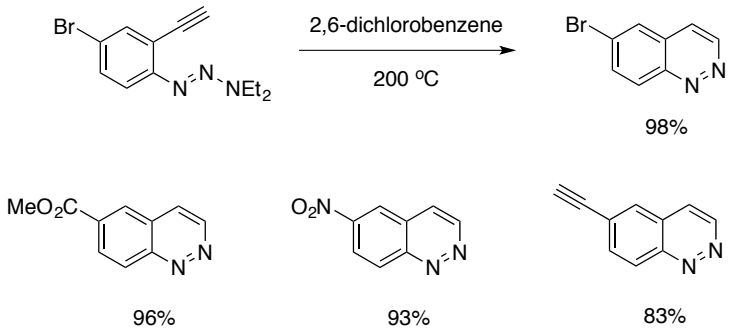


Figure 2.2

Other routes to cinnolines include intramolecular cyclisations involving aryl hydrazones,[81] aryl hydrazines[82] and nitriles,[83] and intermolecular cycloadditions.[84] However, there are significant limitations to these routes, particularly those involving diazotisation. Strongly acidic conditions are required and the construction of the cinnoline framework frequently results in substitution at the 4-, and often 3-, positions. To access cinnolines with substitution exclusively on the benzo- ring,

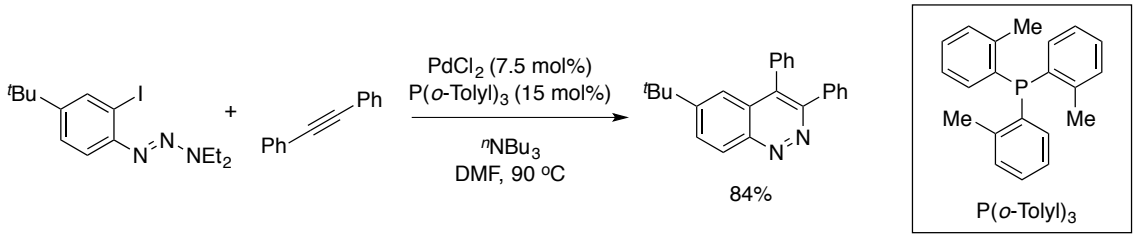
extensive transformations and often harsh conditions are required to remove substituents on the pyridazine ring.

A modified modern version of the Von Richter synthesis utilises triazenes as masked diazionium ion equivalents.[85, 86] However very high temperatures are still required and the accessible substitution patterns are limited (Scheme 2.1).[85]



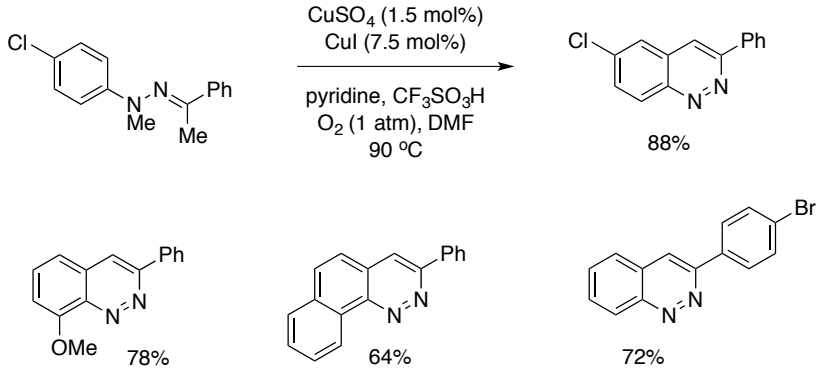
Scheme 2.1

Recently a palladium-catalysed route has been reported using a similar triazene strategy. Annulation of 2-iodophenyltriazenes with an internal alkyne led to the generation of cinnoline products. Although this represents an improvement in terms of the reaction conditions, the requirement for internal alkynes means that complete synthetic control of substitution on the cinnoline backbone cannot be exerted. Only 3,4-disubstituted products can be obtained (Scheme 2.2).[87]



Scheme 2.2

A route involving copper catalysis has also recently been reported. Employment of an aerobic dehydrogenative cyclisation strategy using *N*-methyl-*N*-phenylhydrazone substrates resulted in a range of 3-aryl cinnolines (Scheme 2.3).[88] Although the reaction conditions are comparatively mild, once again, full synthetic control of the substitution pattern is not possible.



Scheme 2.3

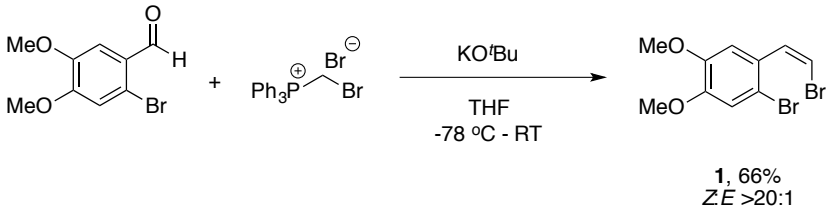
The majority of the routes described above involve frameworks that already contain the key nitrogenous functionality in place. Thus, a strategy involving tandem formation of both C-N bonds represents a distinct departure from existing synthetic procedures. Harsh reaction conditions and poor substrate scopes are common features of current synthetic protocols. Therefore, a mild procedure, whereby complete

synthetic control of the substitution pattern displayed by the product can be attained, would also represent a key development in cinnoline chemistry.

2.2 Initial Investigations

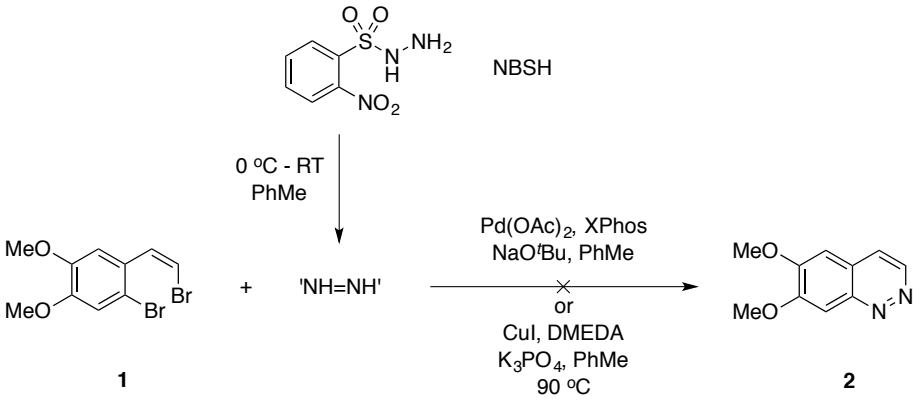
A range of different strategies involving different hydrazine-derived coupling partners were explored. Initial investigations focused on the development of a direct route from (*ortho*-haloalkenyl)aryl halides to cinnolines.

(*Z*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **1** was chosen as the subject for these investigations as it was postulated that use of a 'challenging' electron-rich substrate would result in the development of more robust methodology. Dihalide **1** was readily synthesised *via* application of the standard Wittig procedure (Section 1.3.1.1) in good yield and with excellent *Z*-selectivity (Scheme 2.4).



Scheme 2.4

The first - and perhaps most ambitious - strategy explored the use of diimide. The realisation of such a strategy would result in a highly efficient and conceptually simple direct synthesis of cinnolines such as **2** (Scheme 2.5).

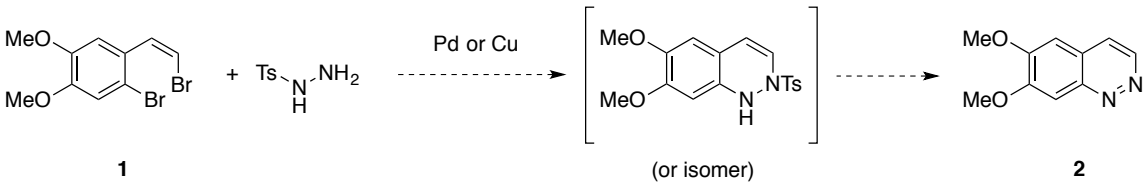


Scheme 2.5

Diimide is highly reactive and must be generated *in situ*, most commonly from a hydrazide precursor such as 2-nitrobenzenesulfonylhydrazide (NBSH).[89] Often used as a reducing agent,[90] control reactions verified that diimide did not result in reduction of the alkene present in **1**. However, initial screening reactions using a palladium catalyst based on dialkylbiaryl ligand XPhos, and a copper catalyst based on 1,2-diamine DMEDA, resulted only in returned starting material. Hence, without literature precedent for C-N bond formations with such a coupling partner, and difficultly in attaining conditions compatible for both the *in situ* generation of diimide using NBSH and catalysed C-N bond formation, this strategy was deemed overly challenging.

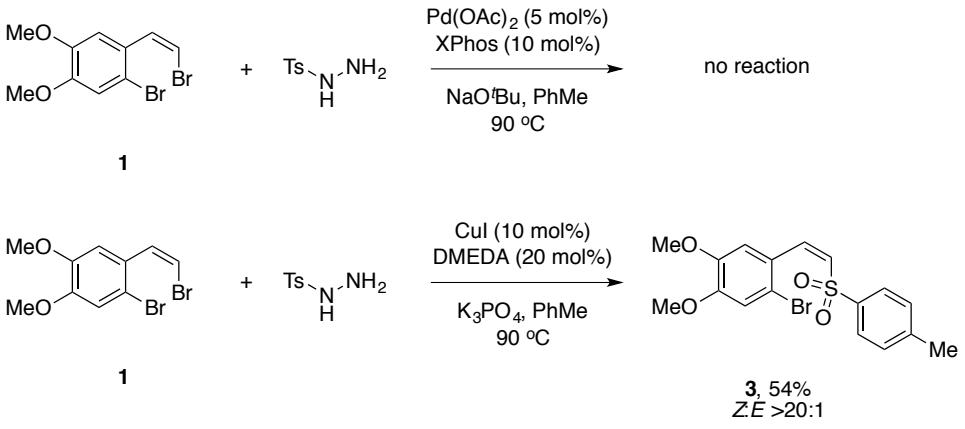
A direct route involving another sulfonyl hydrazide, namely *p*-toluenesulfonyl hydrazide, was also explored. Literature precedent for palladium- and copper-catalysed reactions with such mono-substituted hydrazine derivatives suggests that reaction preferentially occurs at the most acidic *N*-centre.[91, 92] In this case the sulfone-bearing *N*-atom would be predicted to react first and so competing indole formation should be avoided. It was postulated that after tandem C-N bond formation, a base-

induced *in situ* elimination reaction could deliver the desired cinnoline product directly (Scheme 2.6).



Scheme 2.6

However, the only product isolated from screening experiments employing both palladium and copper catalysis was alkenyl sulfone **3** (Scheme 2.7). This product was isolated in 54% yield when a copper-based catalytic system employing diamine ligand DMEDA was used. Palladium-catalysed conditions using XPhos afforded only returned starting material.

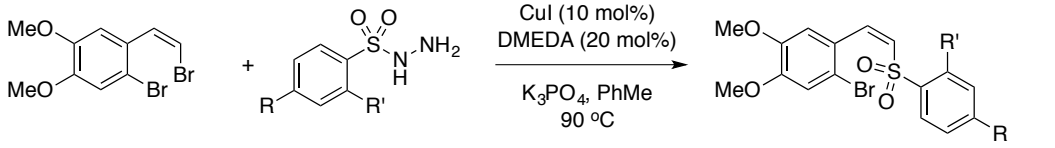


Scheme 2.7

p-Toluenesulfonyl hydrazide is a known diimide precursor,[93] hence it was hypothesised that such a decomposition occurred and led to the generation of a sulfinate species. This was then poised to undergo C-S bond formation preferentially

with the alkenyl bromide of dihalide **1**. Such copper-catalysed sulfinate salt couplings are known in the literature.[94] Notably the *Z*-configuration of the alkene was retained in the product.

To discourage this premature decomposition, the electronics of the sulfonyl hydrazide were modulated. Analogues **4** and **5**, bearing one and two methoxy-groups respectively, were synthesised and subjected to the same copper catalysed process (Scheme 2.8). It was postulated that inclusion of such an electron-donating group would lead to destabilisation of the resultant sulfinate species and hence disfavour its formation. However, use of hydrazide **4** resulted in formation of alkenyl sulfone **6** in a 67% yield; while hydrazide **5** resulted in decomposition. No trace of a product derived from a C-N bond-forming process was detected.

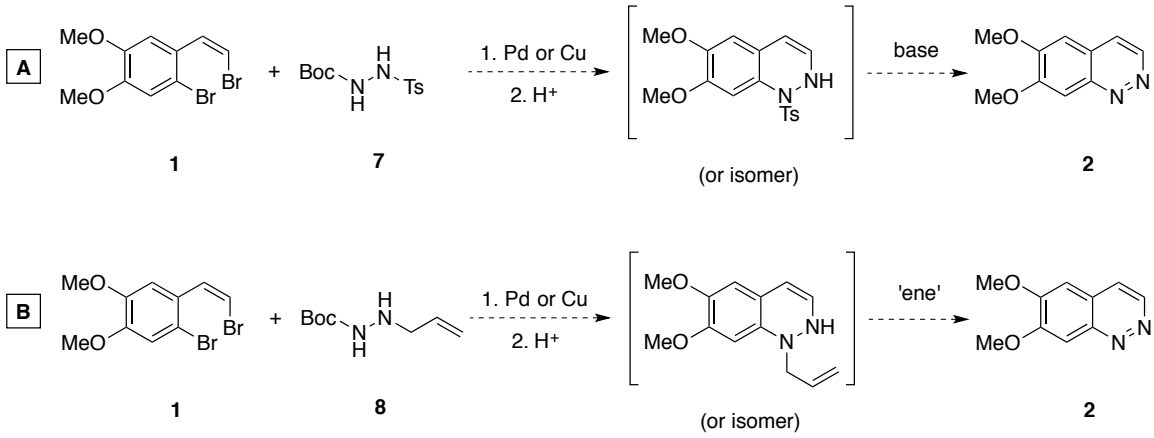


1 **4**, R = OMe, R' = H; **5**, R, R' = OMe **6**, R = OMe, R' = H, 67%, *Z*:*E* >20:1

Scheme 2.8

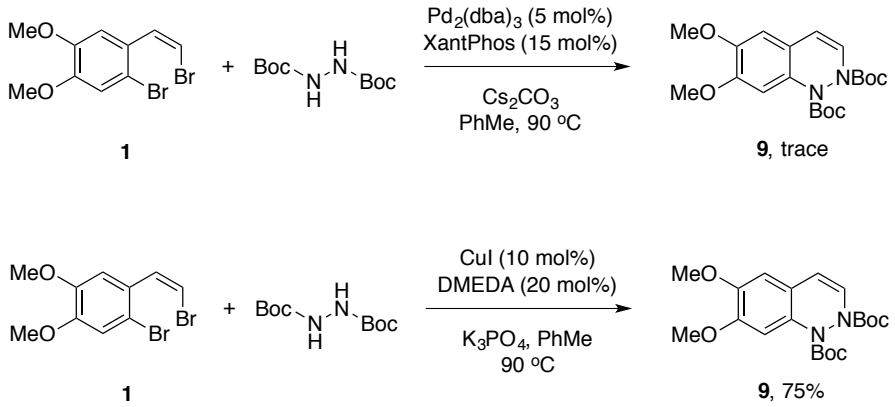
After these explorations towards a direct route to cinnolines proved ineffective, the development of an indirect, two-step route, was pursued. Maintaining hopes of the use of an elimination strategy, *tert*-butyl 2-tosylhydrazine-1-carboxylate **7** was synthesised. With an added *N*-Boc group to prevent decomposition, it was postulated that after tandem C-N bond formation the protecting group could be removed and base-induced elimination prompted (route A, Scheme 2.9). Alternatively, *via* a similar strategy, it was hoped that *tert*-butyl 2-allylhydrazine-1-carboxylate **8** could partake in

a cinnoline-forming ene reaction after tandem C-N bond formation and Boc deprotection (route B, Scheme 2.9). However, implementation of neither strategy proved fruitful. Trial reactions led only to decomposition.



Scheme 2.9

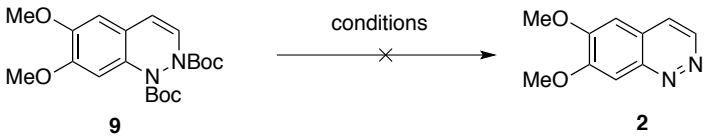
1,2-Dihydrocinnolines have received scant mention in the literature. As such little is known about their stability and it was hypothesised that such a structure could undergo aerial oxidation to the corresponding aromatic cinnoline. To implement such a tactic, commercially available di-*tert*-butyl hydrazodicarboxylate was investigated as the coupling partner. It was hoped that after annulation, double removal of the Boc protecting groups would reveal the 1,2-dihydrocinnoline. There is literature present for arylation of this hydrazide using palladium catalysis.[92, 95] However, these conditions using bidentate diphenylphosphino ligand XantPhos proved ineffective (Scheme 2.10). After a brief evaluation of conditions, a copper-based catalyst proved to be most capable for the tandem C-N bond formation. Di-*tert*-butyl dihydrocinnoline-1,2-dicarboxylate **9** was formed in 75% yield with the action of a DMEDA-ligated catalyst (Scheme 2.10).



Scheme 2.10

A variety of strategies were explored in an attempt to affect the acid-promoted removal of the Boc protecting groups. Selected experiments are detailed in Table 2.1.

Table 2.1 – Optimisation: attempts at acid-promoted cinnoline formation[a]



Entry	Reagent	Solvent	Temp./Time	2 (%)
1	TFA	MeCN	50 °C, 2 h	-
2	TFA	MeCN	RT, 2 h	-
3	$HCl_{(aq)}$	DCM	RT, 2 h	-
4	TMSOTf	DCM	RT, 2 h	-
5	-	DMF	120 °C, 16 h	-

[a]*Reaction conditions: di-tert-butyl dihydrocinnoline-1,2-dicarboxylate **9** (1.0 eq), reagent (3.0 eq), solvent (0.5 M), temperature, time. All reactions were left open to air.*

Attempts using standard Boc deprotection conditions[96] employing TFA at elevated temperature resulted in decomposition (Entry 1). Allowing the reaction to proceed at room temperature resulted in the same outcome (Entry 2). An attempt using

hydrochloric acid was similarly unsuccessful (Entry 3). Milder deprotection conditions were also explored; conditions using TMSOTf were trialled.[96] However, decomposition was observed once again (Entry 4). Thermal removal was investigated by heating dihydrocinnoline derivative **9** at 120 °C in DMF for 16 h. Such a strategy also resulted in decomposition (Entry 5).

All attempts to affect the removal of the Boc protecting groups proved ineffective. Hence, the conclusion was drawn that problems with instability were encountered upon treatment with acid or high temperatures. Therefore a hydrazide bearing protecting groups that could be removed under basic conditions was focused on, namely commercially available diethyl 1,2-hydrazinedicarboxylate. Preliminary studies indicated that such a strategy could indeed provide access to the desired cinnoline products.

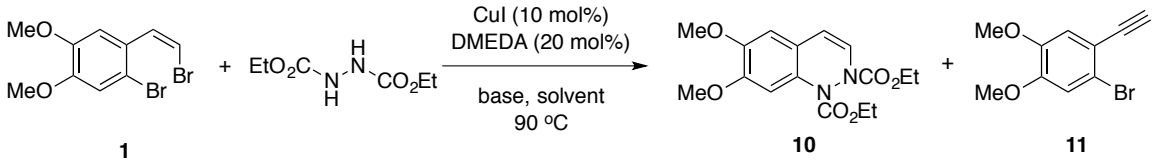
2.3 Optimisation Using Diethyl 1,2-Hydrazinedicarboxylate

With the appropriate coupling partner in hand, an exploration into the most effective reaction conditions for the tandem C-N bond formation could be performed. Given the success of copper catalysis in the synthesis of di-*tert*-butyl dihydrocinnoline-1,2-dicarboxylate **9**, such a system was again focused on.

The key reaction parameters investigated were the base, solvent, ligand and temperature employed. The copper(I) source was also briefly explored, though this proved to be less influential. Thus copper(I) iodide was selected as it is both readily

available and cheap. However, the choice of inorganic base and solvent proved to be crucial (Table 2.2).

Table 2.2 – Optimisation: focus on base and solvent[a]



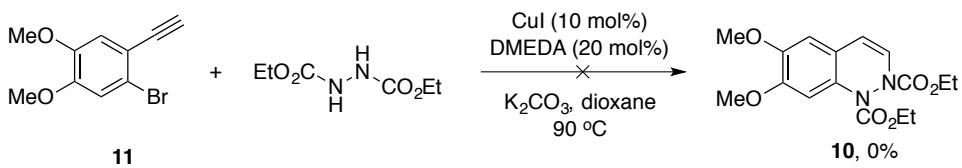
Entry	Base	Solvent	10 (%)[b]	11 (%)[b]
1	K_3PO_4	PhMe	71	-
2	K_2CO_3	PhMe	79	-
3	Cs_2CO_3	PhMe	54	29
4	NaO^tBu	PhMe	-	76
5	TEA	PhMe	trace	-
6	K_3PO_4	dioxane	68	-
7	K_2CO_3	dioxane	95	-
8	Cs_2CO_3	dioxane	79	11
9	K_2CO_3	DMF	31	61
10	K_2CO_3	^{t}BuOH	22	-

[a]*Reaction conditions: dihalide **1** (1.0 eq), hydrazide (2.0 eq), CuI (10 mol%), DMEDA (20 mol%), base (2.5 eq), dioxane (0.8 M), 90 °C, 18 h.* [b]*Yield of isolated product.*

Initially, the same conditions as used in the synthesis of di-*tert*-butyl dihydrocinnoline-1,2-dicarboxylate **9** were applied (Entry 1). Pleasingly these provided the desired diethyl dihydrocinnoline-1,2-dicarboxylate **10**, in 71% yield. A range of bases and solvent combinations were explored and it was discovered that both the nature of the base employed and its relative solubility in the solvent used had

a large effect. Too strong a base, such as sodium *tert*-butoxide (Entry 4), resulted in a competing elimination pathway and the generation of an alkyne side product **11**. If a weaker base, such as caesium carbonate, was used in conjunction with a solvent in which it has particular solubility, such as toluene (Entry 3), such a side reaction was also promoted. An attempt with potassium carbonate in toluene (Entry 2) led to an encouraging yield of 79% of the desired product, while an attempt with the organic base triethylamine (Entry 5) was unsuccessful. A solvent switch to dioxane (Entries 6,7 and 8) proved crucial and its combination with potassium carbonate provided the necessary solubility balance (Entry 7). Thus dihydrocinnoline derivative **10** was provided in an excellent 95% yield. Combination of such a base with DMF proved too soluble and favoured alkyne formation (Entry 9) while its combination with *tert*-butanol proved ineffective (Entry 10).

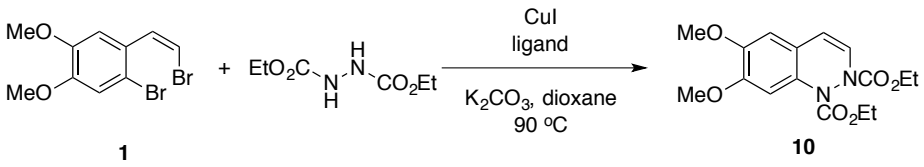
Buchwald has demonstrated that hydrazides of this type can take part in copper-catalysed tandem C-N bond-formation / hydroamidation processes.[97] If such a pathway was in operation in this case, alkyne **11** would not be an unproductive side-product but rather a reaction intermediate. To explore this possibility, alkyne **11** was resubjected to the reaction conditions (Scheme 2.11). No product was formed and hence a hydroamidation pathway was ruled out.



Scheme 2.11

The nature of the ligand used was found to be important. A selection of ligands were screened featuring each common type of bidentate chelation: *N*,*N*, *N*,*O* and *O*,*O* (as discussed in Section 1.2). The copper/ligand loading was also investigated (Table 2.3).

Table 2.3 - Optimisation: focus on ligand and catalyst loading[a]



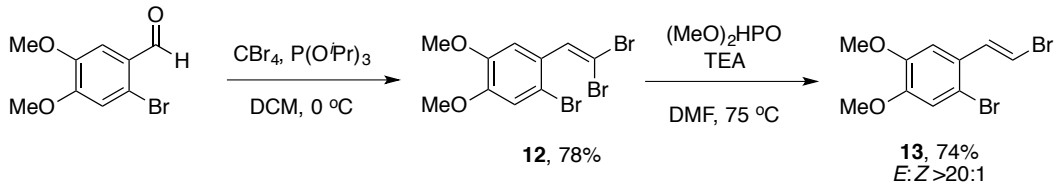
Entry	CuI loading	Ligand	Ligand loading	10 (%)[b]
1	10 mol%	DMEDA	20 mol%	95
2	10 mol%	1,10-phen	20 mol%	31
3	10 mol%	L-proline	20 mol%	24
4	10 mol%	ketoester A[c]	20 mol%	72
5	10 mol%	diketone A[d]	20 mol%	75
6	10 mol%	DMEDA	10 mol%	79
7	5 mol%	DMEDA	10 mol%	61
8	10 mol%	-	-	13

*[a]Reaction conditions: dihalide **1** (1.0 eq), hydrazide (2.0 eq), CuI, ligand, K_2CO_3 (2.5 eq), dioxane (0.8 M), 90 °C, 18 h. [b]Yield of isolated product. [c]Ketoester A refers to ethyl 2-oxocyclohexanecarboxylate. [d]Diketone A refers to 2,2,6,6-tetramethyl-3,5-heptanedione.*

The 1,2-diamine DMEDA was found to be optimal (Entry 1). Use of an alternative *N*,*N* chelator such as 1,10-phenanthroline was less effective (Entry 2), as was an attempt invoking *N*,*O* chelation using L-proline (Entry 3). Ligands based on *O*,*O* chelation proved more successful. Ketoester A and diketone A provided the desired product in good yields of 72% and 75% respectively (Entries 4 and 5). With DMEDA

selected as the optimal ligand, the copper and ligand loading were explored. Use of a 1:1 ratio of copper(I) iodide and DMEDA resulted in a significant drop in yield (Entry 6). Maintaining a 1:2 ratio but halving the respective loadings also resulted in a reduced yield of product (Entry 7). The necessity of the presence of a chelating ligand was verified by an attempt using copper(I) iodide only. A very low yield of product **10** was obtained (Entry 8). Thus, use of 10 mol% of copper iodide in a 1:2 ratio with DMEDA was found to be optimal. Due to the low cost and abundance of both components, no further attempts to reduce the catalyst loading were investigated.

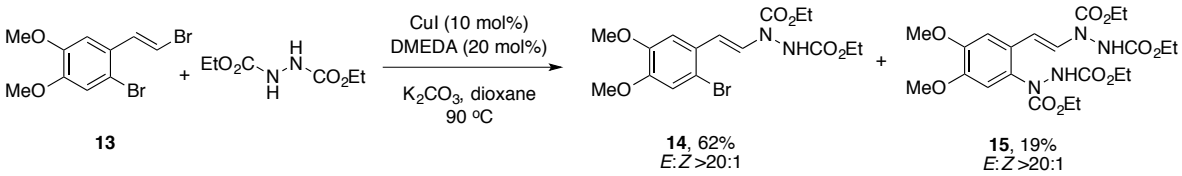
Dihalide **1** was obtained with very high *Z*-selectivity. To test if the corresponding *E*-isomer could be employed, (*E*)-1-bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **13** was synthesised *via* a phosphite-mediated reduction of tribromide **12**, itself synthesised *via* a Ramirez olefination[98] (Scheme 2.12).



Scheme 2.12

Previous reports detailing the use of (*ortho*-haloalkenyl)aryl halide precursors in indole synthesis (Section 1.3.1) have found that both *Z*- and *E*-isomers are compatible when combined with both palladium- and copper-based catalytic systems. Geometric isomerisation of the intermediate enamine formed is presumed to occur *in situ* so that the annulation reaction can proceed.

However, when dihalide **13** was subjected to the optimised reaction conditions, no cyclized product was observed (Scheme 2.13). Instead, coupling products **14** and **15** were formed from reaction with one and two equivalents of hydrazide respectively. The *E*-geometry was retained in each. It is not fully understood why isomerisation does not occur with this system.



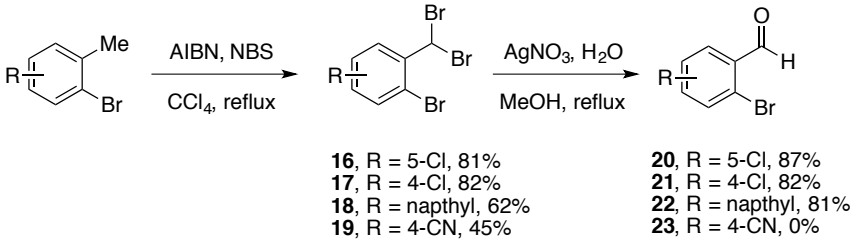
Scheme 2.13

A brief screen of the reaction temperature was performed to assess whether this could influence isomerisation. Increased temperatures proffered no beneficial effects while temperatures lower than 90 °C proved less effective for the coupling reaction. With this final parameter explored, the optimisation studies were deemed complete.

2.4 Reaction Scope: Synthesis of Functionalised (*ortho*-Haloalkenyl)aryl Halides and Derivatives

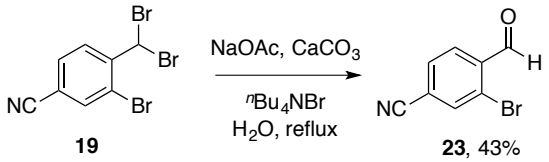
In order to explore the scope and generality of the procedure in terms of the functionality tolerated, a range of (*ortho*-haloalkenyl)aryl halide precursors were sought, accessible *via* the standard Wittig procedure (Section 1.3.1.1). Many 2-bromobenzaldehydes are commercially available. However, in cases where the aldehyde starting material had to be synthesised, several strategies were utilised.

A two-step route from commercially available 2-bromotoluenes proved successful. A radical bromination allowed the formation of dibromomethyl derivatives **16-19**, before a silver nitrate-mediated hydrolysis provided access to the desired benzaldehydes **20-23** in good yields (Scheme 2.14).



Scheme 2.14

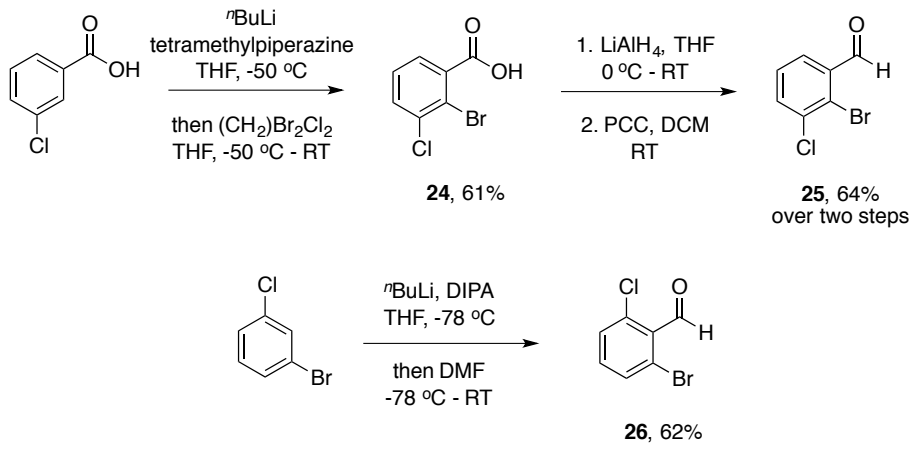
However, access to 3-bromo-4-formylbenzonitrile **23** was not possible using this hydrolysis protocol. Instead, a complex mixture of products was obtained, perhaps originating from Ritter-type side reactions.[99] Alternative mild hydrolysis conditions could be utilised which allowed access to the desired aldehyde **23** (Scheme 2.15).[100]



Scheme 2.15

Directed *ortho* lithiation proved to be a successful tactic in the pursuit of chloro-substituted 2-bromobenzaldehydes. Lithiation of 3-chlorobenzoic acid followed by reaction with 1,2-dibromochloroethane installed the desired 2-bromo substituent and provided 2-bromo-3-chlorobenzoic acid **24** in 61% yield. A subsequent reduction/oxidation strategy allowed access to 3-chlorobenzaldehyde **25** in 64% over

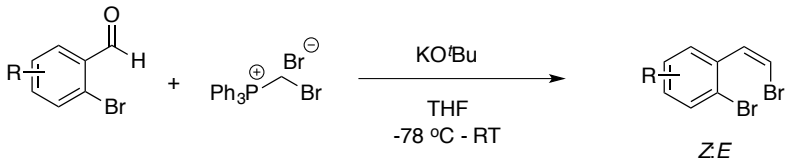
two steps (Scheme 2.16). 6-Chloro-2-bromobenzaldehyde **26** could be accessed directly by lithiation of 1-bromo-3-chlorobenzene using LDA and subsequent installation of the formyl group *via* reaction with DMF (Scheme 2.16).

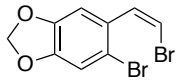
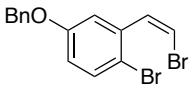
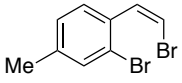
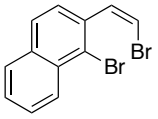
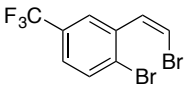
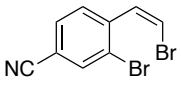
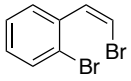
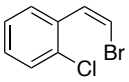
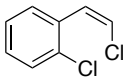
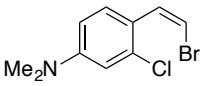
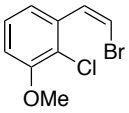
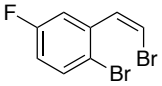
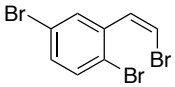
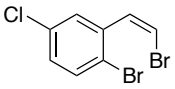
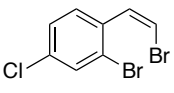
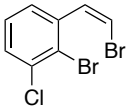
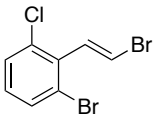


Scheme 2.16

With these, and a selection of commercially available benzaldehydes in hand, the corresponding (*ortho*-haloalkenyl)aryl halides could be readily accessed using the standard Wittig procedure (Table 2.4).

Table 2.4 – Reaction Scope: Synthesis of functionalised (*ortho*-haloalkenyl)aryl halides[a]



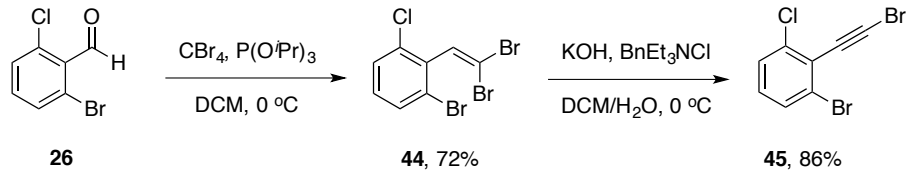
 **27**, 58% >20:1	 **28**, 67% 10:1	 **29**, 71% 10:1
 **30**, 63% 5:1	 **31**, 61% 10:1	 **32**, 57% >20:1
 **33**, 64% 10:1	 **34**, 61% 10:1	 **35**, 64% 10:1
 **36**, 63% 15:1	 **37**, 82% 10:1	 **38**, 64% 14:1
 **39**, 65% 10:1	 **40**, 62% 10:1	 **41**, 52% 10:1
 **42**, 42% 10:1	 **43**, 56% 1:20	

[a]*See experimental section for reaction conditions. Yields reported are of isolated product. Z:E ratios are calculated from ^{1}H NMR spectra.*

A range of dihalides were synthesised in moderate to good yields and with generally high *Z*-selectivity. Electron-rich (**27**-**28)**, more electron-neutral (**29, 30** and **33)** and

electron poor substrates (**31-32)** were all readily accessed. Several (*ortho*-bromoalkenyl)aryl chlorides were synthesised, **34** and **36-37**, so that the effect of an aryl chloride on the coupling reaction could be probed. A range of precursors bearing extraneous halides, **38-43**, were also obtained. While substrates bearing a chloro-substituent at every position of the benzo-ring could be accessed; trihalide **43** was synthesised with surprising, and problematic, *E*-selectivity.

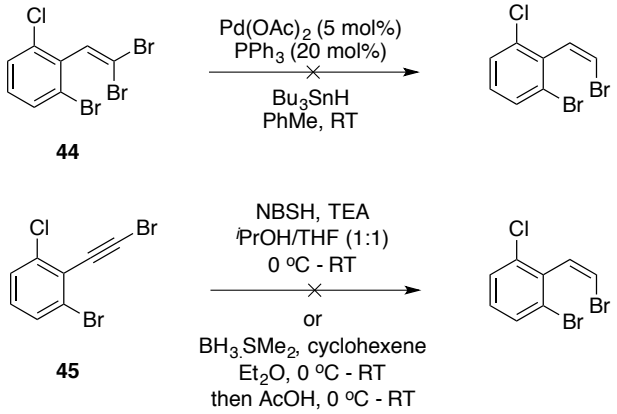
A range of strategies were pursued in an attempt to obtain precursor **43** with reversed double bond geometry. Ramirez olefination product **44** and the corresponding bromo-alkyne **45** - formed by base-induced elimination under phase transfer conditions - were key starting materials in this pursuit (Scheme 2.17).



26 **44**, 72% **45**, 86%

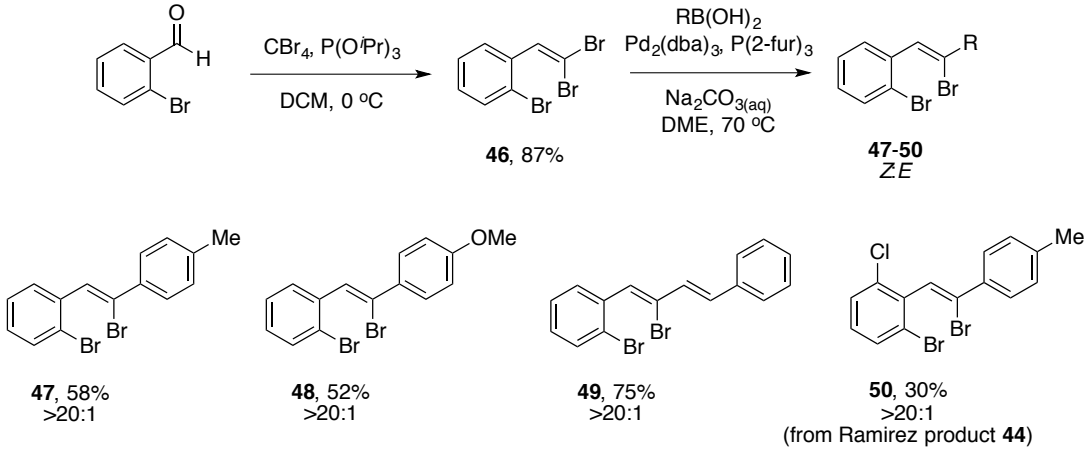
Scheme 2.17

Several literature protocols for selective *Z*-alkene synthesis were investigated. Ventures involving regioselective palladium-catalysed hydrogenolysis of **44** using tributyltin hydride[101] proved ineffective. Attempts at NBSH-mediated diimide reduction[102] and hydroboration protocols[103] using **45** were similarly unsuccessful (Scheme 2.18).



Scheme 2.18

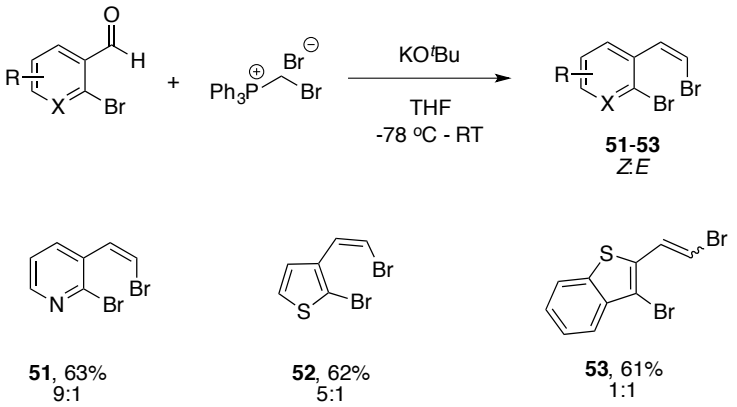
A range of substrates bearing aryl or alkenyl substituents on the alkene moiety **47-50** could be obtained *via* a two-step Ramirez / Suzuki protocol *via* trihalide **46**, as described in Section 1.3.1.1. This strategy was also adopted to circumvent the problematic *E*-selectivity encountered with alkenyl bromide **43**. Thus product **50** was synthesized bearing a chloro- substrate in the 3-position (Scheme 2.19).



Scheme 2.19

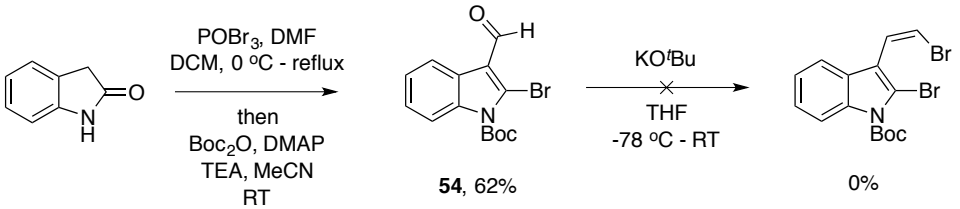
To complete the synthesis of substrates to be trialed in the diethyl dihydrocinnoline-1,2-dicarboxylate-forming reaction, a range of heterocyclic analogues were sought.

The standard Wittig procedure allowed the synthesis of pyridine- and thiophene-based products **51**-**53** (Scheme 2.20). Unfortunately, these heterocyclic analogues were obtained with poor *Z* selectivity, particularly benzothiophene derivative **53**. This precursor was obtained as an inseparable 1:1 mixture of *Z*- and *E*-isomers.



Scheme 2.20

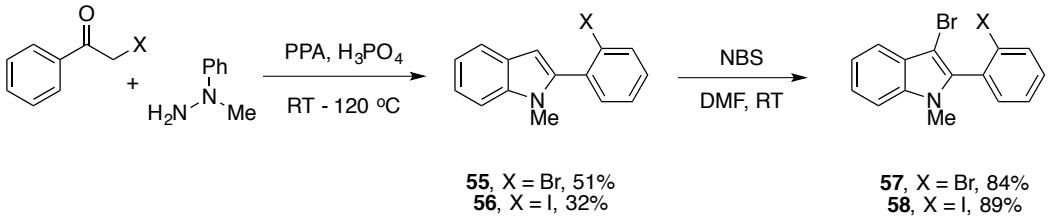
A series of precursors based on an indole framework were also investigated. Protected 2-bromo-3-formylindole **54** was attained from 2-oxindole *via* a two-step, one-pot procedure (Scheme 2.21). Unfortunately, the subsequent Wittig olefination was unsuccessful.



Scheme 2.21

Hence, an alternative route to indole-based precursors was explored. A traditional Fischer indole synthesis generated 2-aryl indoles **55** and **56**, bearing a bromo- and an

iodo- substituent respectively, before a simple bromination with NBS delivered the dihalide-bearing products **57** and **58** in good yields (Scheme 2.22).



55, X = Br, 51%
56, X = I, 32%

57, X = Br, 84%
58, X = I, 89%

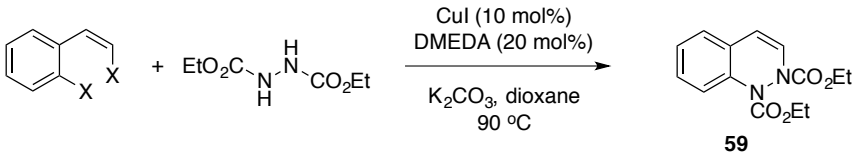
Scheme 2.22

Thus, a broad range of substrates featuring a range of different functionalities were synthesised, ready to be subjected to the copper-catalysed tandem C-N bond forming conditions.

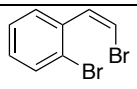
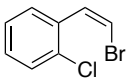
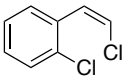
2.5 Reaction Scope: Diethyl Dihydrocinnoline-1,2-dicarboxylate Synthesis

(*Z*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **1**, the dihalide employed for optimisation studies, features two reactive bromide centres that partake in C-N bond formation. To assess whether chlorides could also be utilised, substrates **33**, **34** and **35** were subjected to the reaction conditions (Table 2.5).

Table 2.5 – Reaction scope: aryl/alkenyl bromides vs. chlorides[a]



59

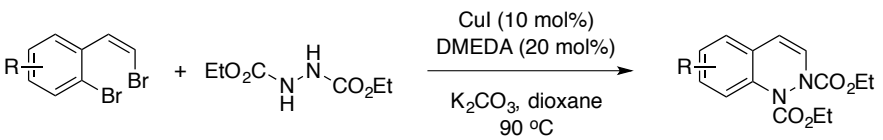
Entry	Substrate	59 (%)[b]
1	 **33**	83
2	 **34**	59
3	 **35**	16

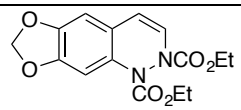
[a]*Reaction conditions: dihalide (1.0 eq), hydrazide (2.0 eq), CuI (10 mol%), DMEDA (20 mol%), K_2CO_3 (2.5 eq), dioxane (0.8 M), 90 °C, 18 h.* [b]*Yield of isolated product.*

Dibromide **33** provided diethyl dihydrocinnoline-1,2-dicarboxylate **59** in an excellent yield (Entry 1). Swapping an aryl bromide for a more challenging aryl chloride (substrate **34**) resulted in a reduced yield (Entry 2). When both reactive bromides were swapped for chlorides the efficiency of the reaction was severely reduced and product **59** was obtained in a very low yield of 16% (Entry 3). The presence of a reactive alkenyl bromide was deemed to be crucial for the success of the reaction.

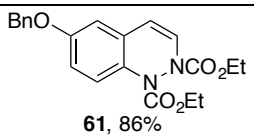
The scope and generality of the copper-catalysed hydrazide coupling reaction was probed by subjecting the range of functionalised (*ortho*-haloalkenyl)aryl halide precursors synthesised to the optimised reaction conditions (Table 2.6).

Table 2.6 - Reaction scope: synthesis of diethyl dihydrocinnoline-1,2-dicarboxylates[a]

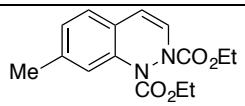




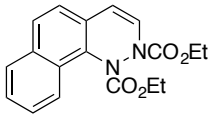
60, 91%



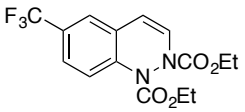
61, 86%



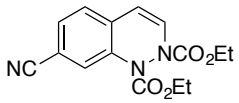
62, 80%



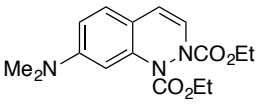
63, 73%[b]



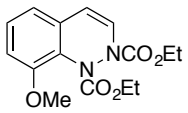
64, 79%



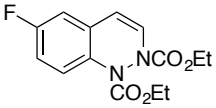
65, 64%



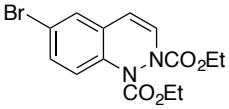
66, 61%
(from ArCl)



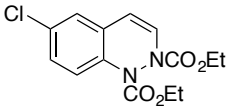
67, 62%
(from ArCl)



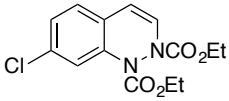
68, 85%



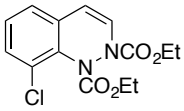
69, 65%



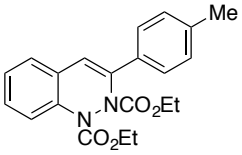
70, 78%



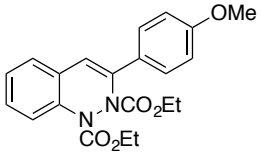
71, 81%



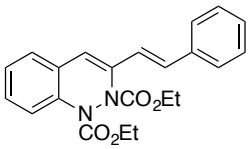
72, 65%



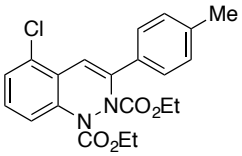
73, 77%



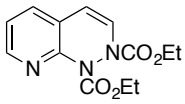
74, 64%



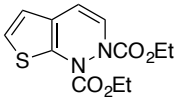
75, 71%



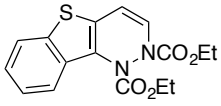
76, 73%



77, 64%



78, 53%[b]

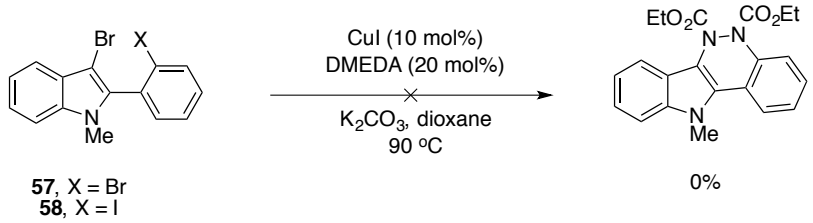


79, 36%[b]

[a]Reaction conditions: dihalide (1.0 eq), hydrazide (2.0 eq), CuI (10 mol%), DMEDA (20 mol%), K_2CO_3 (2.5 eq), dioxane (0.8 M), 90 °C, 18 h. Yields reported are of isolated products. [b]Dihalide precursor used with particularly low Z selectivity.

Thus, the methodology developed could be used to provide access to electron-rich (**60**-**61** and **66**-**67**), more electron-neutral (**62**-**63**) and electron-poor (**64**-**65**) products in good to excellent yields. Use of functionalised (*ortho*-bromoalkenyl)aryl chloride substrates also proved successful, though products **66** and **67** were obtained in slightly reduced yields of 61% and 62%, respectively. A range of extraneous halogens could also be tolerated, providing products **68**-**72** and **76** with potential for further synthetic elaboration. Notably, a chloro-substituent could be incorporated at every position of the benzo-ring. Substrates bearing an additional aryl- or alkenyl-substituent on the alkenyl bromide moiety provided ready access to a range of 3-substiuted diethyl dihydrocinnoline-1,2-dicarboxylate derivatives **73**-**76** in good yields. Heterocyclic products could also be readily attained using the copper-catalysed conditions; pyridine- and thiophene-derived products **77**, **78** and **79** were generated in moderate to good yields of 64%, 53% and 34% respectively. Unfortunately, use of starting materials with poor *Z*-selectivity translated to a reduced yield of the corresponding diethyl dihydrocinnoline-1,2-dicarboxylate product. Examples **63**, **78** and **79** were significantly affected.

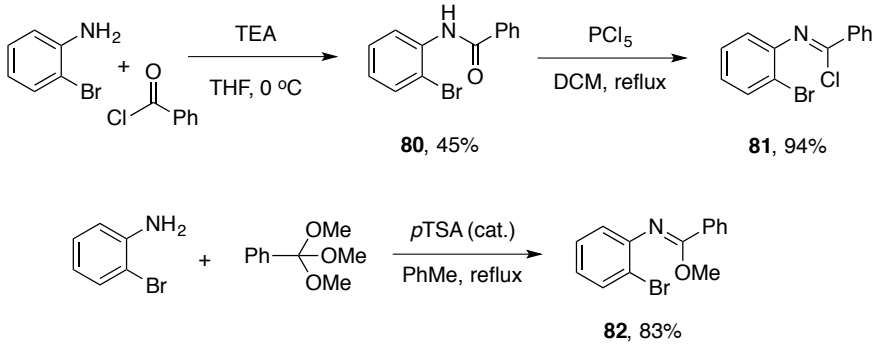
Lamentably, indole-based dibromide **57** proved ineffective under the reaction conditions. Use of analogue **58** bearing an aryl iodide was also similarly unsuccessful (Scheme 2.23). A brief screen of alternative reaction conditions failed to result in the formation of the desired indole-derived product.



57, X = Br
58, X = I

Scheme 2.23

As described in Section 1.3.1, analogous nitrogenous versions of (*ortho*-haloalkenyl)aryl halides have been used in the pursuit of novel methods for heterocycle synthesis. To test their applicability in this context, imidoyl chloride **81** – *via* amide **80** - and imidate **82** were synthesised from 2-bromoaniline (Scheme 2.24).[54]



80, 45%

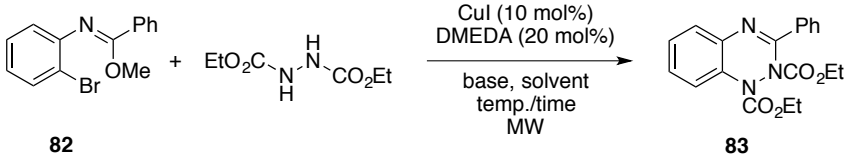
81, 94%

82, 83%

Scheme 2.24

Direct application of the established reaction conditions with imidoyl chloride **81** resulted in decomposition. Attempts at a two-step one-pot procedure, involving nucleophilic substitution followed by copper-catalysed intramolecular cyclisation, were also ineffectual. However, when the standard conditions were attempted with imidate precursor **82**, a trace of the desired product was generated. Thus modifications of the standard reaction conditions were briefly explored; selected experiments are detailed in Table 2.7.

Table 2.7 - Reaction scope: exploration of diethyl benzotriazine-1,2-dicarboxylate synthesis using microwave irradiation[a]



82 **83**

Entry	Base	Solvent	Temp./Time	83 (%)[b]
1	K_2CO_3	dioxane	135 °C, 2 h	43
2	K_2CO_3	BTF	135 °C, 2 h	11
3	K_2CO_3	DMF	135 °C, 2 h	-
4	K_2CO_3	NMP	135 °C, 2 h	-
5	K_2CO_3	THF	135 °C, 2 h	18
6	K_2CO_3	EtOH	135 °C, 2 h	-
7	K_2CO_3	dioxane/DMF (3:1)	135 °C, 2 h	35
8	NaO^tBu	dioxane	135 °C, 2 h	-
9	K_2CO_3	dioxane	135 °C, 4 h	48
10	K_2CO_3	dioxane	150 °C, 2 h	38

*[a]Reaction conditions: imidate **82** (1.0 eq), hydrazide (2.0 eq), CuI (10 mol%), DMEDA (20 mol%), base (2.5 eq), solvent (0.8 M), temperature, time. Heated using microwave irraditation. [b]Yield of isolated products.*

There is literature precedent for imidates such as **82** reacting under microwave conditions (see Scheme 1.24).[54] Pleasingly, when the standard conditions were attempted using such a technique, diethyl benzotriazine-1,2-dicarboxylate **83** was formed in 42% yield (Entry 1). A brief solvent screen (Entries 2-7) indicated that dioxane was the most effective of those investigated. Surprisingly, use of DMF and NMP (Entries 3 and 4) - solvents that are known to be effective when combined with microwave irradiation[104] - were ineffectual. Use of a stronger base caused the reaction

to cease (Entry 8). Doubling the reaction time and raising the reaction temperature (Entries 9 and 10) resulted in a slight increase and a slight decrease in yield respectively.

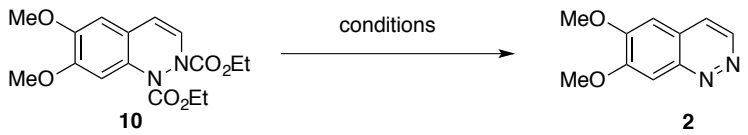
As difficulty was encountered with attempts to adjust the standard conditions to allow the synthesis of diethyl benzotriazine-1,2-dicarboxylate **83** in yields above 50%, further exploration was abandoned.

2.6 Transformation into the Cinnoline Products

With an extensive range of diethyl dihydrocinnoline-1,2-dicarboxylate products in hand, transformation to the corresponding aromatic cinnolines was investigated. As previously discussed (Section 2.2), it was hypothesised that the dihydrocinnoline would be revealed upon removal of the carbamate protecting groups and that such a structure could undergo aerial oxidation *in situ* resulting in direct formation of the desired cinnoline product.

To explore the feasibility of this conjecture, a range of deprotection conditions were explored. Selected examples are detailed in Table 2.8.

Table 2.8 – Optimisation: revealing the cinnoline products[a]



10 2

Entry	Reagent	Solvent	Temp./Time	2 (%)[b]
1	$NaOH_{(aq)}$	H_2O	100 °C, 16 h	37
2	$LiOH_{(aq)}$	H_2O	100 °C, 16 h	35
3	$LiOOH_{(aq)}$	THF/H_2O	50 °C, 16 h	54
4	NaOTMS	THF	50 °C, 16 h	46
5	NaSEt	THF	50 °C, 16 h	-
6	$^{n}Bu_4NOH$	EtOH	70 °C, 16 h	82
7	$NaOH_{(aq)}$	EtOH	70 °C, 16 h	94
8	$NaOH_{(aq)}$	EtOH	RT, 16 h	42

[a]*Reaction conditions: diethyl dihydrocinnoline-1,2-dicarboxylate* ***10*** *(1.0 eq), reagent (5.0 eq), solvent (0.2 M), temperature, time. All reactions were left open to air.* [b]*Yield of isolated product.*

Upon application of standard ethyl carbamate deprotection conditions[96] using aqueous sodium hydroxide at elevated temperature, the desired cinnoline product **2** was obtained in a low 37% yield (Entry 1). Alongside the desired product, another product was observed. This product was never isolated without incurring decomposition and was tentatively supposed to be an unstable dihydrocinnoline. No spectroscopic nor mass spectrometry-based evidence was ever obtained to verify this supposition. Swapping the hydroxide source to lithium hydroxide provided a similar result (Entry 2). Taking inspiration from Evans' mild conditions for oxazolidinone removal,[105] lithium hydroperoxide was explored (Entry 3). Formed *in situ*, it was hoped that such a reagent would have a dual function; to remove the protecting groups and also

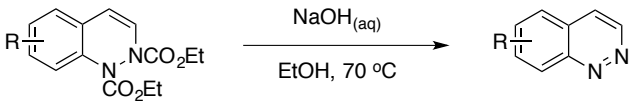
facilitate oxidation. Cinnoline **2** was formed in an improved, yet still moderate yield of 54%. At this juncture, non-hydroxide based strategies were explored. Attempts with sodium trimethylsilanolate and sodium ethanethiolate (Entries 4 and 5) were low yielding or unsuccessful, respectively. Use of hydroxide-based conditions was explored in conjunction with an organic solvent. *tetra*-Butylammonium hydroxide and aqueous sodium hydroxide in ethanol were employed at elevated temperature (Entries 7 and 8). Pleasingly, the desired product was formed in 82% and 94% yield respectively. An attempt using aqueous sodium hydroxide in ethanol at room temperature confirmed that use of an elevated temperature was necessary; cinnoline **2** was obtained with a significantly reduced yield (Entry 8).

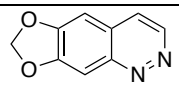
Mechanistic investigations of this transformation focused on efforts to prove the intermediacy of an unstable dihydrocinnoline. Thus, attempts were made to 'trap' such a structure *via* an *in situ* reaction of the nitrogenous centres. However, potential 'trapping' processes, such as acetylation, were thwarted by incompatibility with the hydroxide-based deprotection conditions. Attempts to remove the hydroxide *via* an initial aqueous work-up resulted in decomposition of the supposed dihydrocinnoline. Thus, the intermediacy of such a product could neither be proved nor disproved.

2.7 Reaction Scope: Cinnoline Synthesis

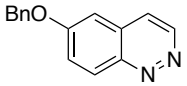
With a set of efficient cinnoline-forming conditions established, the range of diethyl dihydrocinnoline-1,2-dicarboxylates synthesised could be thus transformed (Table 2.9).

Table 2.9 - Reaction scope: synthesis of functionalised cinnolines[a]

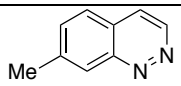




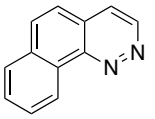
84, 98%



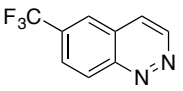
85, 81%



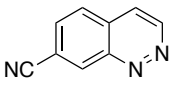
86, 88%



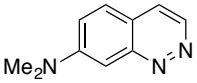
87, 73%



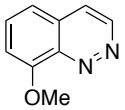
88, 0%



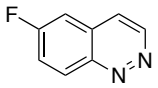
89, 0%



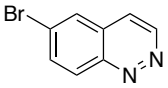
90, 90%



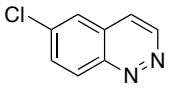
91, 56%



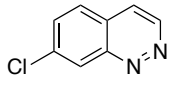
92, 0%



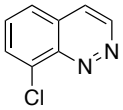
93, 65%



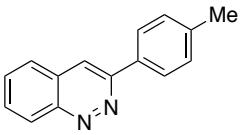
94, 70%



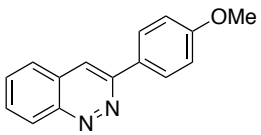
95, 68%



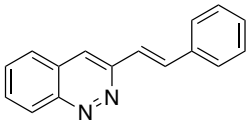
96, 56%



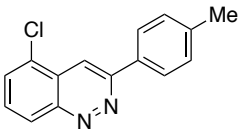
97, 64%



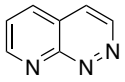
98, 65%



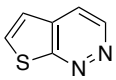
99, 68%



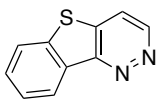
100, 68%



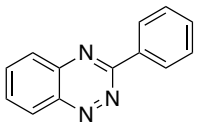
101, 0%



102, 58%



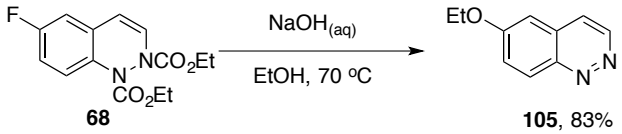
103, 47%



104, 66%

[a]*Reaction conditions: diethyl dihydrocinnoline-1,2-dicarboxylate (1.0 eq), sodium hydroxide (5 M, 5.0 eq), ethanol (0.2 M), 70 °C, 16 h, air. Yields reported are of isolated products.*

Electron-rich cinnoline products **84**-**85** and **90** were readily formed in excellent yields, perhaps because of their increased propensity for oxidation. Less electron-rich products were obtained in moderate to good yields. A range of halogen-bearing cinnolines could be readily accessed, although 6-fluorocinnoline **92** proved elusive. When diethyl 6-fluorodihydrocinnoline-1,2-dicarboxylate **68** was subjected to the reaction conditions, 6-ethoxycinnoline **105** was exclusively formed (Scheme 2.25). It is not known whether a nucleophilic substitution reaction occurred prior to, or after, cinnoline formation.



68 **105**, 83%

Scheme 2.25

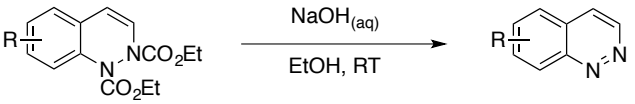
Unfortunately, significantly electron-deficient cinnolines were difficult to attain with this procedure (products **88**, **89** and **101**). Cinnolines **97**-**100** bearing an aryl- or alkenyl-substituent at the 3-position were readily attained, as were thiophene-derived products **102** and **103**. These sulfur-containing products are particularly notable since they present completely novel heterocyclic scaffolds.

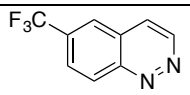
Pleasingly, triazine product **104** was readily attained in 66% yield using these general hydrolysis conditions. Given the failure of the protocol in the synthesis of pyridine-derived product **101**, this is perhaps somewhat surprising.

A modified strategy was required to allow access to other electron deficient cinnoline products. Although additional external oxidants were explored, it was discovered that

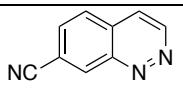
simply allowing the reaction to proceed at room temperature for an extended period of time, 36 h, proved effective (Table 2.10).

Table 2.10 - Reaction scope: synthesis of electron deficient cinnolines[a]

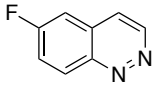




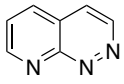
88, 42%



89, 0%



92, 37%



101, 51%

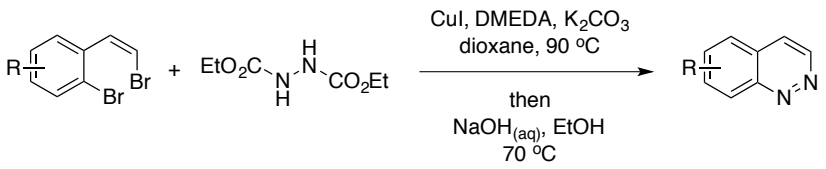
[a]*Reaction conditions: diethyl dihydrocinnoline-1,2-dicarboxylate (1.0 eq), sodium hydroxide (5 M, 5.0 eq), ethanol (0.2 M), RT, 36 h, air. Yields reported are of isolated products.*

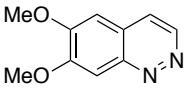
Products such as trifluoromethyl-substituted **88** and pyridine-derived **101** could be obtained, albeit in low to moderate yields. 6-Fluorocinnoline **92** could also be isolated using these conditions as the lower reaction temperature suppressed nucleophilic substitution. However, cinnoline **89** could not be accessed. Instead, a complex mixture of products was obtained. This was attributed to an incompatibility of the cyano- group with the hydrolysis conditions.

Finally, with the reaction conditions optimised and the scope of the reaction explored, the feasibility of a 'one-pot' synthesis of cinnolines from (*ortho*-haloalkenyl)aryl halides was explored. Pleasingly, such a synthesis was readily achieved. The crude reaction mixture from the copper-catalysed transformation could simply be filtered through Celite®, concentrated *in vacuo* and subjected to the cinnoline-forming

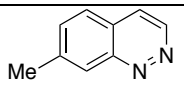
conditions. This protocol was demonstrated with a second synthesis of a small selection of cinnoline products (Table 2.11).

Table 2.11 - Reaction scope: 'one-pot' synthesis of cinnolines[a]

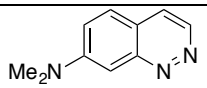




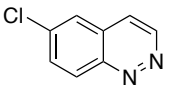
2, 87%



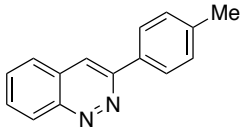
86, 58%



90, 51%
(from ArCl)



94, 42%



97, 39%

[a]*Reaction conditions: dihalide (1.0 eq), hydrazide (2.0 eq), CuI (10 mol%), DMEDA (20 mol%), K_2CO_3 (2.5 eq), dioxane (0.8 M), 90 °C, 18 h. Then sodium hydroxide (5 M, 10.0 eq), ethanol (0.2 M), 70 °C, 16 h, air. Yields reported are of isolated products.*

Electron-rich (**2** and **90**), alkyl- and aryl-substituent bearing (**86** and **97**) and a chlorinated cinnoline (**94**) were synthesised using this procedure. Yields were comparable to the overall yield obtained *via* the two-step procedure. Cinnoline **2** was synthesised on a one gram-scale using this protocol.

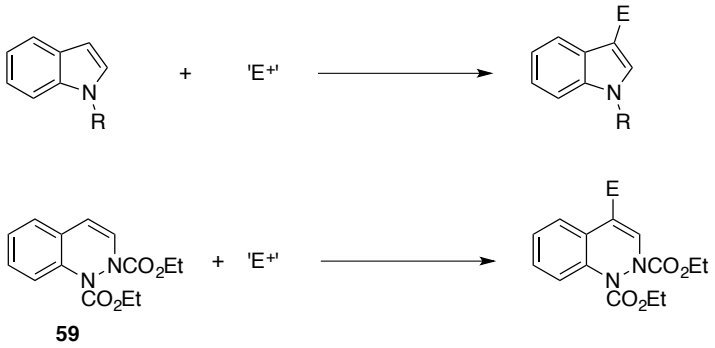
Thus, a mild and general route to the unusual cinnoline framework was established.[106] This synthesis marks a departure from the traditional protocols, which are characterised by the need for harsh reaction conditions and poor functional group tolerance. Instead, the two-step procedure developed features mild reaction conditions and tolerates a variety of different functionalities and substitution patterns.

Chapter 3. An Exploration of the Reactivity of Diethyl Dihydrocinnoline-1,2-dicarboxylates

3.1 Functionalisation of Diethyl Dihydrocinnoline-1,2-dicarboxylates

During the investigation of the scope of the cinnoline-forming process outlined in Chapter 2, examples of products bearing functionality at every position except C4 were demonstrated. The lack of substitution at C4 stems from the use of Wittig chemistry for the preparation of (*ortho*-haloalkenyl)aryl halide precursors (Section 1.3.1.1). To access C4 substituents directly would require the Wittig reactions to be performed on ketone substrates; these reactions are generally low yielding and poorly selective. This is particularly problematic since *Z*-alkenes are required for the diethyl dihydrocinnoline-1,2-dicarboxylate-forming reaction.

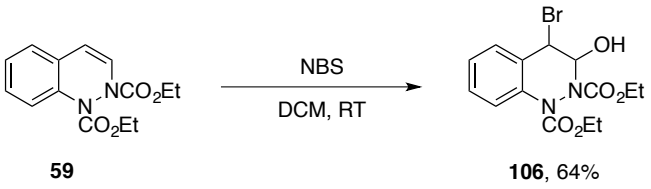
In order to circumvent this problem, and so attain full synthetic control of the substituent pattern displayed by the products, it was proposed that the inherent reactivity of the diethyl dihydrocinnoline-1,2-dicarboxylate intermediates could be harnessed. Inspired by reactions of the indole framework, it was hoped that the electron rich double bond with enamine-like character within diethyl dihydrocinnoline-1,2-dicarboxylate **59** would selectively react with a range of electrophiles at C4 (Scheme 3.1).



Scheme 3.1

Halogenation was the first process explored. Halogen substituents are an extremely useful synthetic handle and their presence would allow for a wide variety of further chemical manipulations. Of these, bromides offer particular synthetic flexibility, especially in cross-coupling processes.

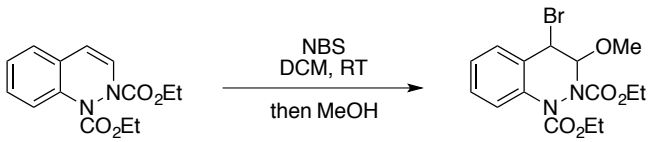
Simple treatment of diethyl dihydrocinnoline-1,2-dicarboxylate **59** with NBS in DCM resulted in the formation of a brominated product, though not the desired diethyl 4-bromodihydrocinnoline-1,2-dicarboxylate. Instead, bromohydrin **106** was isolated (Scheme 3.2).



Scheme 3.2

Assumed to have been formed during exposure to water during purification, the regiochemistry of bromohydrin **106** was confirmed by nOe spectroscopy. Alternative bromination conditions using both a variety of solvents and bromine sources led to the

same outcome. Diethyl 4-bromodihydrocinnoline-1,2-dicarboxylate was never observed. Bromohydrin **106**, and derivatives thereof, may have some interesting chemistry of their own. With two potential centres for elimination - a hemiaminal-like centre and a benzylic centre - such structures are worthy of further investigation. It was postulated that alternative nucleophiles could be deliberately added to intercept the reactive brominated intermediate, and yield a range of different substituents at the 3-position. This potential was explored through the addition of methanol to the reaction mixture. Methoxy-analogue **107** was readily obtained in an 88% yield (Scheme 3.3).

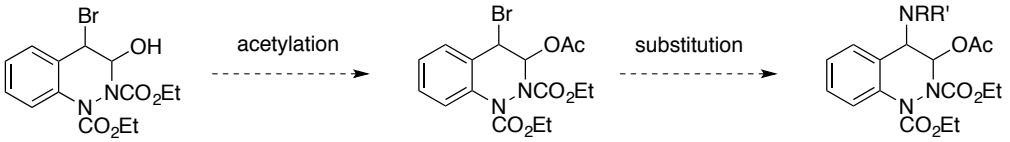


59 **107**, 88%

Scheme 3.3

However, attempts using *N*-based nucleophiles were less successful: either resulting in a complex mixture of products or returned starting material.

A strategy involving acetylation of bromohydrin **106** and subsequent nucleophilic substitution of the benzylic bromide was also explored (Scheme 3.4). It was hoped that this could provide a route to diethyl 4-aminodihydrocinnoline-1,2-dicarboxylates *via* elimination of acetic acid.



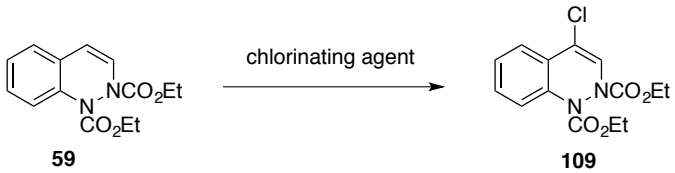
106 **108**

Scheme 3.4

Unfortunately, acetylation proved non-trivial, perhaps due to poor stability of acetylated intermediate **108**. As such this strategy was abandoned.

At this juncture, an alternative halogenation approach was explored. NCS, while being very much related in structure to its bromine-bearing counterpart NBS, is thought to react *via* a different process. Rather than proceeding *via* a bromonium-type intermediate, reactions with NCS are thought to occur following a simple nucleophilic displacement pathway.[107] Hence, the use of this reagent and an alternative chlorinating agent, benzyltrimethylammonium dichloroiodate, was explored. Selected experiments are detailed in Table 3.1.

Table 3.1 – Optimisation: synthesis of diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate 109 *via* regioselective chlorination[a]



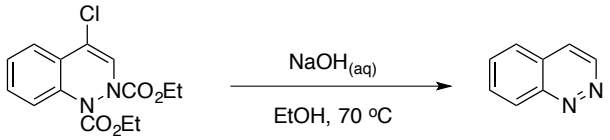
59 **109**

Entry	Chlorinating agent	Solvent	Temp. (°C)	Time (h)	109 (%)[b]
1	NCS	MeCN	50	18	-
2	NCS	THF	50	18	-
3	NCS + 10 mol% TFA	MeCN	50	18	-
4	$BnNMe_3ICl_2$	DCM	RT	3	-
5	$BnNMe_3ICl_2$	DCM	RT	16	-
6	NCS	MeCN	80	16	27
7	NCS	DCE	80	16	44
8	NCS	DMF	80	16	87

*[a]Reaction conditions: diethyl dihydrocinnoline-1,2-dicarboxylate **59** (1.0 eq), chlorinating agent (1.2 eq), solvent (0.5 M), temperature, time. [b]Yield of isolated product.*

Use of NCS or benzyltrimethylammonium dichloroiodate in a range of solvents at reaction temperatures between RT and 50 °C yielded no desired product. Invoking an acid additive also failed to lead to a chlorinated product (Entries 1-5). However, increasing the temperature to 80 °C using NCS in acetonitrile did furnish a low yield of the desired product (Entry 6). Switching the solvent to DCE resulted in an improved yield (Entry 7) while a further switch to DMF dramatically increased the yield of chloride **109** to 87% (Entry 8).

Diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** was subjected to the general cinnoline-forming conditions detailed in Chapter 2. However, 4-chlorocinnoline was not formed; instead cinnoline **110** was generated in 54% yield (Scheme 3.5). This surprising result may be due the dominance of an alternative mechanistic pathway other than that previously proposed in Chapter 2. Perhaps this pathway is prevalent due to the presence of a labile group at C4.

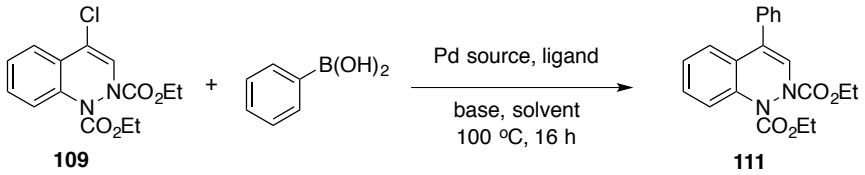


109 **110**, 54%

Scheme 3.5

To demonstrate the synthetic utility of the installed chloro- substituent in diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109**, a Suzuki reaction was explored. This would provide ready access to diethyl 4-aryldihydrocinnoline-1,2-dicarboxylate products. Phenyl boronic acid was utilised for screening experiments, as documented in Table 3.2.

Table 3.2 – Optimisation: synthesis of diethyl 4-phenyldihydrocinnoline-1,2-dicarboxylate 111 *via* Suzuki reaction with phenyl boronic acid[a]



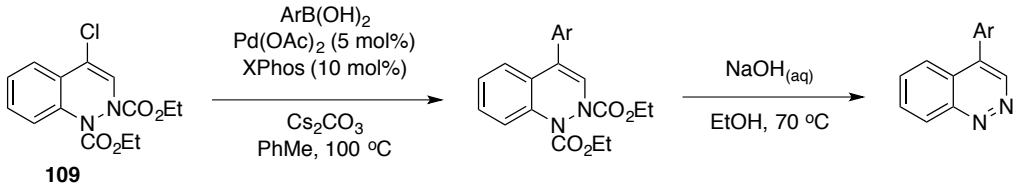
Entry	Pd source	Ligand	Base	Solvent	111 (%)[b]
1	$Pd(OAc)_2$	DavePhos	Cs_2CO_3	PhMe	77
2	$Pd_2(dba)_3$	$P^tBu_3.HBF_4$	K_2CO_3	dioxane	18
3	$Pd(OAc)_2$	SPhos	Cs_2CO_3	PhMe	85
4	$Pd(OAc)_2$	XPhos	Cs_2CO_3	PhMe	91
5[c]	$Pd(OAc)_2$	XPhos	Cs_2CO_3	PhMe	87

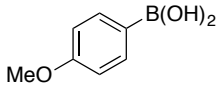
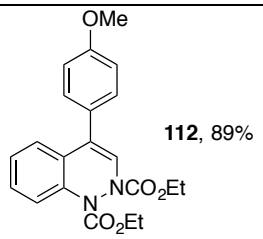
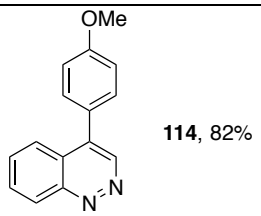
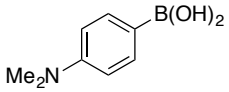
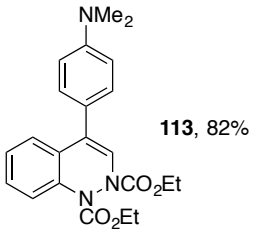
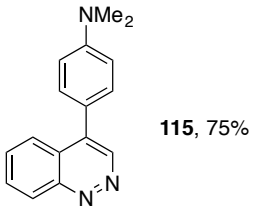
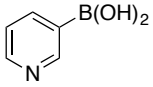
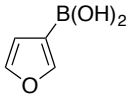
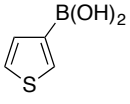
*[a]Reaction conditions: diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** (1.0 eq), phenyl boronic acid (1.5 eq), palladium source (5 mol%), ligand (10 mol%), base (2.0 eq), solvent (0.5 M), 100 °C, 16 h. [b]Yield of isolated product. [c]$Pd(OAc)_2$ (2.5 mol%) and XPhos (5 mol%) used.*

Following literature precedent for Suzuki coupling with an alkenyl chloride partner,[108] conditions using palladium(II) acetate and the dialkylbiaryl phosphine DavePhos were explored. Gratifyingly, diethyl 4-phenyldihydrocinnoline-1,2-dicarboxylate **111** was formed in 77% yield (Entry 1). Use of alternative literature conditions employing tris(dibenzylideneacetone)dipalladium(0) and the tetrafluoroborate salt of tri-*tert*-butylphosphine proved less successful (Entry 2).[109] Returning to dialkylbiaryl phosphine-ligated systems, the use of SPhos and XPhos were explored.[110] Both ligands promoted an increase in yield, with product **111** being formed in 85% and 91% yield respectively (Entries 3 and 4). Pleasingly, the catalytic loading could be halved, to 2.5 mol%, with negligible reduction in yield (Entry 5).

Having established a set of effective Suzuki coupling conditions, the installation of a variety of aryl and heteroaryl units at the 4-position was explored. Table 3.3 details attempts with a range of different boronic acid coupling partners.

Table 3.3 – Reaction scope: two-step synthesis of 4-arylcinnolines *via* a Suzuki reaction[a]



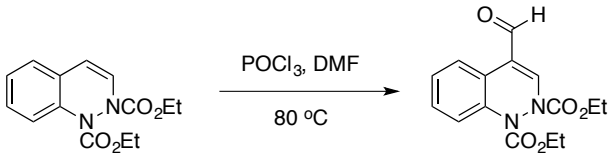
Entry	Boronic Acid	Diethyl dihydrocinnoline-1,2-dicarboxylate	Cinnoline
1		 **112**, 89%	 **114**, 82%
2		 **113**, 82%	 **115**, 75%
3		no reaction	-
4		no reaction	-
5		no reaction	-

[a]*Reaction conditions: Step one: diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate* ***109*** *(1.0 eq), boronic acid (1.5 eq), Pd(OAc)₂ (5 mol%), XPhos (10 mol%), Cs₂CO₃ (2.0 eq), toluene (0.5 M), 100 °C, 16 h. Step two: sodium hydroxide (5 M, 5.0 eq), ethanol, 70 °C, 16 h, air. Yields reported are of isolated products.*

4-Methoxy- and 4-dimethylamino-boronic acids were amenable under the developed Suzuki conditions, delivering diethyl 4-aryldihydrocinnoline-1,2-dicarboxylates **112** and **113** in excellent yields of 89% and 82%, respectively (Entries 1 and 2). These products were readily converted to the corresponding cinnolines **114** and **115** in good yields of 82% and 75%, respectively. However, the use of heteroaryl boronic acids proved less fruitful. 3-Pyridinylboronic acid, 3-furanylboronic acid and 3-thienylboronic acid failed to partake in the reaction.

Attempts were made to furnish diethyl 4-aryldihydrocinnoline-1,2-dicarboxylates directly *via* transition metal-catalysed C-H functionalisation processes. However, application of conditions such as Larossa's palladium-catalysed direct arylation of indoles[111] and Gaunt's copper-catalysed alkene arylation with diaryliodonium salts[112] proved ineffectual.

Having achieved success with a halogenation procedure, alternative functionalisation protocols were investigated. Looking to the reactions of indole for inspiration once more, classical Vilsmeier-Haack formylation conditions were explored.[113] It was discovered that using DMF as the solvent and performing the reaction at elevated temperature resulted in the generation of diethyl 4-formyldihydrocinnoline-1,2-dicarboxylate **116** in 82% yield (Scheme 3.6). The regiochemistry of **116** was confirmed by nOe spectroscopy.

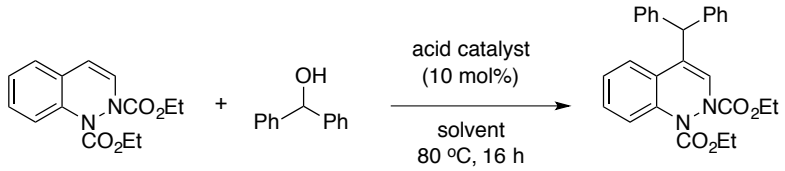


59 **116**, 82%

Scheme 3.6

Given the success of the Vilsmeier-Haack protocol, traditional Friedel-Crafts reactions were considered. Unfortunately, attempts to affect Friedel-Crafts acylation proved unsuccessful. However, processes involving Friedel-Crafts alkylation were more fruitful. A system comprising of diethyl dihydrocinnoline-1,2-dicarboxylate **59** and diphenyl methanol was explored using a variety of acid catalysts. The conditions investigated are detailed in Table 3.4.

Table 3.4 – Optimisation: synthesis of diethyl 4-benzhydryldihydrocinnoline-1,2-dicarboxylate 117 *via* Friedel-Crafts alkylation[a]



59 **117**

Entry	Acid Catalyst	Solvent	117 (%)[b]
1	$In(OTf)_3$	DCE	79
2	$FeCl_3$	DCE	61
3	$Sc(OTf)_3$	DCE	72
4	$AlCl_3$	DCE	-
5	*p*TSA	DMF	-
6	*p*TSA	PhMe	86

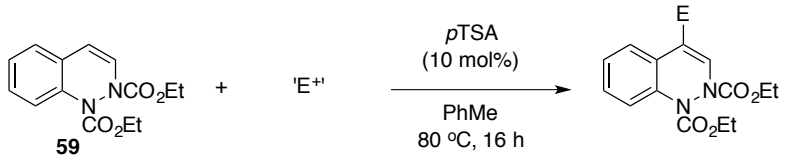
[a]*Reaction conditions: diethyl dihydrocinnoline-1,2-dicarboxylate **59** (1.0 eq), diphenyl methanol (1.5 eq), acid catalyst (10 mol%), solvent (0.5 M), 80 °C, 16 h.* [b]*Yield of isolated product.*

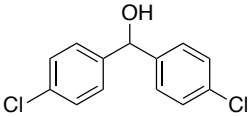
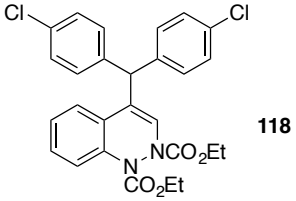
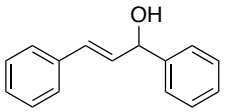
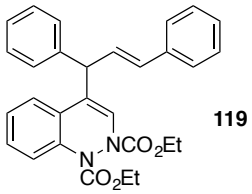
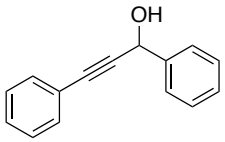
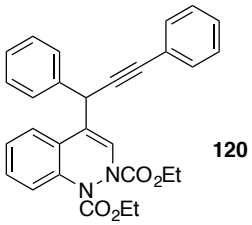
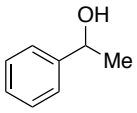
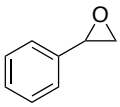
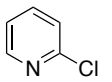
Indium(III) triflate has recently found successful application in a range of Friedel-Crafts-type procedures.[114] Pleasingly, when it was trialed in this context in conjunction with DCE as the solvent at 80 °C, the desired diethyl 4-benzhydryldihydrocinnoline-1,2-dicarboxylate **117** was formed in 79% (Entry 1).

Alternative Lewis acid catalysts iron(III) chloride and scandium(III) triflate were less effective (Entries 2 and 3). An attempt with aluminium(III) chloride was completely ineffective and resulted only in decomposition (Entry 4). Conditions employing a *para*-toluenesulfonic acid catalyst were also investigated. Its use in DMF failed to result in product formation (Entry 5). When toluene was invoked as the solvent, diethyl 4-benzhydryldihydrocinnoline-1,2-dicarboxylate **117** was generated in an improved yield of 86% (Entry 6).

With a set of Friedel-Crafts alkylation conditions established, a range of electrophiles could be trialed. Table 3.5 details those investigated.

Table 3.5 – Reaction scope: synthesis of 4-substituted diethyl dihydrocinnoline-1,2-dicarboxylates *via* Friedel-Crafts alkylation [a]



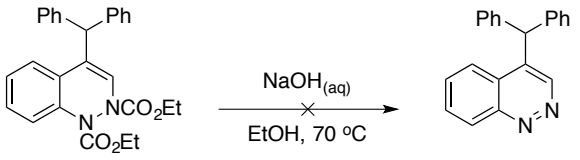
Entry	Electrophile	Product	Yield (%)[b]
1		 **118**	83
2		 **119**	63
3		 **120**	71
4		no reaction	-
5		no reaction	-
6		no reaction	-

*[a]Reaction conditions: diethyl dihydrocinnoline-1,2-dicarboxylate **59** (1.0 eq), electrophile (1.5 eq), pTSA (10 mol%), toluene (0.5 M), 80 °C, 16 h. [b]Yield of isolated product.*

A chlorinated analogue of diphenyl methanol could be readily incorporated, resulting in trityl derivative **118** in 83% (Entry 1). This product is notable as the halogen

substituents signify the potential for further synthetic elaboration. An alkenyl- and an alkynyl-alcohol were also amenable under the reaction conditions, resulting in products **119** and **120** in yields of 63% and 71%, respectively (Entries 2 and 3). Unfortunately, 1-phenylethanol proved an ineffective substrate in the Friedel-Crafts reaction (Entry 4). Use of the alternative electrophiles styrene oxide and 2-chloropyridine also proved unsuccessful in the reaction. These substrates were also trialed using an indium(III) triflate catalyst (see Entry 1, Table 3.4). However these attempts were futile.

With a selection of Friedel-Crafts alkylation products in hand, attempts were made to access the corresponding cinnolines. However, the transformation proved non-trivial and when the standard conditions were applied, decomposition was observed (Scheme 3.7). This was attributed to the presence of an acidic dibenzylic proton. Endeavours to affect the transformation by allowing the reaction to proceed at room temperature, or use of alternative conditions utilising sodium trimethylsilanolate (see Entry 4, Table 2.7) were similarly ineffective.



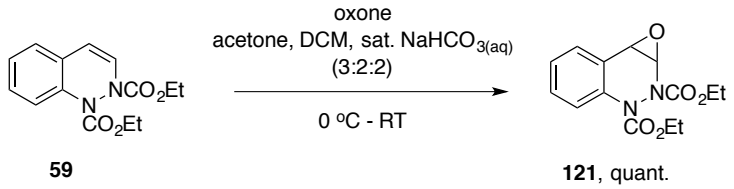
117 0%

Scheme 3.7

The origins of the functionalisation processes demonstrated thus far can be attributed to literature reactions of the indole framework. However, diethyl dihydrocinnoline-

1,2-dicarboxylate **59** is significantly different from indole. As such, it was postulated to be able to partake in chemistry pertaining to electron-rich double bonds.

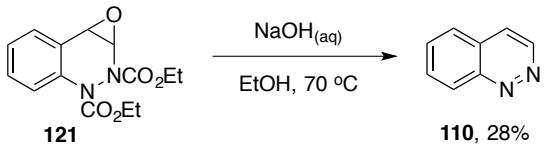
Hence, an epoxidation process was investigated. A range of protocols were explored, including the use of *m*CPBA in a variety of solvents. However, conditions originally developed for the epoxidation of D-glucal and D-galactal derivatives with *in situ* generated DMDO[115] proved particularly effective and resulted in the quantitative formation of epoxide **121** (Scheme 3.8).



Scheme 3.8

With epoxide **121** in hand, its reactivity could be probed. Attempts at ring-opening with Grignard reagents resulted in a complex mixture of products and/or decomposition. Investigations into ring-opening with benzyl amine, both with and without acid catalysis, also proved unsuccessful.

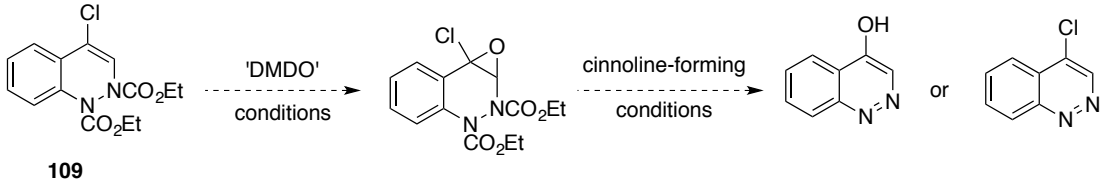
Surprising results have been obtained during attempts at cinnoline formation (see Scheme 3.5). Hence, epoxide **121** was subjected to the general hydrolysis conditions in an attempt to probe whether the epoxide could be opened during the course of the reaction and result in a dihydroxylated product. However, the only product isolated was cinnoline **110**, in 28% yield (Scheme 3.9).



121 **110**, 28%

Scheme 3.9

Given this surprising result, it was postulated that epoxidation of diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** and subsequent application of the cinnoline-forming conditions could lead to an interesting outcome. 4-Hydroxycinnoline or 4-chlorocinnoline were postulated as potential products (Scheme 3.10). However, the intermediate epoxide proved unstable and *in situ* attempts with the sodium hydroxide-based conditions resulted in decomposition.



109

Scheme 3.10

The interesting reactivity displayed by diethyl dihydrocinnoline-1,2-dicarboxylate **59** and the high regioselectivity of its transformations were hypothesized to stem from an unusual structural conformation. To probe this theory, X-ray crystallography was performed (Figure 3.1). The structure obtained of protected dihydrocinnoline derivative **59** showed that, in the solid state, the enamine-like double bond is out of conjugation with the aromatic ring due to the twisting of the *N*-containing six-membered ring. This conformation could serve to explain the high regioselectivity of functionalisation reactions at C4 as the influence of the benzo-ring is minimised.

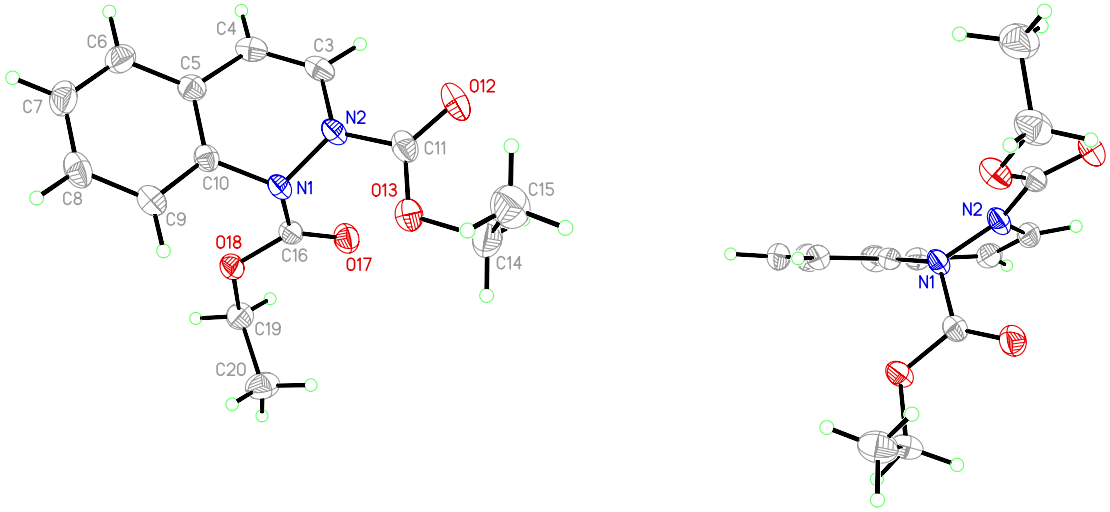
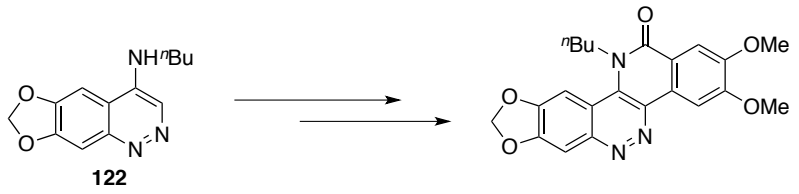


Figure 3.1

3.2 Synthesis of a Pharmaceutical Cinnoline Target

Two factors prompted the pursuit of a pharmaceutically relevant cinnoline target. Firstly, to demonstrate the synthetic utility of the cinnoline-forming methodology developed, and secondly to demonstrate the synthetic flexibility gained by preparing cinnolines *via* protected dihydrocinnoline intermediates. It was therefore sought to synthesize a product whereby the key step involved functionalisation of the diethyl dihydrocinnoline-1,2-dicarboxylate intermediate.

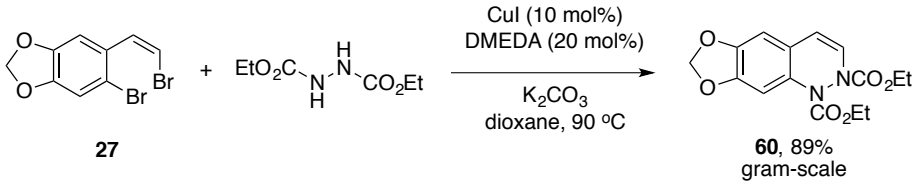
The target selected was *N*-butyl-[1,3]dioxolo[4,5-*g*]cinnolin-4-amine **122**, precursor of a topoisomerase-targeting agent shown to have exceptional antitumor activity against the human tumor xenograft, MDA-MB-435 (Scheme 3.11).[116]



Scheme 3.11

Its synthesis was envisaged to proceed *via* chlorination of electron rich diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **60**. A subsequent Buchwald-Hartwig amination and hydrolysis using the general cinnoline-forming conditions were anticipated to complete the synthesis. Previously, cinnoline **122** was made *via* a traditional Von Richter synthesis using diazonium chemistry (see Figure 2.2).[116]

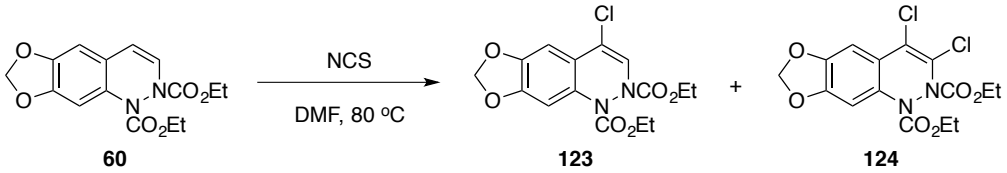
Diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **60**, the basis of the target synthesis strategy, was readily synthesised on a one gram-scale in 89% yield from dihalide **27** (Scheme 3.12).



Scheme 3.12

Thus, the chlorination of electron rich product **60** could be investigated. The effect of the presence of electron donating substituents on the regioselectivity of the process was unknown. Experimental outcomes are detailed in Table 3.6.

Table 3.6 – Optimisation: synthesis of diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate 123 *via* chlorination[a]



60 123 124

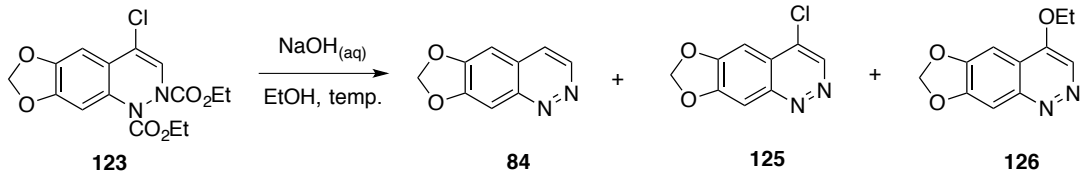
Entry	Eq. of NCS	123 (%)[b]	124 (%)[b]
1	1.2	65	22
2	1.1	73	13
3	1.05	82	8

[a]*Reaction conditions: diethyl [1,3]dioxolo[4,5-g]dihydrocinnoline-1,2-dicarboxylate **60** (1.0 eq), NCS, DMF (0.5 M), 80 °C, 16 h.* [b]*Yield of isolated product.*

Pleasingly, when the conditions used for the regioselective chlorination of diethyl dihydrocinnoline-1,2-dicarboxylate **59** were directly applied, a 65% yield of the desired 4-chloro product **123** was obtained. Also isolated was dichlorinated product **124**, in 22% yield (Entry 1). However, a simple reduction in the equivalents of NCS to 1.1 served to favour the formation of the mono-chlorinated product and resulted in dihydrocinnoline derivative **123** in 73% yield (Entry 2). A further reduction to 1.05 equivalents boosted the yield of the desired product to 82% (Entry 3).

With diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **123** in hand, an exploration into the synthesis of the corresponding chlorinated cinnoline product was undertaken. A previous attempt to synthesize 4-chlorocinnoline from diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** had proven unsuccessful (Scheme 3.5). Therefore, a more rigourous approach was adopted with this substrate. The experiments undertaken are detailed in Table 3.7.

Table 3.7 – Optimisation: attempted synthesis of 4-chloro-[1,3]dioxolo[4,5-*g*]cinnoline 125[a]



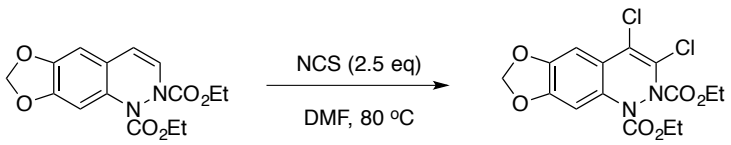
Entry	Eq. of $NaOH_{(aq)}$	Temp. (°C)	RSM (%)[b]	84 (%)[b]	125 (%)[b]	126 (%)[b]
1	5	70	-	52	-	11
2	2.5	70	17	48	13	-
3	5	RT	39	32	-	-
4	2.5	RT	67	16	-	-

[a]*Reaction conditions: diethyl 4-chloro-[1,3]dioxolo[4,5-g]dihydrocinnoline-1,2-dicarboxylate **123** (1.0 eq), $NaOH_{(aq)}$ (5 M), EtOH, temp., 16 h.* [b]*Yield of isolated product.*

When the general cinnoline-forming conditions were applied, the major product isolated was [1,3]dioxolo[4,5-*g*]cinnoline **84** in 52% yield (Entry 1). This is consistent with the result obtained from the attempt with diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** (Scheme 3.5). However, ethoxy-bearing cinnoline **126** was also isolated in a low yield (Entry 1). This product was presumably formed *via* a nucleophilic aromatic substitution process of chlorocinnoline **125**. Such a process has been observed with other halogen-containing analogues (see Scheme 2.25). Lowering the equivalents of hydroxide used from 5 to 2.5 resulted in the formation of the desired chlorinated cinnoline **125**, albeit in a low 13% yield (Entry 2). The major product was again [1,3]dioxolo[4,5-*g*]cinnoline **84**. A portion of the protected dihydrocinnoline starting material was also recovered. Attempts at running the reaction at room temperature failed to result in the formation of the desired cinnoline

product **125**. Instead, returned starting material was the major component of the reaction mixture along with cinnoline **84** (Entries 3 and 4).

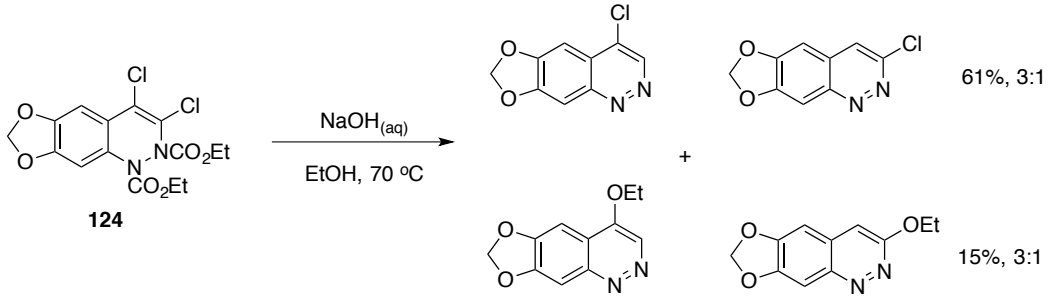
The studies shown in Table 3.7 inspired an investigation into a potential regioselective synthesis of the 3-chlorinated cinnoline product. It was postulated that if dichlorinated product **124** was subjected to the same reaction conditions then the 4-chloro substituent may be 'eliminated' resulting in the selective formation of 3-chloro-[1,3]dioxolo[4,5-*g*]cinnoline. To test this theory, diethyl 3,4-dichloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **124** was formed selectively *via* the reaction of diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **60** with 2.5 equivalents of NCS. The desired dichlorinated product was formed in 78% yield (Scheme 3.13).



60 **124**, 78%

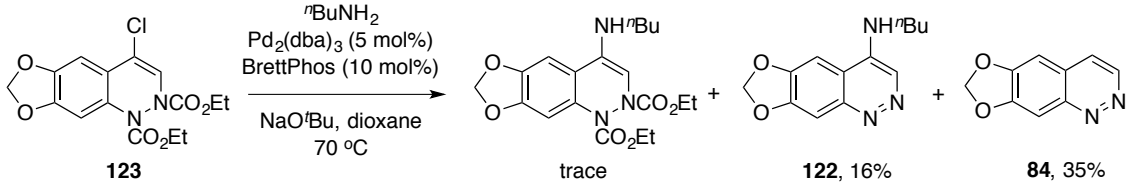
Scheme 3.13

With product **124** in hand, it was subjected to the general cinnoline forming conditions. However, the hypothesized outcome of the reaction did not transpire. Instead, an inseparable mixture of both the 4- and 3-chlorinated regioisomers was obtained in a 61% yield and a 3:1 ratio respectively. Also isolated was an inseparable mixture of the 4- and 3-ethoxy substituted regioisomers in a 15% yield and a 3:1 ratio respectively (Scheme 3.14).



Scheme 3.14

With this foray having proven unfruitful, diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **123** was focused on once more as the substrate to continue the target synthesis. To this end, a Buchwald-Hartwig amination process with *n*-butylamine was explored. To effect such a challenging C-N bond formation between an alkenyl chloride and a primary amine, a catalyst system featuring Buchwald's specialised dialkylbiaryl phosphine BrettPhos was initially explored.[17] However, when trial reactions were performed, a surprising outcome was observed (Scheme 3.15). Although returned starting material accounted for most of the reaction mixture, several other interesting components were isolated.

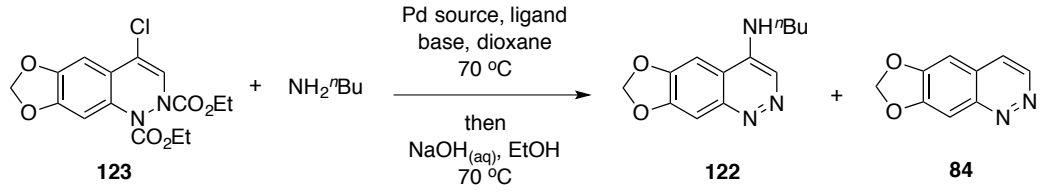


Scheme 3.15

A trace of the desired dihydrocinnoline derivative was obtained, along with the corresponding cinnoline product **122** in 16% and cinnoline **84** in 35% yield. This surprising product mixture led to several conclusions. Firstly, that a particularly

effective palladium catalyst would need to be invoked to outcompete transformation of the starting material to the unproductive cinnoline **84**. Secondly, that the process should be performed as a 'one-pot' two-step process to simplify purification and aid analysis of the outcome of the reaction. As such, a variety of screening reactions were performed. A selection of these are detailed in Table 3.8.

Table 3.8 – Optimisation: two-step synthesis of *N*-butyl-[1,3]dioxolo[4,5-*g*]cinnolin-4-amine 122 *via* a Buchwald-Hartwig amination reaction[a]



Entry	Pd source	Ligand	Base	Solvent	122 (%)[b]	84 (%)[b]
1	$Pd_2(dba)_3$	BrettPhos	K_2CO_3	dioxane	-	49
2	$Pd_2(dba)_3$	BrettPhos	K_2CO_3	^{t}BuOH	-	46
3	$Pd_2(dba)_3$	BrettPhos	LiHMDS	dioxane	14	32
4	$Pd_2(dba)_3$	CyPF-^{t}Bu	NaO^{t}Bu	dioxane	12	42
5	$Pd_2(dba)_3$	Cata*C*Xium® A	NaO^{t}Bu	dioxane	trace	51
6	BrettPhos precat.	-	NaO^{t}Bu	dioxane	62	trace
7	BrettPhos precat.	-	NaO^{t}Bu	PhMe	43	15
8	BrettPhos precat.	-	K_2CO_3	dioxane	18	37

*[a]Reaction conditions: step one diethyl 4-chloro-[1,3]dioxolo[4,5-g]dihydrocinnoline-1,2-dicarboxylate **123** (1.0 eq), n-butylamine (1.5 eq), palladium source (5 mol%), ligand (10 mol%), base (2.0 eq), solvent (0.5 M), 70 °C, 16 h. Step two, sodium hydroxide (5 M, 5.0 eq), ethanol, 70 °C, 16 h, air. [b]Yield of isolated product.*

In an attempt to disfavour competing cinnoline formation during the coupling process, use of a weaker base was explored, namely potassium carbonate. However, none of the desired aminocinnoline was formed, and only cinnoline **84** was isolated in 49% yield (Entry 1). Use of this base in conjunction with *tert*-butanol – a combination advocated by Buchwald[17] – also proved ineffective (Entry 2). Returning to the use of strong bases, lithium bis(trimethylsilyl)amide in dioxane allowed access to the desired *N*-butyl-[1,3]dioxolo[4,5-*g*]cinnolin-4-amine **122** in 14% yield. [1,3]Dioxolo[4,5-*g*]cinnoline **84** was also isolated in 32% yield (Entry 3). Two alternative ligands, specially developed for use with aryl chloride substrates, were trialed. When Hartwig's JosiPhos derivative CyPF-^{t}Bu[15] was employed, the desired cinnoline was obtained in 12% yield (Entry 4). However, a system based on Beller's bulky trialkylphosphine cata*C*Xium® A[117] was found to be ineffectual (Entry 5). At this juncture, an alternative palladium/ligand system was explored. Buchwald has recently developed so-called pre-catalysts featuring a variety of his dialkylbiaryl phosphine ligands, whereby the active mono-ligated palladium(0) species can be readily and rapidly generated.[118] The BrettPhos-containing analogue was trialed in the reaction system and, gratifyingly, was found to be highly active. The desired cinnoline product **122** was formed in 62% yield, and only a trace of side product **84** was observed (Entry 6). Attempts using toluene as an alternative solvent, or using Buchwald's preferred potassium carbonate/*tert*-butanol combination proved less effective (Entries 7 and 8).

Hence, the synthesis of target cinnoline **122** was achieved in 4-steps from (*ortho*-haloalkenyl)aryl halide precursor **27**. This is in marked contrast to its previous synthesis, whereby diazonium chemistry and harsh conditions were employed. A two-

step literature process completes the conversion of cinnoline **122** into the key topoisomerase-targeting agent.[116]

Thus, the synthetic utility of the cinnoline-forming methodology established has been fully demonstrated. Furthermore, the development of an indirect route *via* protected dihydrocinnoline intermediates has been shown to be advantageous rather than synthetically inefficient. Diethyl dihydrocinnoline-1,2-dicarboxylates proffer distinct properties and interesting reactivity. As such, synthetic modifications can be readily performed on these intermediates; procedures that would not be possible with the analogous cinnoline products. A summary of the transformations demonstrated is shown in Figure 3.2.

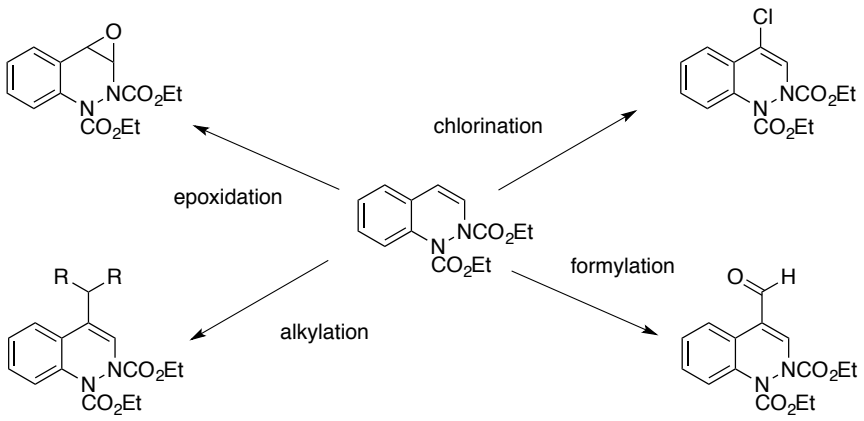


Figure 3.2

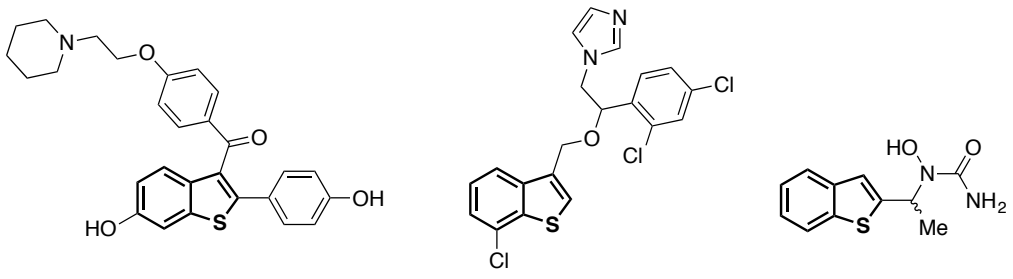
After the employment of these procedures, a range of cinnoline products bearing functionality at C4 can be attained. Thus, the methodology employing (*ortho*-haloalkenyl)aryl halide precursors can be used to access cinnolines bearing functionality at each position of the heterocyclic framework. The aim to create a general and mild synthesis of cinnolines was thus fulfilled.[106]

Chapter 4. Studies Towards the Synthesis of Benzothiophenes from (*ortho*-Haloalkenyl)aryl Halide and α-(*ortho*-Haloaryl)ketone Precursors

4.1 Exploration of (*ortho*-Haloalkenyl)aryl Halide Precursors

Having expanded the repertoire of heterocyclic frameworks accessible from (*ortho*-haloalkenyl)aryl halide precursors with a novel preparation of cinnolines, the synthesis of another heterocyclic class was pursued. To this end, benzothiophenes were targeted.

Benzothiophenes are an important class of heterocycle, and compounds containing such a motif have been found to exhibit a variety of interesting and useful properties.[119] As such, these frameworks form the core of a number of medicinally important molecules such as raloxifene,[120] sertaconazole[121] and zileuton[122] (Figure 4.1).



raloxifene sertaconazole zileuton

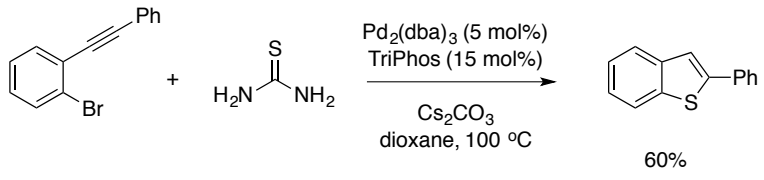
Figure 4.1

Although a plethora of syntheses based on traditional approaches exist,[4, 123] catalytic routes to benzothiophenes have only recently been developed.[3, 124] Of these,

procedures incorporating a key palladium- or copper-catalysed C-S bond formation are few in number.[5, 52] This can perhaps be attributed to the initial lag in the development of C-S bond-forming protocols. However, now that such methodologies have been thoroughly explored,[125] use of these techniques in novel syntheses of benzothiophenes is an expanding area of research.

(*ortho*-Haloalkenyl)aryl halides have been rarely used in conjunction with C-S bond forming processes. A copper-catalysed synthesis of 2-trifluoromethyl benzothiophenes employing sodium sulfide nonahydrate has been reported (see Scheme 1.27).[64] However, the 2-trifluoromethyl moiety was found to be crucial to the success of the reaction and hence the substrate scope was very limited. Thus, a more general route to benzothiophenes from (*ortho*-haloalkenyl)aryl halide precursors was pursued.

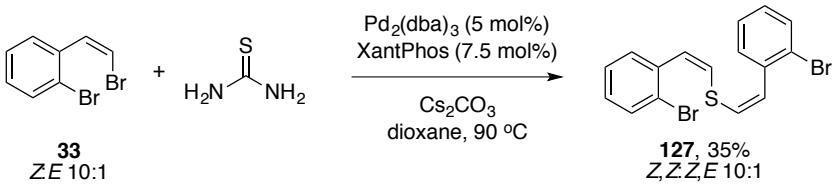
A palladium-catalysed route using thiourea as the so-called 'hydrogen sulfide surrogate' was explored. Thiourea has previously found application in the synthesis of benzothiophenes using *ortho*-alkynylhaloarene heterocycle precursors (see Figure 1.6) and a TriPhos-based palladium catalyst (Scheme 4.1).[31] This synthesis was a direct application of methodology developed for the preparation of symmetrical diaryl thioethers (see Scheme 1.9).



Scheme 4.1

Unlike many other sulfur surrogates, such as the sodium sulfide salts commonly used in conjunction with copper catalysts, thiourea is not foul-smelling nor is it hydroscopic. It is also cheap and readily available.

Initial investigations into the coupling of (*ortho*-haloalkenyl)aryl halide precursors were conducted with dihalide **33** and a catalyst system based on the bidentate ligand XantPhos. This system has been shown to be effective in the synthesis of diaryl thioethers using thiourea.[31] However, the expected benzothiophene product was not observed; instead, dimer product **127** was isolated in 35% yield (Scheme 4.2).



33
Z:*E* 10:1

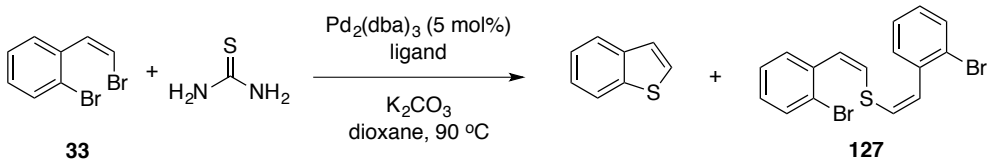
127, 35%
Z,*Z*:*Z*,*E* 10:1

Scheme 4.2

This surprising result was verified by HRMS and NMR spectroscopy. The predominant *Z*,*Z*-configuration was confirmed by comparison of the double bond coupling constants with literature values for di((*Z*)-styryl)sulfane.[126]

It was hypothesised that the intramolecular ring-forming reaction was disfavoured due to the wide bite angle of XantPhos.[127] Based on this conjecture, a range of ligands were explored to identify their influence on the reaction outcome (Table 4.1). For these screening experiments, the base was switched from cesium carbonate to potassium carbonate as it was found that this resulted in a much more free-flowing reaction mixture.

Table 4.1 – Optimisation: focus on the ligand employed[a]



33 **127**

Entry	Ligand[b]	Benzothiophene	127 (%)[c]
1	XantPhos	not formed	52
2	dppp	not formed	75
3	dppm	not formed	trace
4	dppf	not formed	58
5	*rac*-BINAP	not formed	62
6	DPEPhos	not formed	82
7	XPhos	not formed	-
8	$P^tBu_3.HBF_4$	not formed	-
9	$P(C_6H_4OMe)_3$	not formed	58
10[d]	-	not formed	-

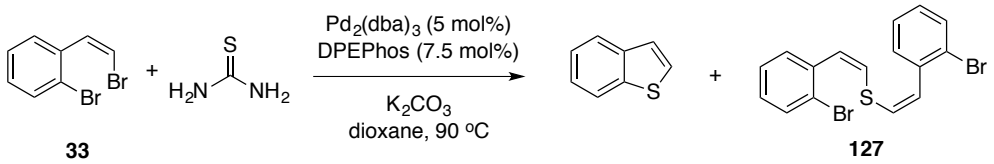
*[a]Reaction conditions: dihalide **33** (1.0 eq), thiourea (2.0 eq), $Pd_2(dba)_3$ (5 mol%), ligand, K_2CO_3 (2.0 eq), dioxane (0.3 M), 90 °C, 16 h. [b]Bidentate ligands were used with 7.5 mol% loading, monodentate ligands with 10 mol% loading. [c]Yield of isolated product. [d]Reaction performed without palladium or ligand.*

Under these modified conditions, using XantPhos as the ligand resulted in a 52% yield of the undesired dimer product **127** (Entry 1). Other bidentate ligands with a variety of bite angles were also explored. Diphenylphosphino ligands dppp and dppm, based on a propane and a methane backbone respectively, were trialled. The former resulted in an increased yield of 75% of side-product **127**, while the latter resulted in no reaction (Entries 2 and 3). The ferrocenyl-based ligand dppf also resulted in a moderate yield of the dimer product (Entry 4), as did *rac*-BINAP (Entry 5).

Startlingly, when DPEPhos was invoked - a ligand akin to XantPhos but with a less rigid backbone - the undesired dimer product was obtained in a high yield of 82% (Entry 6). Monodentate ligands were also explored. Use of the dialkylbiaryl phosphine XPhos and the trialkylphosphine tri-*tert*-butylphosphine (as the tetrafluoroborate salt) resulted in no reaction (Entries 7 and 8). However tri(4-methoxyphenyl)phosphine afforded a 58% yield of the dimer product (Entry 9). An attempt without palladium or ligand resulted in no reaction (Entry 10).

With no sign of the desired benzothiophene product, the proposed influence of the nature of the ligand was reconsidered. Instead, the concentration of the reaction was probed as a means to attempt to favour the intramolecular reaction. DPEPhos was selected as the ligand of choice for these investigations as it resulted in the most active catalytic system. The conditions explored and the experimental outcomes are described in in Table 4.2.

Table 4.2 – Optimisation: focus on the concentration[a]



33 **127**

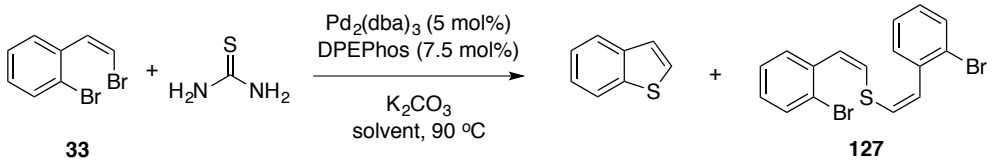
Entry	Dilution factor	Concentration (M)	Benzothiophene	127 (%)[b]
1	-	0.3	not formed	82
2	2.5	0.17	not formed	71
3	5	0.07	not formed	65
4	10	0.03	not formed	60

[a]*Reaction conditions: dihalide **33** (1.0 eq), thiourea (2.0 eq), $Pd_2(dba)_3$ (5 mol%), DPEPhos (7.5 mol%), K_2CO_3 (2.0 eq), dioxane, 90 °C, 16 h.* [b]*Yield of isolated product.*

Astonishingly, when the reaction was performed at a range of more dilute concentrations, dimer **127** was the only product observed. Diluting the reaction mixture by a factor of 2.5 resulted in a modest drop in yield to 71% (Entry 5), while a dilution factor of 5 led to a yield of 65% (Entry 6). Performing the reaction at a concentration of 0.03 M - a dilution factor of 10 - led to the intermolecular reaction product in a 60% yield (Entry 4).

With dilution having proved an unsuccessful tactic in attempting to favour benzothiophene formation, the reaction solvent was explored. The systems trialled are detailed in Table 4.3.

Table 4.3 – Optimisation: focus on the reaction solvent[a]



33 **127**

Entry	Solvent	Additive	Benzothiophene	127 (%)[b]
1	PhMe	-	not formed	21
2	DMF	-	not formed	68
3	^{t}BuOH	-	not formed	13
4	dioxane	H_2O (5%)	not formed	61

[a]*Reaction conditions: dihalide **33** (1.0 eq), thiourea (2.0 eq), $Pd_2(dba)_3$ (5 mol%), DPEPhos (7.5 mol%), K_2CO_3 (2.0 eq), solvent (0.3 M), 90 °C, 16 h.* [b]*Yield of isolated product*

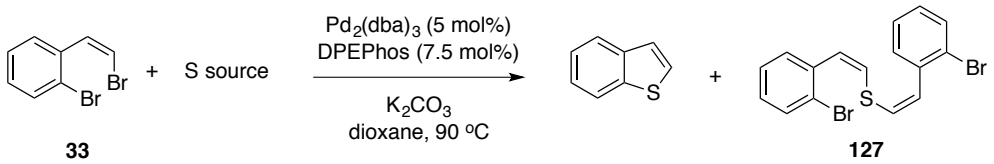
Once again, the desired benzothiophene product was not observed. Instead, the use of a range of different solvents resulted in the formation of unwanted dimer product **127** in a variety of yields. When toluene was employed, a low yield of 21% was obtained,

while the use of DMF resulted in a higher yield of 68% (Entries 1 and 2). Utilising *tert*-butanol as the reaction solvent also resulted in a low yielding reaction (Entry 3). Including a water additive failed to promote any desired reactivity; the dimer product was formed in a 61% yield (Entry 4).

At this juncture, the nature of the sulfur source employed was investigated. Little is known about the mechanism by which thiourea donates its *S*-atom; no mechanistic studies have been performed, nor have putative routes been suggested. However, *N*-aryl thiourea substrates have recently been used in a copper-catalysed synthesis of arylcyanamides.[128] Hence, it can be postulated that the interaction of thiourea with a metal centre leads to a metal-sulfur species and a cyanamide side product, presumably generated *via* decomposition of an intermediate thiouronium species (see Scheme 1.9).

It was hypothesised that the unknown process by which thiourea donates its *S*-atom could be a contributing factor in the unexpected formation of dimer product **127**. Hence, a range of other sulfur sources used in the transition metal-catalysed synthesis of thioether products were explored (Table 4.4).

Table 4.4 – Optimisation: focus on the sulfur source employed[a]



33 **127**

Entry	S source	Benzothiophene	127 (%)[b]
1	$NaSH.xH_2O$	not formed	56
2	$Na_2S.9H_2O$	not formed	73
3	KSAc	not formed	-
4	thiourea (10 eq)	not formed	84

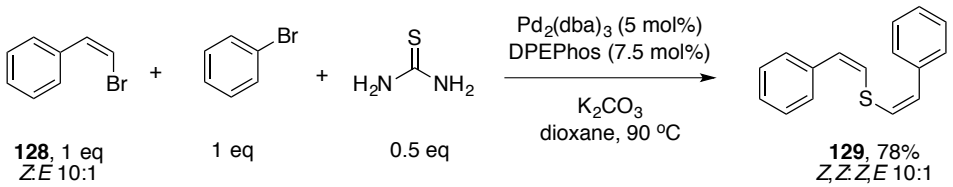
*[a]Reaction conditions: dihalide **33** (1.0 eq), S source (2.0 eq), $Pd_2(dba)_3$ (5 mol%), DPEPhos (7.5 mol%), K_2CO_3 (2.0 eq), dioxane (0.3 M), 90 °C, 16 h. [b]Yield of isolated product.*

Sodium sulfide salts are most commonly used in conjunction with copper catalysts. Despite this, when sodium hydrosulfide hydrate and sodium sulphide nonahydrate were employed in the reaction, sulfur incorporation was observed. Unfortunately the product observed was dimer **127** rather than the desired benzothiophene. Use of sodium hydrosulfide hydrate and sodium sulfide nonahydrate resulted in yields of 56% and 73% respectively (Entries 1 and 2). An attempt using potassium thioacetate as the sulfur source resulted in decomposition (Entry 3). Use of thiourea in vast excess led to the generation of dimer product **127** in 84% yield (Entry 4). No trace of the desired benzothiophene product was observed in any case.

At this stage, the nature of the (*ortho*-haloalkenyl)aryl halide employed was probed. When these precursors were utilised in the synthesis of diethyl dihydrocinnoline-1,2-dicarboxylates it was assumed that the alkenyl bromide reacted prior to the aryl bromide. As no explicit competition experiments were performed, this was concluded

from observation of the product mixture isolated when the *E*-isomer was utilised (see Scheme 2.13) and from parallels drawn between investigations reported by Barluenga.[129, 130] He recounted results from competition experiments using alkenyl bromides and aryl bromides in an amination process with an alkyl amine or aniline-based coupling partner. High selectivity for coupling with the alkenyl bromide substrate was observed in each case.[130]

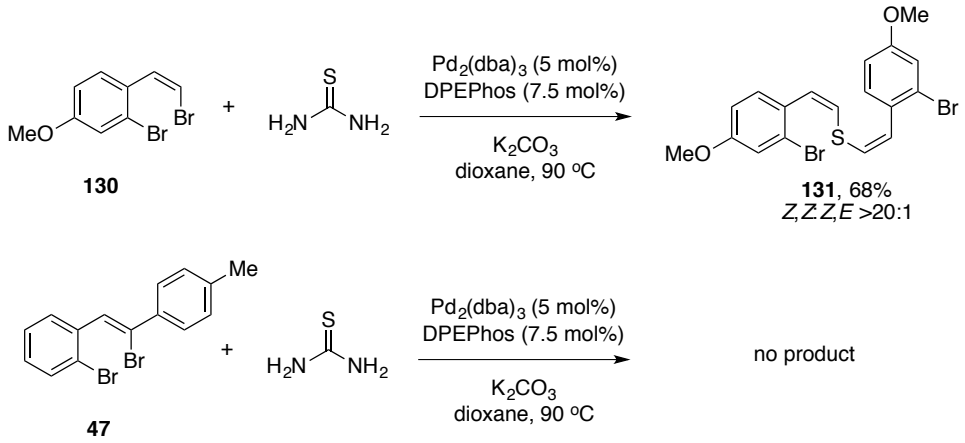
To probe the unusual selectivity observed in the C-S bond-forming process with dihalide **33**, a competition experiment was performed using (*Z*)-(2-bromovinyl)benzene **128** and bromobenzene. Di((*Z*)-styryl)sulfane **129** was the sole product observed, isolated in 78% yield, indicating that the reaction is highly selective for the alkenyl bromide (Scheme 4.3).



Scheme 4.3

With this result in hand, a range of modified substrates were synthesised and subjected to the reaction conditions. Methoxy-substituted and tolyl-bearing dihalides **130** and **47** were explored. However, modulating the electronics of the substrate *via* inclusion of the electron-donating substituent in precursor **130** proved to be an ineffective strategy. The reactivity of the alkenyl halide was insufficiently diminished and electron-rich dimer product **131** was formed in 68% yield. An attempt with dihalide **47** to depress reactivity *via* inclusion of a substituent on the alkenyl moiety

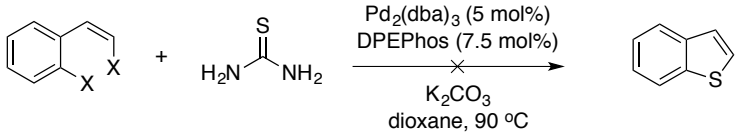
resulted in no product formation: neither of a dimer product nor a benzothiophene (Scheme 4.4).

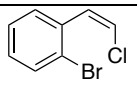
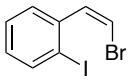
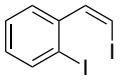


Scheme 4.4

A selection of substrates bearing biased halide combinations were also synthesised. In an attempt to harness the differing reactivity of C-X bonds in palladium catalysis, alkenyl chloride-aryl bromide substrate **132**, alkenyl bromide-aryl iodide substrate **133** and alkenyl iodide-aryl iodide substrate **134** were subjected to the reaction conditions. Experimental outcomes are detailed in Table 4.5.

Table 4.5 – Optimisation: effect of the halide combination in the (*ortho*-haloalkenyl)aryl halide precursor[a]

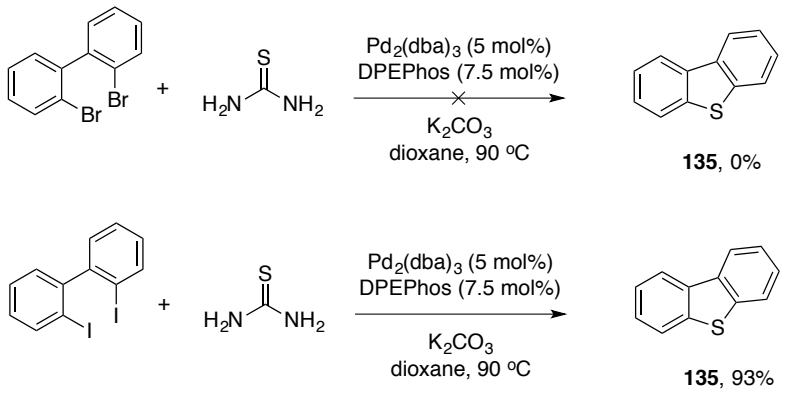


Entry	Substrate	Benzothiophene
1	 **132**	not formed
2	 **133**	not formed
3	 **134**	not formed

[a]*Reaction conditions: dihalide (1.0 eq), thiourea (2.0 eq), $Pd_2(dba)_3$ (5 mol%), DPEPhos (7.5 mol%), K_2CO_3 (2.0 eq), dioxane (0.3 M), 90 °C, 16 h.*

However, use of substrates **132**, **133** and **134** failed to result in formation of the desired benzothiophene. Instead, starting material and a complex mixture of inseparable products were observed.

With all strategies attempted having failed to favour the intramolecular reaction and generate the desired product, a related substrate was invoked. 2,2'-Dibromo-1,1'-biphenyl was trialled to explore the feasibility of the intramolecular reaction. Containing two identical aryl bromides, no disparity between the reactive halide centres could be exploited to generate a dimer product. The iodo-bearing analogue, 2,2'-diiodo-1,1'-biphenyl, was also investigated (Scheme 4.5).



Scheme 4.5

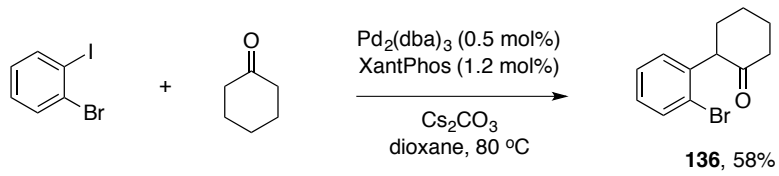
Unfortunately, use of 2,2'-dibromo-1,1'-biphenyl failed to result in the formation of dibenzo[*b*,*d*]thiophene **135**. However, when 2,2'-diiodo-1,1'-biphenyl was utilised, the desired product was obtained in a 93% yield. This result indicates the system employed is capable of an intramolecular five-membered ring-forming reaction, but the nature of the reactive halide centre is very influential.

With these conclusions drawn, it was decided to investigate alternative substrates in the quest for a novel benzothiophene synthesis.

4.2 Exploration of α-(*ortho*-Haloaryl)ketone Precursors

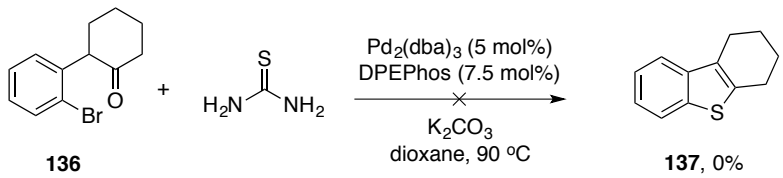
α-(*ortho*-Haloaryl)ketones, like (*ortho*-haloalkenyl)aryl halides, have been shown to act as precursors to a variety of heterocyclic frameworks (see Section 1.3.2). Although their *ortho*-haloacetanilide counterparts have been shown to be adept in procedures involving C-S bond formation (see Scheme 1.35), α-(*ortho*-haloaryl)ketones have not been used with such protocols. Hence, these substrates were explored as benzothiophene precursors.

Aryl iodide-containing substrates are difficult to obtain using the standard procedures developed for α-(*ortho*-haloaryl)ketone synthesis outlined in Section 1.3.2.1. As such, an aryl bromide-containing starting material was selected as the subject for explorations and 2-(2-bromophenyl)cyclohexan-1-one **136** was synthesised in 58% yield by following the general α-arylation protocol (Scheme 4.6).



Scheme 4.6

Using this substrate it was hoped that the desired benzothiophene product would be formed *via* a palladium- or copper-catalysed C-S bond formation followed by a condensation process, or *vice versa*. To test this hypothesis, the previously developed palladium-catalysed conditions employing thiourea were directly applied (Scheme 4.7).

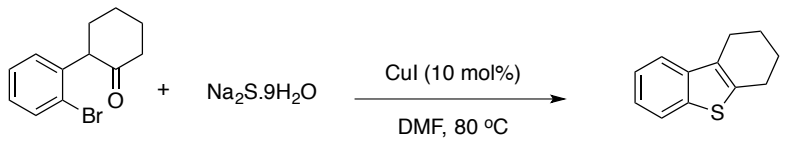


Scheme 4.7

Perhaps unsurprisingly, 1,2,3,4-tetrahydrodibenzo[*b*,*d*]thiophene **137** was not produced. Hence, alternative transition metal-catalysed thioetherification conditions were explored.

The use of sodium sulfide salts in conjunction with a copper catalyst was investigated. Conditions of this type were used with *ortho*-haloacetanilide precursors in a synthesis of benzothiazoles (Scheme 1.35).[71] In this case, intermolecular C-S bond formation was found to readily outcompete intramolecular C-O bond formation.

To begin the exploration using ketone **136**, the copper-catalysed conditions used with *ortho*-haloacetanilides were directly applied (Scheme 4.8).



136 **137**, trace

Scheme 4.8

Pleasingly, a trace of the desired benzothiophene product was observed. The major component of the reaction mixture was returned starting material: no benzofuran product resulting from an intramolecular *O*-arylation was detected.

With an encouraging initial result obtained, a brief investigation of the reaction temperature was undertaken. Experimental outcomes are detailed in Table 4.6.

Table 4.6 – Optimisation: effect of reaction temperature[a]

136 **137**

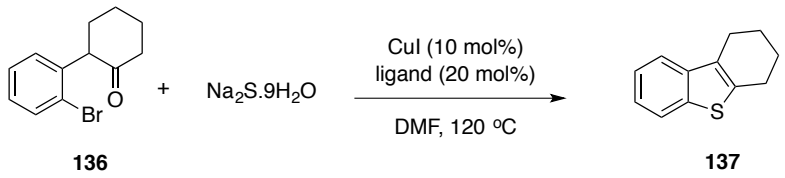
Entry	Temp. (°C)	137 (%)[b]
1	100	trace
2	120	11
3	140	5

[a]*Reaction conditions: ketone* ***136*** *(1.0 eq), $Na_2S.9H_2O$ (3.0 eq), CuI (10 mol%), DMF (0.5 M), temperature, 16 h.* [b]*Yield of isolated product.*

Increasing the reaction temperature to 100 °C had little effect on the outcome of the reaction, and only a trace of the desired benzothiophene **137** was obtained (Entry 1). Pleasingly, an increase to 120 °C afforded an 11% yield of product **137** (Entry 2). Raising the reaction temperature further to 140 °C resulted in a reduced yield of the desired product and evidence of decomposition (Entry 3).

With 120 °C having been selected as the reaction temperature of choice, the use of a ligand to facilitate the process was explored. Although many copper-catalysed C-S bond-forming processes employing sodium sulfide salts operate without ligation,[51] such a tactic was explored in an attempt to ameliorate the process. A range of ligands featuring *N*,*N*, *N*,*O* and *O*,*O* chelation were explored. The experimental results obtained are detailed in Table 4.7.

Table 4.7 – Optimisation: effect of ligation[a]



136 **137**

Entry	Ligand	Mode of chelation	137 (%)[b]
1	DMEDA	*N*,*N*	20
2	TMEDA	*N*,*N*	16
3	1,10-phen	*N*,*N*	26
4	L-proline	*N*,*O*	48
5	*N*-methyl glycine	*N*,*O*	39
6	*N*,*N*-dimethyl glycine	*N*,*O*	7
7	2-picolinic acid	*N*,*O*	9
8	8-hydroxyquinoline	*N*,*O*	12
9	ketoester A[c]	*O*,*O*	trace
10	diketone A[d]	*O*,*O*	9
11[c]	-	-	5

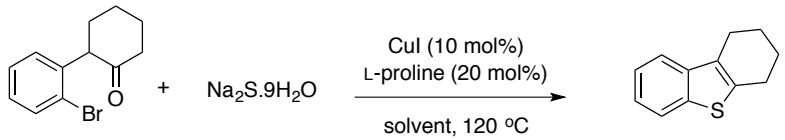
*[a]Reaction conditions: ketone **136** (1.0 eq), $Na_2S.9H_2O$ (3.0 eq), CuI (10 mol%), ligand (20 mol%), DMF (0.5 M), 120 °C, 16 h. [b]Yield of isolated product. . [c]Ketoester A refers to ethyl 2-oxocyclohexanecarboxylate. [d]Diketone A refers to 2,2,6,6-tetramethyl-3,5-heptanedione.*

The inclusion of a ligand was found to have a broadly beneficial effect on the reaction. Use of common diamines such as DMEDA and TMEDA resulted in increased yields of 20% and 16% of benzothiophene **137** respectively (Entries 1 and 2). The traditional *N*,*N* chelator 1,10-phenanthroline also proffered in an increase in yield: the desired product was obtained in 26% yield (Entry 3). When *N*,*O* chelation was invoked by the use of L-proline, an encouraging yield of 48% of benzothiophene **137** was furnished (Entry 4). When alternative amino acid derivatives *N*-methyl

glycine and *N*,*N*-dimethyl glycine were utilised, yields of 39% and 7% were obtained respectively (Entries 5 and 6). Pyridine-derived *N*,*O* chelators were also investigated. However 2-picolinic acid and 8-hydroxyquioline proved ineffective (Entries 7 and 8). To complete the ligand exploration, two *O*,*O* chelators were employed. Unfortunately, use of diester A and diketone A resulted in low yields of the desired benzothiophene product (Entries 9 and 10). A trial reaction was also performed whereby the copper(I) iodide was omitted and a low yield of 5% of benzothiophene **137** was obtained (Entry 11). Encouragingly, no evidence of a competing intramolecular *O*-arylation pathway was observed in any case.

The next parameter selected for investigation was the reaction solvent. A range of different systems were tested and the experimental outcomes are detailed in Table 4.8.

Table 4.8 – Optimisation: effect of reaction solvent[a]



136 **137**

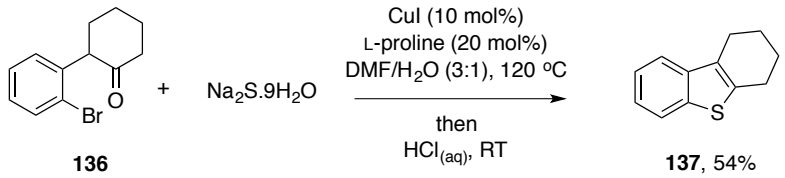
Entry	Solvent	137 (%)[b]
1	dioxane	-
2	PhMe	-
3	NMP	14
4	DMA	24
5	DMSO	-
6	DMF/H_2O (3:1)	51
7	DMF/H_2O (1:1)	16

*[a]Reaction conditions: ketone **136** (1.0 eq), $Na_2S.9H_2O$ (3.0 eq), CuI (10 mol%), L-proline (20 mol%), solvent (0.5 M), 120 °C, 16 h. [b]Yield of isolated product.*

The nature of the solvent, and the relative solubility of the sulfur source, proved very influential. Dioxane and toluene were found to proffer poor solubility and were ineffectual (Entries 1 and 2). Attempts using NMP and DMA proved more successful, though the desired product was formed in low yields of 14% and 24% respectively (Entries 3 and 4). Use of DMSO - a solvent renowned for its solubilising properties - resulted in decomposition (Entry 5). Perhaps, in this case, the sulfur source was too solubilised. Inspired by the aqueous solvent combinations often used with palladium- and copper-catalysed hydroxide couplings (see Schemes 1.7 and 1.17), the implementation of a mixed solvent system was explored. In order to attain an effective solubility balance a 3:1 mixture of DMF and water was trialled. An

improved, yet still moderate, yield of 51% was obtained (Entry 6). Changing the ratio to 1:1 proved detrimental; benzothiophene **137** was isolated in 16% yield (Entry 7).

Again, no evidence of an undesired *O*-arylation pathway was observed. Instead, returned starting material was isolated, though poor mass balance was obtained. This confusing observation was thought to perhaps be attributable to incomplete cyclisation following C-S bond formation. When *ortho*-haloacetanilide precursors were invoked in the synthesis of benzothiazoles, a separate acid-catalysed step was required to complete the cyclisation (see Scheme 1.35).[71] Hence, a similar approach was trialled with ketone **136**. As such, benzothiophene **137** was obtained in an unaltered yield of 54% (Scheme 4.9).

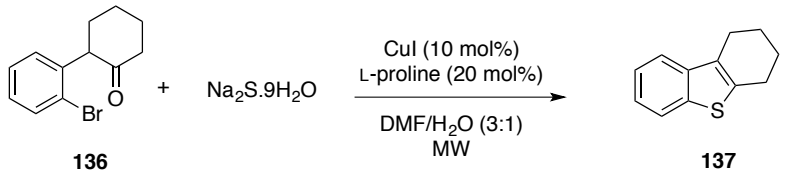


136 **137**, 54%

Scheme 4.9

With a separate acid-catalysed step having proved unnecessary, microwave irradiation was investigated as a tactic to boost the yield of the benzothiophene **137**. Such a strategy has proven effective in the amelioration of a variety of transformations, including transition metal-catalysed processes.[131] The conditions explored and the experimental outcomes are described in Table 4.9.

Table 4.9 – Optmisation: effect of microwave irradiation[a]



136 **137**

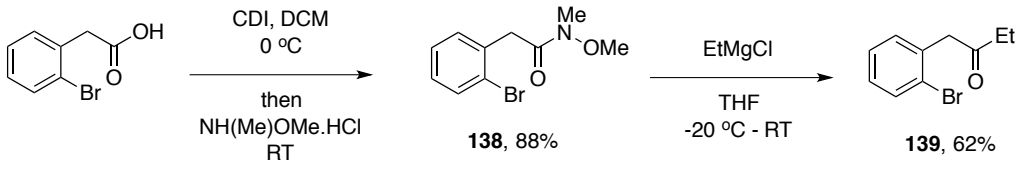
Entry	Temp. (°C)	Time (h)	137 (%)[b]
1	100	2	34
2	120	2	51
3	130	2	49
4	140	2	47
5	120	4	42

*[a]Reaction conditions: ketone **136** (1.0 eq), $Na_2S.9H_2O$ (3.0 eq), CuI (10 mol%), L-proline (20 mol%), DMF/H_2O (3:1) (0.5 M), temp., time, MW irradiation. [b]Yield of isolated product.*

Evidence of a clear microwave effect was not observed. Instead, comparable yields to those obtained with conventional heating were afforded. Heating at 100 °C for 2 hours resulted in a low yield of 34% (Entry 1). Increasing the temperature to 120 °C resulted in an analogous outcome compared to conventional heating at the same temperature for 16 hours (Entry 2). Further increases in temperature to 130 °C and 140 °C promoted no increase in yield. The desired benzothiophene product was obtained in yields of 49% and 47% respectively (Entries 3 and 4). Increasing the duration of the reaction to 4 hours at 120 °C, led to a slightly reduced yield and evidence of decomposition (Entry 5).

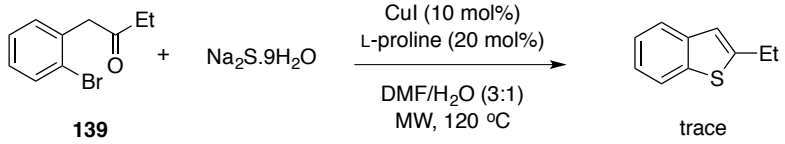
At this juncture, an upper limit of around 50% yield of the desired benzothiophene product appeared to have been reached. Alternative α-(*ortho*-haloaryl)ketones were sought to explore if this could be improved.

The synthesis of α-(*ortho*-haloaryl)ketones was discussed in Section 1.3.2.1. However, an alternative two-step route was developed to provide facile access to a non-cyclic alkyl ketone derivative. Preparation of Weinreb amide **138** from commercially available 2-bromophenylacetic acid was readily achieved. Formation of an imidazolo-intermediate with CDI preceded reaction with *N*,*O*-dimethylhydroxylamine hydrochloride. The desired ethyl ketone **139** could then be obtained *via* treatment of amide **138** with ethylmagnesium chloride (Scheme 4.10).



Scheme 4.10

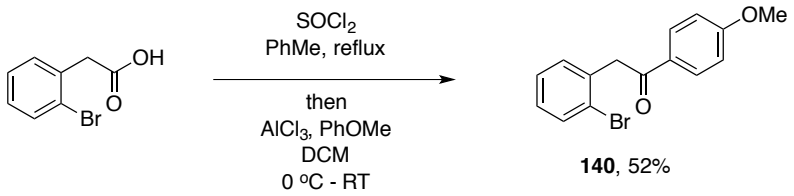
With an alternative ketone substrate in hand, the copper-catalysed conditions were applied. Unfortunately, only a trace of the desired benzothiophene product was observed (Scheme 4.11).



Scheme 4.11

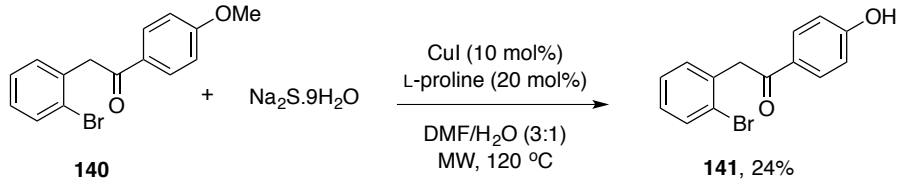
This adverse result indicated that the conditions developed thus far were not general. Hence, an alternative and more challenging ketone substrate was sought with the hope that more robust methodology could be created. To this end, an electron-rich aryl ketone was synthesised according to the standard Friedel-Crafts acylation procedure

(see Section 1.3.2.1). *In situ* formation of the acid chloride of 2-bromophenylacetic acid, before aluminium(III) chloride-catalysed reaction with anisole, generated aryl ketone **140** in 52% yield (Scheme 4.12).



Scheme 4.12

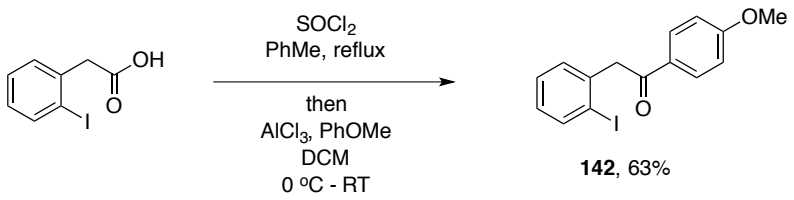
Exploration of the use of this substrate in benzothiophene synthesis began with the previously developed copper-catalysed conditions. Unsurprisingly, when aryl ketone **140** was subjected to such a system, the desired benzothiophene was not formed. As well as returned starting material, phenol **141** was formed in 24% yield *via* sulfide-mediated demethylation (Scheme 4.13).



Scheme 4.13

Subsequently, a variety of screening reactions were performed. Investigations into the nature of the ligand employed, the duration and temperature of the reaction, as well as the use of conventional and microwave heating techniques were all carried out. Unfortunately, the desired benzothiophene product was never observed and only returned starting material and phenol **141** were isolated.

In a final attempt to access the desired heterocyclic product, aryl iodide **142** was synthesised *via* the standard Friedel-Crafts acylation procedure (Scheme 4.14).



Scheme 4.14

Use of this substrate was hoped to facilitate C-S bond formation *via* inclusion of a more labile aryl iodide. However, when trial reactions were performed no benzothiophene product was observed.

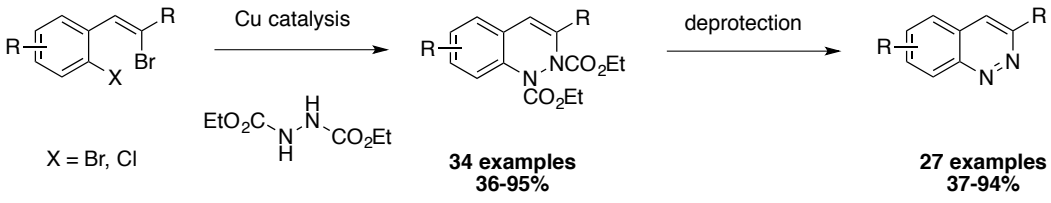
At this juncture, the difficulty incurred in developing general and high yielding conditions applicable to a range of substrates prompted the termination of investigations into a novel route to benzothiophenes from α-(*ortho*-haloaryl)ketone precursors.

Thus, two general heterocyclic precursors, namely (*ortho*-haloalkenyl)aryl halides and α-(*ortho*-haloaryl)ketones, had been explored in the synthesis of benzothiophenes. Ultimately, a robust and general synthesis could not be developed, although interesting and unusual reactivity was observed.

Chapter 5. Summary and Future Work

The use of palladium- and copper-catalysed processes in the preparation of heterocycles from general precursors has become an established synthetic strategy.[52] Of these general substrates, (*ortho*-haloalkenyl)aryl halides and α-(*ortho*-haloaryl) ketones have been found to proffer particular synthetic flexibility and allow access to a variety of diverse heterocyclic frameworks.

A novel synthesis of cinnolines was explored as a means to expand the range of products attainable from (*ortho*-haloalkenyl)aryl halide precursors. This unusual class of heterocycle presents a worthy target in its own right as a general and mild synthetic route has remained elusive. To this end, a two-step protocol was developed. Firstly, a tandem copper-catalysed C-N bond formation with diethyl 1,2-hydrazinedicarboxylate resulted in novel diethyl dihydrocinnoline-1,2-dicarboxylate products. Deprotection with ethanolic sodium hydroxide then allowed ready access to the desired cinnolines (Scheme 5.1).

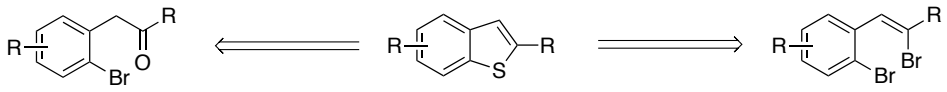


Scheme 5.1

The inherent reactivity of the intermediate diethyl dihydrocinnoline-1,2-dicarboxylate products was exploited to allow substitution at every position of the cinnoline framework. A range of processes such as halogenation, Vilsmeier-Haack formylation,

Friedel-Crafts alkylation and epoxidation could be invoked to produce a range of functionalised products. Thus, a novel and general synthesis of cinnolines was created featuring mild conditions and complete synthetic control of the substitution pattern accessible.[106]

The initial lag in the development of palladium- and copper-catalysed C-S bond forming processes has meant that the use of such protocols in conjunction with general heterocyclic precursors remains underexplored. To this end, the synthesis of benzothiophenes was investigated using both (*ortho*-haloalkenyl)aryl halide and α-(*ortho*-haloaryl) ketone precursors (Scheme 5.2).

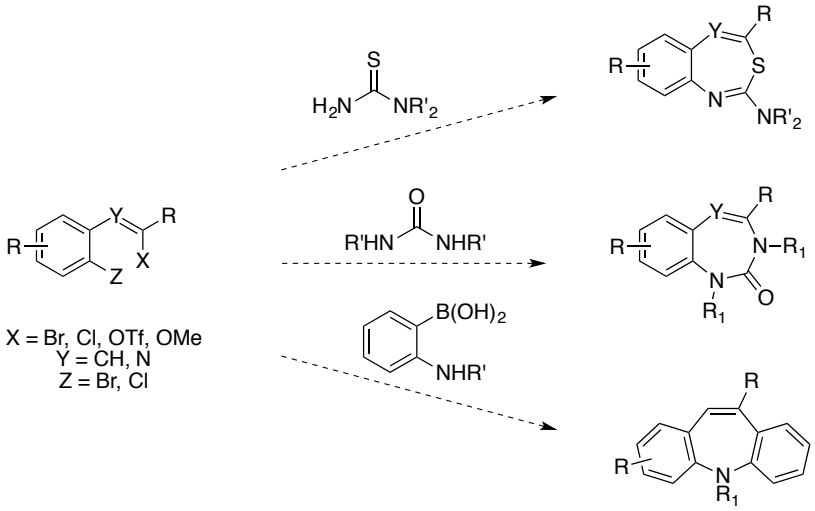


Scheme 5.2

Although a general and high-yielding synthesis could not be established, interesting and unusual reactivity was discovered.

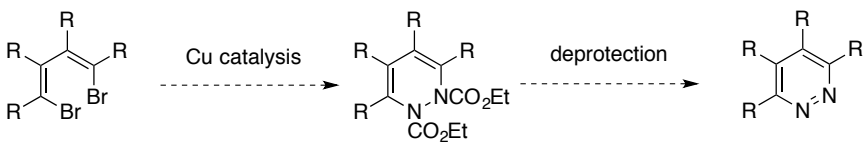
Further studies could strive to further expand the repertoire of heterocycles accessible from such general precursors. (*ortho*-Haloalkenyl)aryl halides have been used to access a range of 5,6- and 6,6-bicyclic heterocycles, *via* coupling with one- and two-atom units respectively. Thus, future work could involve the use of three-atom based fragments, such as ureas or thioureas, to access 5,7-bicyclic products (Scheme 5.3). Benzodiazepine-like derivatives could be accessed *via* coupling with a (2-aminophenyl)boronic acid derivative. Lautens has demonstrated the use of catalytic

systems capable of both Suzuki and Buchwald-Hartwig amination processes,[132] and the difference in reactivity between the alkenyl halide and the aryl halide could be exploited to create a regioselective synthesis (Scheme 5.3). Preliminary experiments exploring such a system showed initial success.



Scheme 5.3

The cinnoline-forming methodology developed could be applied to alternative substrates to access monocyclic products. 1,4-Dibromobutadienes have been used in conjunction with palladium and copper catalysis in the synthesis of a variety of heterocycles, including pyrroles[133] and thiophenes.[134] Thus, a general synthesis of pyridazines could be envisaged from these precursors (Scheme 5.4). Such substrates are readily accessible *via* zironocene-chemistry.[135]



Scheme 5.4

Thus, the range of heterocycles attainable from general substrates could be expanded and their utility consolidated. These potential future studies, along with the explorations and investigations already performed, mean that the use and relevance of these general precursors will only continue to increase.

Chapter 6. Experimental Section

6.1 General Considerations

All chemicals were purchased from Sigma Aldrich, Alfa Aesar or Fluorochem and used without further purification. Anhydrous acetonitrile, DCM, methanol, THF and toluene were collected fresh from an in-house Innovative Technology Inc. PS-400-7 solvent purification system having been passed through anhydrous alumina columns. 1,2-Dimethoxyethane and 1,4-dioxane were distilled from calcium hydride and stored over 3 Å molecular sieves. Anhydrous DCE, DMA, DMF and DMSO were purchased from Sigma Aldrich in Sure/Seal^{TM} bottles. All other solvents were used as purchased at HPLC grade. Petroleum ether refers to the fraction of light petroleum boiling in the range 40-60 °C.

Reactions were conducted in oven-dried glassware, in anhydrous solvents with continuous magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Glassware was dried at >200 °C for a minimum of 16 h prior to use and allowed to cool to room temperature under a flow of nitrogen. Cooling of reaction mixtures to 0 °C was achieved using an ice-water bath. Cooling to -78 °C was achieved using a dry ice-acetone bath. All inorganic bases were dried in a vacuum drying pistol (120 °C, 10 mbar) for 16 h prior to use and subsequently stored under nitrogen.

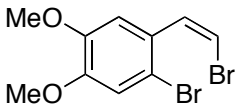
Analytical thin layer chromatography was carried out using pre-coated aluminium backed silica plates (Merck Kieselgel 60F254). Plates were visualised under ultraviolet light (254 nm) and/or by staining with vanillin. Flash column

chromatography was carried out using Apollo scientific silica gel 60 (0.040 – 0.063 nm). Pressure was applied at the column head *via* hand bellows.

^{1}H and ^{13}C nuclear magnetic resonance spectroscopy was carried out using Bruker DPX-200, DQX-250, AVN-400, DQX-400, DRX-500 or AVC-500 spectrometers. Chemical shifts (δ) are given in parts per million (ppm). Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Assignments are made using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br.) and apparent (ap.). Low resolution mass spectra were recorded using a Fisons Platform spectrometer (ESI). High resolution mass spectra were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford. *m*/*z* Ratio values are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of 5 ppm. Melting points were determined using a Leica Galen III hot-stage microscope. Infrared measurements were determined neat using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}.

6.2 Synthetic Procedures and Characterisation Data

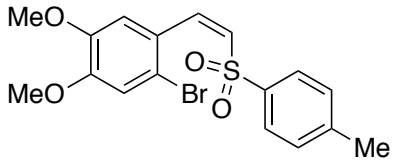
General Procedure A for the synthesis of (*ortho*-haloalkenyl)aryl halides, as exemplified by the preparation of (*Z*)-1-bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene, 1



Prepared according to a literature procedure.[53] Potassium *tert*-butoxide (2.65 g, 40.0 mmol, 1.2 eq) was added portion-wise to a stirred solution of (bromomethyl)triphenylphosphonium bromide (14.2 g, 40.0 mmol, 1.2 eq) in THF (100 mL) at -78 °C. Stirring at this temperature was maintained for 1 h before 6-bromoveratraldehyde (10.6 g, 33.0 mmol, 1.0 eq) was added portion-wise to the resulting bright yellow suspension. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The resulting suspension was then diluted with petroleum ether (50 mL) and poured onto further petroleum ether (150 mL). The suspension was filtered through a pad of Celite®, washing with further petroleum ether (100 mL) and the filtrate concentrated *in vacuo*. Column chromatography (100% petroleum ether) yielded alkenyl bromide **1** (7.01 g, 66%, *Z*:*E* >20:1) as a white solid: ν_{max} (neat)/cm^{-1} 3027, 2985, 1597, 1502, 1465, 1436, 1384, 1268, 1215, 1154, 1029; δ_H (400 MHz, $CDCl_3$) 7.49 (1H, s, Ar*H*), 7.18 (1H, d, *J* 8.0, ArC*H*=CHBr), 7.07 (1H, s, Ar*H*), 6.50 (1H, d, *J* 8.0, ArCH=C*H*Br), 3.91 (3H, s, ArOCH_3), 3.90 (3H, s, ArOCH_3); δ_C (100 MHz, $CDCl_3$) 149.4, 147.6, 131.7, 126.9,

115.1, 114.7, 112.7, 107.6, 56.2, 56.1; *m/z* HRMS (FI^+) 321.9046 ($[M]^+$, $C_{10}H_{10}{}^{81}Br^{79}BrO_2$ requires 321.9027). Data in accordance with the literature.[53]

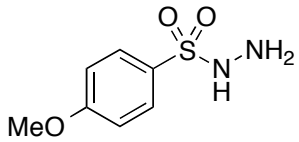
(*Z*)-1-Bromo-4,5-dimethoxy-2-(2-tosylvinyl)benzene, 3



(*Z*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **1** (130 mg, 0.4 mmol, 1.0 eq), *p*-toluenesulfonyl hydrazide (112 mg, 0.6 mmol, 1.5 eq), K_3PO_4 (170 mg, 0.8 mmol, 2.0 eq) and CuI (8 mg, 0.04 mmol, 0.1 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before toluene (0.5 mL) and DMEDA (10 μl, 0.08 mmol, 0.2 eq) were added. The reaction mixture was stirred in a pre-heated oil bath at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered through a pad of Celite®, washing the pad with further DCM (15 mL). The resulting filtrate was concentrated *in vacuo*. Column chromatography (25-50% diethyl ether in petroleum ether) yielded *sulfonylvinyl benzene* **3** (86 mg, 54%, *Z*:*E* >20:1) as an off-white solid: mp 130-132 °C; ν_{max} (neat)/cm^{-1} 3016, 2957, 1596, 1499, 1270, 1141, 1022; δ_H (500 MHz, $(CD_3)_2SO$) 7.63 (2H, d, *J* 8.5, 2 × Ar*H*), 7.39 (2H, d, *J* 8.5, 2 × Ar*H*), 7.21 (1H, s, Ar*H*), 7.17 (1H, d, *J* 11.5, ArC*H*=CHSO2), 7.15 (1H, s, Ar*H*), 6.90 (1H, d, *J* 11.5, ArCH=C*H*SO_2), 3.81 (3H, s, ArOCH_3), 3.76 (3H, s, ArOCH_3), 2.38 (3H, s, ArCH_3); δ_C (125 MHz, $(CD_3)_2SO$) 150.3, 147.2, 144.3, 139.7, 137.7, 131.9, 129.8, 127.0, 124.6, 114.9, 114.8, 113.7, 56.1, 55.6, 21.1; *m/z* LRMS (ESI^+) 421.0 (^{81}Br,

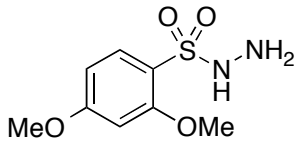
[(M+Na)$^+$], 100%), 419.0 (^{79}Br, [(M+Na)$^+$], 90%), 399.0 (^{81}Br, [(M+H)$^+$], 70%), 397.0 (^{79}Br, [(M+H)$^+$], 70%); HRMS (ESI$^+$) 420.9890 ([(M+Na)$^+$], $C_{17}H_{17}{}^{81}BrO_4SNa$ requires 420.9903).

4-Methoxybenzenesulfonohydrazide, 4



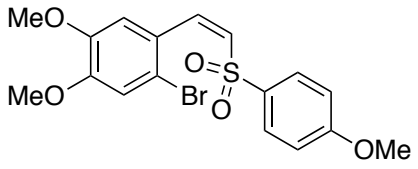
Hydrazine monohydrate (0.61 mL, 12.5 mmol, 2.5 eq) was added drop-wise to a solution of 4-methoxybenzenesulfonyl chloride (1.0 g, 5.0 mmol, 1.0 eq) in THF (40 mL) at 0 °C. The resulting reaction mixture was allowed to stir at this temperature for 1 h before ethyl acetate (25 mL) and sat. $NaHCO_{3(aq)}$ (25 mL) were added. The organic phase was separated and washed with brine (2 × 25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford *hydrazide* **4** (0.90 g, 89%) as a white solid: mp 105-107 °C; ν_{max} (neat)/cm^{-1} 3378, 3252, 2991, 2956, 1594, 1496, 1324, 1261, 1154, 1012; δ_H (400 MHz, $(CD_3)_2SO$) 8.27 (1H, br. s, N*H*), 7.79 (2H, d, *J* 9.0, 2 × Ar*H*), 7.17 (2H, d, *J* 9.0, 2 × Ar*H*), 4.08 (2H, br. s, NH_2), 3.88 (3H, s, ArOCH_3); δ_C (100 MHz, $(CD_3)_2SO$) 162.9, 130.3, 130.0, 114.7, 56.1; *m/z* LRMS (ESI$^+$) 225.1 ([(M+Na)$^+$], 100%), 203.1 ([(M+H)$^+$], 90%); HRMS (ESI$^+$) 225.0305 ([(M+Na)$^+$], $C_7H_{10}N_2O_3SNa$ requires 225.0304).

2,4-Dimethoxybenzenesulfonohydrazide, 5



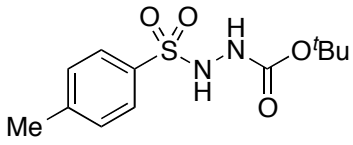
Hydrazine monohydrate (0.61 mL, 12.5 mmol, 2.5 eq) was added drop-wise to a solution of 2,4-dimethoxybenzenesulfonyl chloride (1.2 g, 5.0 mmol, 1.0 eq) and triethylamine (2.1 mL, 15.0 mmol, 3.0 eq) in THF (40 mL) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred for 2 h before ethyl acetate (25 mL) and sat. $NaHCO_{3(aq)}$ (25 mL) were added. The organic phase was separated and washed with brine (2 × 25 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford *hydrazide* **5** (0.72 g, 62%) as an off-white solid: mp 106-108 °C; ν_{max} (neat)/cm^{-1} 3384, 3288, 2956, 2921, 1576, 1467, 1295, 1160, 1074, 1022; δ_H (400 MHz, $(CD_3)_2SO$) 7.79 (1H, br. s, N*H*), 7.67 (1H, d, *J* 8.5, Ar*H*), 6.71 (1H, d, *J* 2.5, Ar*H*), 6.66 (1H, dd, *J* 8.5 and 2.5, Ar*H*), 4.02 (2H, br. s, NH_2), 3.88 (3H, s, ArOCH_3), 3.85 (3H, s, ArOCH_3); δ_C (100 MHz, $(CD_3)_2SO$) 165.0, 158.5, 133.2, 117.5, 105.5, 99.6, 56.7, 56.2; *m/z* LRMS (ESI^+) 255.1 ([$(M+Na)^+$], 40%), 233.1 ([$(M+H)^+$], 100%); HRMS (ESI^+) 255.0405 ([$(M+Na)^+$], $C_8H_{12}N_2O_4SNa$ requires 255.0410).

(*Z*)-1-Bromo-4,5-dimethoxy-2-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, 6



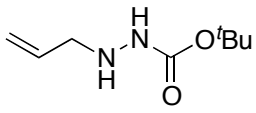
(*Z*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **1** (130 mg, 0.4 mmol, 1.0 eq), 4-methoxybenzenesulfonyl hydrazide **4** (162 mg, 0.8 mmol, 2.0 eq), K_3PO_4 (170 mg, 0.8 mmol, 2.0 eq) and CuI (8 mg, 0.04 mmol, 0.1 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before toluene (0.5 mL) and DMEDA (10 μl, 0.08 mmol, 0.2 eq) were added. The reaction mixture was stirred in a pre-heated oil bath at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered through a pad of Celite®, washing the pad with further DCM (15 mL). The resulting filtrate was concentrated *in vacuo*. Column chromatography (25-50% diethyl ether in petroleum ether) yielded *sulfonylvinyl benzene* **6** (110 mg, 67%, *Z*:*E* >20:1) as a pale yellow solid: mp 162-163 °C; ν_{max} (neat)/cm^{-1} 3049, 2934, 1593, 1462, 1271, 1183, 1136, 1020; δ_H (500 MHz, $(CD_3)_2SO$) 7.66 (2H, d, *J* 9.0, 2 × Ar*H*), 7.21 (1H, s, Ar*H*), 7.15 (1H, s, Ar*H*), 7.13 (1H, d, *J* 11.5, ArC*H*=CHSO$_2$), 7.09 (2H, d, *J* 9.0, 2 × Ar*H*), 6.88 (1H, d, *J* 11.5, ArCH=C*H*SO$_2$), 3.84 (3H, s, ArOCH_3), 3.81 (3H, s, ArOCH_3), 3.77 (3H, s, ArOCH_3); δ_C (125 MHz, $(CD_3)_2SO$) 163.2, 150.2, 147.2, 139.2, 132.4, 132.0, 129.3, 124.7, 124.6, 114.9, 114.8, 114.6, 56.1, 55.8, 55.7; *m/z* LRMS (ESI$^+$) 437.0 (^{81}Br, [(M+Na)$^+$], 50%), 435.0 (^{79}Br, [(M+Na)$^+$], 60%), 415.0 (^{81}Br, [(M+H)$^+$], 100%), 413.0 (^{79}Br, [(M+H)$^+$], 90%); HRMS (ESI$^+$) 436.9840 ([(M+Na)$^+$], $C_{17}H_{17}{}^{81}BrO_5SNa$ requires 436.9852).

tert-Butyl 2-tosylhydrazinecarboxylate, 7



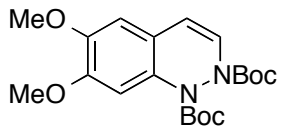
A solution of *p*-toluenesulfonyl chloride (2.58 g, 13.5 mmol, 1.0 eq) in DCM (10 mL) was added drop-wise to a suspension of *tert*-butyl carbazate (1.98 g, 15.0 mmol, 1.1 eq) and potassium carbonate (2.21 g, 16.0 mmol, 1.2 eq) in DCM (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The resulting suspension was then concentrated *in vacuo* and the residue partitioned between ethyl acetate (20 mL) and $HCl_{(aq)}$ (1 M, 20 mL). The organic phase was separated and washed with $HCl_{(aq)}$ (1 M, 2 × 20 mL), sat. $NaHCO_{3(aq)}$ (2 × 20 mL) and brine (20 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10-25% ethyl acetate in petroleum ether) afforded *hydrazide* **7** (3.25 g, 84%) as a white solid: mp 89-91 °C; ν_{max} (neat)/cm^{-1} 3274, 3243, 2982, 2932, 1715, 1626, 1495, 1341, 1289, 1160; δ_H (400 MHz, $(CD_3)_2SO$) 9.46 (1H, s, N*H*), 9.16 (1H, br. s, N*H*), 7.66 (2H, *J* 8.0, 2 × Ar*H*), 7.37 (2H, d, *J* 8.0, 2 × Ar*H*), 2.38 (3H, s, ArCH_3), 1.23 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $(CD_3)_2SO$) 155.0, 143.5, 136.6, 129.7, 128.2, 79.9, 28.2, 21.5; *m/z* LRMS (ESI^+) 309.1 ([$(M+Na)^+$], 100%), 287.1 ([$(M+H)^+$], 40%); HRMS (ESI^+) 309.0879 ([$(M+Na)^+$], $C_{12}H_{18}O_4N_2SNa$ requires 309.0879).

tert-Butyl 2-allylhydrazinecarboxylate, 8



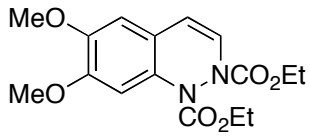
Prepared according to a literature procedure.[136] *n*Butyl lithium (2.5 M in hexanes, 32.0 mL, 80.0 mmol, 4.0 eq) was added drop-wise using a syringe pump to a solution of *tert*-butyl carbazate (5.28 g, 40.0 mmol, 2.0 eq) in THF (200 mL) at -78 °C. The resulting reaction mixture was allowed to warm to -50 °C for 20 min before allyl bromide (1.8 mL, 20.0 mmol, 1.0 eq) was added drop-wise. After an hour at -50 °C, a second portion of allyl bromide (1.8 mL, 20.0 mmol, 1.0 eq) was added. The reaction mixture was allowed to stir at -50 °C for a further hour before being quenched with methanol (4 mL) and then water (4 mL). After warming to room temperature, the reaction mixture was concentrated *in vacuo* and partitioned between DCM (75 mL) and brine (75 mL). The organic phase was separated and the aqueous phase extracted with DCM (2 × 75 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% ethyl acetate in petroleum ether) afforded hydrazide **8** (3.52 g, 52%) as a clear oil: ν_{max} (neat)/cm^{-1} 3316, 2980, 2933, 1714, 1645, 1477, 1368, 1283, 1162; δ_H (400 MHz, $CDCl_3$) 6.23 (1H, br. s, N*H*), 5.87-5.80 (1H, m, CH_2=C*H*CH_2), 5.24-5.13 (2H, m, C*H*$_2$=CHCH_2), 3.76 (1H, br. s, N*H*), 3.45 (2H, d, *J* 6.0, CH_2=CHC*H*$_2$), 1.45 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 156.7, 134.2, 118.1, 80.5, 54.5, 28.3; *m/z* HRMS (FI^+) 172.1210 ([M^+], $C_8H_{16}O_2N_2$ requires 172.1212). Data in accordance with the literature.[136]

Di-*tert*-butyl 6,7-dimethoxydihydrocinnoline-1,2-dicarboxylate, 9



(*Z*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **1** (130 mg, 0.4 mmol, 1.0 eq), di-*tert*-butylhydrazodicarboxylate (140 mg, 0.6 mmol, 1.5 eq), K_3PO_4 (170 mg, 0.8 mmol, 2.0 eq) and CuI (8 mg, 0.04 mmol, 0.1 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before toluene (0.5 mL) and DMEDA (10 μl, 0.08 mmol, 0.2 eq) were added. The reaction mixture was stirred in a pre-heated oil bath at 80 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered through a pad of Celite®, washing the pad with further DCM (15 mL). The resulting filtrate was concentrated *in vacuo*. Column chromatography (30% diethyl ether in petroleum ether) yielded *di-tert-butyl dihydrocinnoline-1,2-dicarboxylate* **9** (118 mg, 75%) as a pale yellow solid: mp 133-134 °C; ν_{max} (neat)/cm^{-1} 3003, 2932, 1731, 1509, 1370, 1270, 1162; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 6.99 (1H, d, *J* 7.0, ArCH=C*H*N), 6.94 (1H, s, Ar*H*), 6.85 (1H, s, Ar*H*), 6.14 (1H, d, *J* 7.0, ArC*H*=CHN), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 1.49 (9H, s, $C(CH_3)_3$), 1.44 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 156.1, 154.0, 148.7, 148.5, 129.9, 127.8, 120.6, 111.3, 110.5, 109.5, 82.6, 82.3, 56.7 (2C), 28.4, 28.2; *m/z* LRMS (ESI^+) 415.2 ([$(M+Na)^+$], 100%), 393.2 ([$(M+H)^+$], 20%); HRMS (ESI^+) 415.1842 ([$(M+Na)^+$], $C_{20}H_{28}N_2O_6Na$ requires 415.1845).

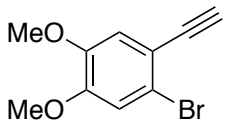
General Procedure B for the synthesis of diethyl dihydrocinnoline-1,2-dicarboxylates, as exemplified by the preparation of diethyl 6,7-dimethoxydihydrocinnoline-1,2-dicarboxylate, 10



(*Z*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **1** (130 mg, 0.4 mmol, 1.0 eq), diethyl hydrazine-1,2-dicarboxylate (140 mg, 0.8 mmol, 2.0 eq), K_2CO_3 (138 mg, 1.0 mmol, 2.5 eq) and CuI (8 mg, 0.04 mmol, 0.1 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before 1,4-dioxane (0.5 mL) and DMEDA (10 μl, 0.08 mmol, 0.2 eq) were added. The reaction mixture was stirred in a pre-heated oil bath at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered through a pad of Celite®, washing the pad with further DCM (15 mL). The resulting filtrate was concentrated *in vacuo*. Column chromatography (15% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **10** (127 mg, 95%) as a white solid: mp 118-120 °C; ν_{max} (neat)/cm^{-1} 3068, 3011, 2980, 2934, 1737, 1721, 1612, 1509, 1371, 1234, 1126, 1048; δ_H (250 MHz, $(CD_3)_2SO$, 90 °C) 7.04-7.00 (2H, m, Ar*H* and ArCH=C*H*N), 6.89 (1H, s, Ar*H*), 6.23 (1H, d, *J* 7.5, ArC*H*=CHN), 4.27-4.14 (4H, m, 2 × CH_2CH_3), 3.82 (3H, s, $ArOCH_3$), 3.80 (3H, s, $ArOCH_3$), 1.29-1.19 (6H, m, 2 × CH_2CH_3); δ_C (62.5 MHz, $(CD_3)_2SO$, 90 °C) 155.7, 152.6, 149.3, 149.0, 129.8, 127.7, 120.7, 112.6, 110.4, 109.8, 63.7, 63.3, 57.1, 57.0, 15.1, 14.9; *m/z* LRMS

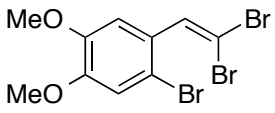
(ESI$^+$) 695.3 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 359.1213 ([(M+Na)$^+$], $C_{16}H_{20}N_2O_6Na$ requires 359.1214).

1-Bromo-2-ethynyl-4,5-dimethoxybenzene, 11



Isolated during screening experiments as a side product in the synthesis of diethyl 6,7-dimethoxydihydrocinnoline-1,2-dicarboxylate **10**: mp 94-96 °C; ν_{max} (neat)/cm^{-1} 3288, 3010, 2965, 2935, 2286, 1504, 1374, 1252, 1210, 1159, 1026, 849; δ_H (400 MHz, $CDCl_3$) 7.03 (1H, s, Ar*H*), 6.99 (1H, s, Ar*H*), 3.89 (3H, s, ArOC*H*$_3$), 3.86 (3H, s, ArOC*H*$_3$), 3.30 (1H, s, C≡C*H*); δ_C (100 MHz, $CDCl_3$) 150.2, 148.0, 116.9, 115.9, 115.8, 115.1, 82.1, 80.1, 56.2, 56.1; *m/z* HRMS (FI$^+$) 241.9768 ([M$^+$], $C_{10}H_9O_2{}^{81}Br$ requires 241.9766).

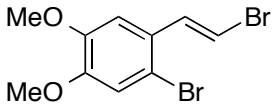
1-Bromo-2-(2,2-dibromovinyl)-4,5-dimethoxybenzene, 12



A solution of tri*iso*propyl phosphite (7.7 mL, 33.0 mmol, 2.2 eq) in DCM (15 mL) was added over 1 h using a syringe pump to a solution of 6-bromoveratraldehyde (3.68 g, 15.0 mmol, 1.0 eq) and carbon tetrabromide (7.47 g, 22.5 mmol, 1.5 eq) in

DCM (75 mL) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred for 2 h before being cooled to 0 °C and slowly quenched with sat. $NaHCO_{3(aq)}$ (50 mL). The resulting biphasic mixture was separated and the organic phase washed with brine (2 × 75 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (25% diethyl ether in petroleum ether) yielded *tribromide* **12** (4.70 g, 78 %) as a pale yellow solid: mp 75-76 °C; ν_{max} (neat)/cm^{-1} 3011, 2959, 2906, 1597, 1505, 1466, 1435, 1382, 1209, 1107; δ_H (400 MHz, $CDCl_3$) 7.49 (1H, s, ArC*H*=CBr_2), 7.21 (1H, s, Ar*H*), 7.04 (1H, s, Ar*H*), 3.89 (6H, s, 2 × OCH_3); δ_C (100 MHz, $CDCl_3$) 149.7, 147.9, 136.3, 127.8, 115.1, 114.0, 112.5, 91.4, 56.2 (2C); *m/z* HRMS (FI^+) 403.8009 ($[M]^+$, $C_{10}H_9{}^{81}Br^{81}Br^{79}BrO_2$ requires 403.8004).

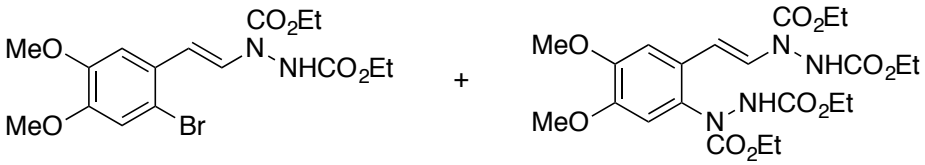
(*E*)-1-Bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene, 13



Triethylamine (0.75 mL, 5.4 mmol, 4.5 eq) and dimethyl phosphite (0.44 mL, 4.8 mmol, 4.0 eq) were added to a solution of 1-bromo-2-(2,2-dibromovinyl)-4,5-dimethoxybenzene **12** (0.50 g, 1.2 mmol, 1.0 eq) in DMF (6 mL). The reaction mixture was heated to 75 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and ethyl acetate (30 mL). The resulting phases were separated and the aqueous phase extracted with ethyl acetate (2 × 30 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$)

and concentrated *in vacuo*. Column chromatography (25% diethyl ether in petroleum ether) yielded *alkenyl bromide* **13** (0.28 g, 74%, *E*:*Z* >20:1) as a pale orange solid: mp 95-97 °C: ν_{max} (neat)/cm^{-1} 3078, 2957, 1627, 1561, 1446, 1337, 1190, 1042, 975; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, d, *J* 14.0, ArC*H*=CHBr), 7.01 (1H, s, Ar*H*), 6.87 (1H, s, Ar*H*), 6.67 (1H, d, *J* 14.0, ArCH=C*H*Br), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 149.8, 148.6, 135.9, 132.3, 128.1, 115.4, 109.0, 107.1, 56.2, 56.1; *m/z* HRMS (FI$^+$) 321.9040 ([M]$^+$, $C_{10}H_{10}O_2{}^{81}Br^{79}Br$ requires 321.9027).

(*E*)-Diethyl 1-(2-bromo-4,5-dimethoxystyryl)hydrazine-1,2-dicarboxylate 14 and (*E*)-Diethyl 1-(2-(1,2-bis(ethoxycarbonyl)hydrazinyl)-4,5-dimethoxystyryl) hydrazine-1,2-dicarboxylate, 15



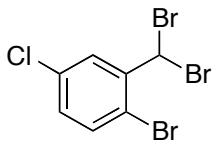
Prepared following general procedure B using (*E*)-1-bromo-2-(2-bromovinyl)-4,5-dimethoxybenzene **13** (260 mg, 0.8 mmol, 1.0 eq). Column chromatography (10% acetone in petroleum ether) yielded, in order of elution, *bromide* **14** (207 mg, 62%, *E*:*Z* >20:1) as a pale yellow solid and *hydrazide* **15** (77 mg, 19%, *E*:*Z* >20:1) also as a pale yellow solid.

14: mp 51-52 °C; ν_{max} (neat)/cm^{-1} 3308, 2980, 2935, 1719, 1651, 1505, 1342, 1255, 1207, 1164; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 9.56 (1H, br. s, N*H*), 7.49 (1H, d, *J* 14.0, ArCH=C*H*N), 7.12 (1H, s, Ar*H*), 7.10 (1H, s, Ar*H*), 6.24 (1H, d, *J* 14.0, ArC*H*=CHN), 4.25 (2H, q, *J* 7.0, CH_2CH$_3$), 4.17 (2H, q, *J* 7.0, CH_2CH$_3$), 3.84 (3H, s,

OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 1.30-1.24 (6H, m, 2 × CH$_2$C*H*$_3$); δ_C (125 MHz, (CD$_3$)$_2$SO, 90 °C) 155.5, 153.5, 149.7, 149.4, 128.6, 128.5, 117.2, 113.4, 110.7, 108.8, 63.3, 61.6, 56.82, 56.79, 14.9, 14.7; *m/z* HRMS (FI$^+$) 418.0565 ([M]$^+$, $C_{16}H_{21}{}^{81}BrN_2O_6$ requires 418.0565).

15: mp 78-80 °C; ν_{max} (neat) / cm^{-1} 3298, 3010, 2981, 2936, 1717, 1654, 1607, 1513, 1376, 1230, 1059; δ_H (500 MHz, (CD$_3$)$_2$SO, 90 °C) 9.35-9.27 (2H, br. s, N*H*), 7.38 (1H, d, *J* 14.0, ArCH=C*H*N), 7.01 (1H, s, Ar*H*), 6.97 (1H, s, Ar*H*), 6.28 (1H, d, *J* 14.0, ArC*H*=CHN), 4.28-4.04 (8H, m, 4 × C*H*$_2$CH$_3$), 3.85 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 1.31-1.12 (12H, m, 4 × CH$_2$C*H*$_3$); δ_C (125 MHz, (CD$_3$)$_2$SO, 90 °C) 156.7, 155.9, 155.7, 154.0, 149.8, 148.9, 133.5, 127.9, 127.8, 113.1, 109.6, 106.8, 63.5, 62.7, 61.9, 61.7, 57.1, 56.9, 15.24, 15.17, 15.10, 15.08; *m/z* HRMS (FI$^+$) 512.2119 ([M$^+$], $C_{22}H_{32}N_4O_{10}$ requires 512.2131).

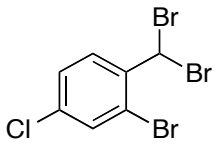
1-Bromo-4-chloro-2-(dibromomethyl)benzene, 16



Prepared according to a literature procedure.[137] AIBN (250 mg, 1.5 mmol, 0.1 eq) was added to a solution of 2-bromo-5-chlorotoluene (2.0 mL, 15.0 mmol, 1.0 eq) and NBS (8.0 g, 45.0 mmol, 3.0 eq) in CCl_4 (150 mL). The reaction was heated to reflux for 13.5 h. During this time, additional AIBN was added to the reaction mixture at 1.5 h (125 mg, 0.75 mmol, 0.05 eq), 6 h (250 mg, 1.5 mmol, 0.1 eq) and 12.5 h (125 mg, 0.75 mmol, 0.05 eq). The resulting reaction mixture was allowed to cool to room

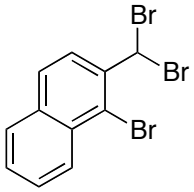
temperature and filtered, washing with DCM (50 mL). The filtrate was washed with water (3 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (100% petroleum ether) yielded tribromide **16** (4.39 g, 81%) as a white solid: mp 37-38 °C; ν_{max} (neat)/cm^{-1} 3024, 2928, 1554, 1455, 1384, 1213, 1096, 1025; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, *J* 2.5, Ar*H*), 7.44 (1H, d, *J* 8.5, Ar*H*), 7.17 (1H, dd, *J* 8.5 and 2.5, Ar*H*), 6.99 (1H, s, C*H*Br_2); δ_C (100 MHz, $CDCl_3$) 141.9, 134.6, 133.7, 131.3, 131.2, 117.5, 38.4; *m/z* HRMS (FI^+) 363.7481 ([M^+], $C_7H_4{}^{81}Br^{81}Br^{79}Br^{35}Cl$ requires 363.7509). Data in accordance with the literature.[137]

1-Bromo-5-chloro-2-(dibromomethyl)benzene, 17



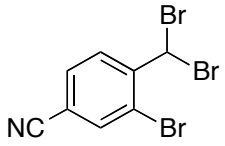
Prepared as for 1-bromo-4-chloro-2-(dibromomethyl)benzene **16** using 2-bromo-4-chlorotoluene (1.0 mL, 7.5 mmol, 1.0 eq), NBS (4.00 g, 22.5 mmol, 3.0 eq) and AIBN (1.23 g, 0.75 mmol, 0.25 eq) in CCl_4 (70 mL). Column chromatography (100% petroleum ether) afforded tribromide **17** (2.24 g, 82%) as an off-white solid: ν_{max} (neat)/cm^{-1} 3087, 3023, 1581, 1463, 1378, 1145, 1103, 1034; δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* 8.5, Ar*H*), 7.53 (1H, d, *J* 2.0, Ar*H*), 7.40 (1H, dd, *J* 8.5 and 2.0, Ar*H*), 7.03 (1H, s, C*H*Br_2); δ_C (100 MHz, $CDCl_3$) 139.1, 136.2, 132.0, 131.6, 129.0, 120.0, 38.7; *m/z* HRMS (FI^+) 363.7497 ([M^+], $C_7H_4{}^{81}Br^{81}Br^{79}Br^{35}Cl$ requires 363.7509). Data in accordance with the literature.[137]

1-Bromo-2-(dibromomethyl)naphthalene, 18



Prepared as for 1-bromo-4-chloro-2-(dibromomethyl)benzene **16** using 1-bromo-2-methylnaphthalene (85%, 5.5 mL, 30.0 mmol, 1.0 eq), NBS (16.0 g, 90.0 mmol, 3.0 eq) and AIBN (1.23 g, 7.5 mmol, 0.25 eq) in CCl_4 (250 mL). Column chromatography (100% hexane) afforded tribromide **18** (7.05 g, 62%) as a white solid: mp 82–84 °C; ν_{max} (neat)/cm^{-1} 3034, 2924, 1556, 1502, 1218, 1140, 974; δ_H (400 MHz, $CDCl_3$) 8.32 (1H, ap. d, *J* 8.5, Ar*H*), 8.08 (1H, ap. d, *J* 8.5, Ar*H*), 7.91 (1H, ap. d, *J* 8.5, Ar*H*), 7.85-7.83 (1H, m, Ar*H*), 7.67-7.63 (1H, m, Ar*H*), 7.61-7.56 (1H, m, Ar*H*), 7.51 (1H, s, C*H*Br_2); δ_C (100 MHz, $CDCl_3$) 137.9, 134.6, 131.2, 129.0, 128.4, 128.3, 128.2, 127.9, 126.8, 119.5, 41.3; *m/z* HRMS (FI^+) 377.8053 ([M^+], $C_{11}H_7{}^{81}Br^{79}Br^{79}Br$ requires 377.8078). Data in accordance with the literature.[137]

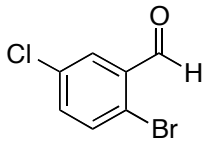
3-Bromo-4-(dibromomethyl)benzonitrile, 19



Prepared as for 1-bromo-4-chloro-2-(dibromomethyl)benzene **16** using 3-bromo-4-methylbenzonitrile (3.90 g, 20.0 mmol, 1.0 eq), NBS (10.7 g, 60.0 mmol, 3.0 eq) and

AIBN (980 mg, 6.0 mmol, 0.3 eq) in CCl_4 (200 mL). Column chromatography (2.5% diethyl ether in petroleum ether) afforded *tribromide* **19** (3.19 g, 45%) as a white solid: mp 51–52 °C; ν_{max} (neat)/cm^{-1} 3035, 3011, 2995, 2235, 1540, 1480, 1385, 1225, 1043; δ_H (400 MHz, $CDCl_3$) 8.14 (1H, d, *J* 8.0, Ar*H*), 7.83 (1H, d, *J* 1.5, Ar*H*), 7.71 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.02 (1H, s, C*H*Br_2); δ_C (100 MHz, $CDCl_3$) 145.0, 136.0, 131.9, 131.8, 120.1, 116.4, 114.8, 37.8; *m/z* HRMS (FI^+) 352.7864 ([M^+], $C_8H_4N^{81}Br^{81}Br^{79}Br$ requires 352.7874).

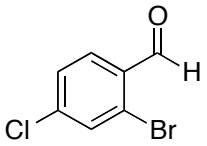
2-Bromo-5-chlorobenzaldehyde, 20



Prepared according to a literature procedure.[56] Silver nitrate (5.64 g, 33.2 mmol, 4.0 eq) and water (22 mL) were added to a solution of 1-bromo-4-chloro-2-(dibromomethyl)benzene **16** (3.0 g, 8.3 mmol, 1.0 eq) in methanol (130 mL). The solution was heated at reflux for 1.5 h. The resulting reaction mixture was allowed to cool to room temperature and filtered, washing with methanol (50 mL). The filtrate was concentrated *in vacuo* and redissolved in DCM (50 mL) before being diluted with water (50 mL). The resulting biphasic mixture was separated and the organic phase washed with water (2 x 50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to yield aldehyde **20** (1.58 g, 87%) as a white solid: mp 62-64 °C; ν_{max} (neat)/cm^{-1} 3018, 2971, 1688, 1647, 1455, 1392, 1247, 1091, 1030; δ_H (400 MHz, $CDCl_3$) 10.30 (1H, s, CO*H*), 7.89 (1H, d, *J* 2.5, Ar*H*), 7.61 (1H, d, *J* 8.5, Ar*H*), 7.44 (1H, dd, *J* 8.5 and 2.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 191.0, 135.3, 135.1, 134.6,

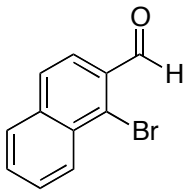
134.3, 129.7, 124.8; *m/z* HRMS (FI^+) 219.9094 ($[M^+]$, $C_7H_4O^{81}Br^{35}Cl$; requires 219.9112). Data in accordance with the literature.[137]

2-Bromo-4-chlorobenzaldehyde, 21



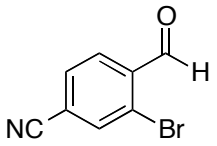
Prepared as for 2-bromo-5-chlorobenzaldehyde **20** using silver nitrate (3.4 g, 20.0 mmol, 4.0 eq) and 1-bromo-5-chloro-2-(dibromomethyl)benzene **17** (1.8 g, 5.0 mmol, 1.0 eq) in methanol (70 mL) and water (13 mL). Aqueous work-up yielded aldehyde **21** (0.90 g, 82%) as a yellow amorphous solid: ν_{max} (neat)/cm^{-1} 3014, 2970, 1686, 1575, 1457, 1368, 1197; δ_H (400 MHz, $CDCl_3$) 10.23 (1H, s, CO*H*), 7.79 (1H, d, *J* 8.5, Ar*H*), 7.61 (1H, d, *J* 1.5, Ar*H*), 7.36 (1H, dd, *J* 8.5 and 1.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 190.5, 141.2, 133.6, 132.0, 130.7, 128.5, 127.3; *m/z* HRMS (FI^+) 219.9098 ($[M^+]$, $C_7H_4O^{81}Br^{35}Cl$; requires 219.9112). Data in accordance with the literature.[137]

1-Bromo-2-naphthaldehyde, 22



Prepared as for 2-bromo-5-chlorobenzaldehyde **20** using silver nitrate (3.4 g, 20.0 mmol, 4.0 eq) and 1-bromo-2-(dibromomethyl)naphthalene **18** (1.9 g, 5.0 mmol, 1.0 eq) in methanol (70 mL) and water (13 mL). Aqueous work-up yielded aldehyde **22** (0.96 g, 81%) as a yellow amorphous solid: mp 114-115 °C; ν_{max} (neat)/cm^{-1} 3058, 2924, 1682, 1643, 1455, 1322, 1215, 967; δ_H (400 MHz, $CDCl_3$) 10.67 (1H, s, CO*H*), 8.52-8.49 (1H, m, Ar*H*), 7.94 (1H, d, *J* 8.5, Ar*H*), 7.89-7.87 (1H, m, Ar*H*), 7.85 (1H, d, *J* 8.5, Ar*H*), 7.70-7.68 (2H, m, 2 × Ar*H*); δ_C (100 MHz, $CDCl_3$) 192.8, 137.2, 132.1, 131.3, 131.2, 129.7, 128.5, 128.3, 128.2, 128.1, 124.1; *m/z* HRMS (FI$^+$) 235.9655 ([M$^+$], $C_{11}H_7O^{81}Br$ requires 235.9660). Data in accordance with the literature.[137]

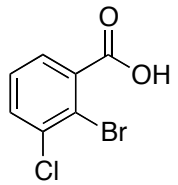
3-Bromo-4-formylbenzonitrile, 23



Prepared according to a literature procedure.[100] 3-Bromo-4-(dibromomethyl)benzonitrile **19** (2.0 g, 5.6 mmol, 1.0 eq) was added to a solution of

sodium acetate (2.0 g, 24.0 mmol, 4.3 eq), calcium carbonate (1.23 g, 12.3 mmol, 2.2 eq) and tetrabutylammonium bromide (350 mg, 1.1 mmol, 0.2 eq) in water (150 mL) and heated at reflux for 24 h. The reaction mixture was allowed to cool to room temperature before being diluted with DCM (75 mL). The resulting biphasic mixture was separated and the aqueous phase extracted with further DCM (2 × 75 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (5–15% diethyl ether in petroleum ether) yielded aldehyde **23** (0.51 g, 43%) as a white solid: mp 108-110 °C; ν_{max} (neat)/cm^{-1} 3038, 2965, 2285, 2230, 1689, 1650, 1596, 1380, 1259, 1194, 1046; δ_H (400 MHz, $CDCl_3$) 10.40 (1H, s, CO*H*), 8.01 (1H, d, *J* 8.0, Ar*H*), 7.98 (1H, d, *J* 1.5, Ar*H*), 7.74 (1H, dd, *J* 8.0 and 1.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 190.2, 137.2, 136.2, 131.3, 130.2, 128.8, 126.8, 118.6; *m/z* HRMS (FI^+) 208.9478 ([M^+], $C_8H_4NO^{81}Br$ requires 208.9476). Data in accordance with the literature.[138]

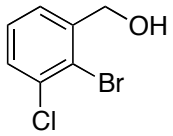
2-Bromo-3-chlorobenzoic acid, 24



Prepared according to a literature procedure.[139] *n*Butyl lithium (1.6 M in hexanes, 25.0 mL, 40.0 mmol, 2.0 eq) was added drop-wise to a solution of 2,2',6,6'-tetramethyl piperazine (6.7 mL, 40.0 mmol, 2.0 eq) in THF (60 mL) at 0 °C. The reaction mixture was allowed to stir for 30 min at 0 °C before being cooled to -50 °C. A solution of 3-

chlorobenzoic acid (3.1 g, 20.0 mmol, 1.0 eq) in THF (15 mL) was added drop-wise and the resulting solution stirred at -50 °C for 4 h. 1,2-Dibromochloroethane (26.1 g, 80.0 mmol, 4.0 eq) was added and the reaction mixture allowed to warm to room temperature and stirred for a further 2 h. Water (20 mL) was added and the mixture basified with $NaOH_{(aq)}$ (1 M, 40 mL). Diethyl ether (60 mL) was added and the phases separated. The aqueous phase was acidified with $HCl_{(aq)}$ (1 M, 50 mL) and extracted with further diethyl ether (2 × 60 mL) before the organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow powder. Recrystallisation (1:1 ethyl acetate/heptane) afforded benzoic acid **24** (2.87 g, 61%) as a pale yellow solid: ν_{max} (neat)/cm^{-1} 3014, 2968, 1685, 1414, 1300, 1256, 1033; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, dd, *J* 7.5 and 1.5, Ar*H*), 7.61 (1H, dd, *J* 7.5 and 1.5, Ar*H*), 7.48 (1H, t, *J* 7.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 167.8, 138.1, 135.2, 132.6, 129.6, 128.5, 119.8; *m/z* LRMS (ESI^+) 234.9 (^{81}Br, ^{35}Cl, $[(M-H)^-]$, 100%), 232.9 (^{79}Br, ^{35}Cl, $[(M-H)^-]$, 90%). Data in accordance with the literature.[139]

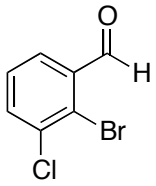
(2-Bromo-3-chlorophenyl)methanol



A solution of 2-bromo-3-chlorobenzoic acid **24** (3.5 g, 15.0 mmol, 1.0 eq) in THF (10 mL) was added slowly to a suspension of lithium aluminium hydride (1.14 g, 30.0 mmol, 2.0 eq) in THF (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The resulting suspension was re-cooled to 0 °C

before water (10 mL) was added, drop-wise at first. $HCl_{(aq)}$ (1 M, 50 mL) and diethyl ether (50 mL) were then added sequentially. The resulting biphasic mixture was separated and the aqueous phase extracted with further diethyl ether (2 × 50 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired alcohol (2.78 g, 84%) as a pale yellow solid: ν_{max} (neat)/cm^{-1} 3293, 3068, 2916, 1599, 1434, 1263, 1152; δ_H (400 MHz, $CDCl_3$) 7.30-7.23 (2H, m, 2 × Ar*H*), 7.17-7.14 (1H, m, Ar*H*), 4.61 (2H, s, CH_2OH), 3.12 (1H, br. s, O*H*); δ_C (100 MHz, $CDCl_3$) 135.0, 128.2, 127.8, 126.3, 124.9, 122.1, 65.4; *m/z* HRMS (FI^+) 221.9272 ([M^+], $C_7H_6O^{81}Br^{35}Cl$ requires 221.9268). Data in accordance with the literature.[56]

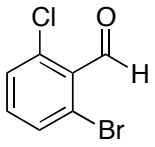
2-Bromo-3-chlorobenzaldehyde, 25



(2-Bromo-3-chlorophenyl)methanol (2.0 g, 9.0 mmol, 1.0 eq) was added to a solution of pyridinium chlorochromate (3.88 g, 18.0 mmol, 2.0 eq) in DCM (80 mL) over molecular sieves (4 Å, 750 mg). The resulting mixture was allowed to stir for 16 h at room temperature before being filtered through a pad of Celite®. The pad was washed with DCM (50 mL) and the filtrate concentrated *in vacuo* before column chromatography (2.5% diethyl ether in petroleum ether) yielded aldehyde **25** (1.5 g, 76%) as a pale yellow solid: ν_{max} (neat)/cm^{-1} 3073, 2929, 1681, 1518, 1275, 1092; δ_H (400 MHz, $CDCl_3$) 10.30 (1H, s, CO*H*), 7.73 (1H, dd, *J* 7.5 and 1.5, Ar*H*), 7.62 (1H, dd, *J* 7.5 and 1.5, Ar*H*), 7.31 (1H, t, *J* 7.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 191.5, 136.4,

135.7, 135.5, 128.4, 127.9, 127.1; *m/z* HRMS (FI^+) 219.9121 ([M^+], $C_7H_4O^{81}Br^{35}Cl$ requires 219.9112). Data in accordance with the literature.[56]

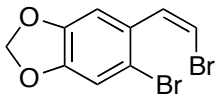
2-Bromo-6-chlorobenzaldehyde, 26



Prepared according to a literature procedure.[56] *n*Butyl lithium (2.5 M in hexanes, 13.2 mL, 16.5 mmol, 1.1 eq) was added drop-wise to a solution of di*iso*propylamine (2.3 mL, 16.5 mmol, 1.1 eq) in THF (6 mL) at -78 °C. The resulting reaction mixture was stirred at this temperature for 20 min before being allowed to warm to room temperature over 10 min. This solution was then added drop-wise to a solution of 1-bromo-3-chlorobenzene (1.76 mL, 15.0 mmol, 1.0 eq) in THF (7 mL) at -78 °C and the resulting mixture allowed to stir for 1 h at this temperature. DMF (1.4 mL, 18.0 mmol, 1.2 eq) was then added drop-wise and the solution slowly warmed to room temperature over 1.5 h. After this time, $HCl_{(aq)}$ (1 M, 20 mL) was added, drop-wise at first, before the reaction mixture was diluted with diethyl ether (20 mL). The phases were separated and the aqueous phase extracted with further diethyl ether (2 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% diethyl ether in petroleum ether) yielded aldehyde **26** (2.03 g, 62%) as a yellow solid: mp 67-69 °C; δ_H (400 MHz, $CDCl_3$) 10.38 (1H, s, CO*H*), 7.61-7.59 (1H, m, Ar*H*), 7.46-7.43 (1H, m, Ar*H*), 7.33-7.29 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 190.0, 136.7, 133.7, 133.0, 131.6,

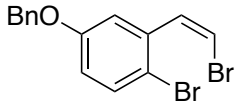
130.4, 124.9; *m/z* HRMS (FI^+) 219.9125 ($[M^+]$, $C_7H_4O^{81}Br^{35}Cl$ requires 219.9112). Data in accordance with the literature.[56]

(*Z*)-5-Bromo-6-(2-bromovinyl)benzo[*d*][1,3]dioxole, 27



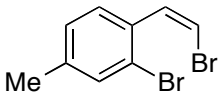
Prepared following general procedure A using potassium *tert*-butoxide (2.96 g, 26.4 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (11.5 g, 26.4 mmol, 1.2 eq) and 6-bromopiperonal (5.00 g, 22.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **27** (3.90 g, 58%, *Z*:*E* >20:1) as a white solid: mp 83-85 °C; ν_{max} (neat)/cm^{-1} 3012, 2924, 2854, 1612, 1504, 1412, 1377, 1244, 1104, 1040; δ_H (400 MHz, $CDCl_3$) 7.35 (1H, s, Ar*H*), 7.13 (1H, d, *J* 8.0, ArC*H*=CHBr), 7.06 (1H, s, Ar*H*), 6.49 (1H, d, *J* 8.0, ArCH=C*H*Br), 6.02 (2H, s, OCH_2O); δ_C (100 MHz, $CDCl_3$) 148.3, 146.8, 132.0, 128.1, 155.2, 112.7, 109.9, 108.2, 102.0; *m/z* HRMS (FI^+) 305.8719 ($[M]^+$, $C_9H_6{}^{81}Br^{79}BrO_2$ requires 305.8714). Data in accordance with the literature.[53]

(*Z*)-4-(Benzyloxy)-1-bromo-2-(2-bromovinyl)benzene, 28



Prepared following general procedure A using potassium *tert*-butoxide (1.15 g, 10.3 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (4.50 g, 10.3 mmol, 1.5 eq) and 5-(benzyloxy)-2-bromobenzaldehyde (2.00 g, 6.9 mmol, 1.0 eq). Column chromatography (5% ethyl acetate in petroleum ether) yielded *alkenyl bromide* **28** (1.69 g, 67%, *Z*:*E* 10:1) as a colourless oil: ν_{max} (neat)/cm^{-1} 3066, 3032, 2914, 2869, 1590, 1564, 1453, 1293, 1229, 1012; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.50-7.48 (1H, m, Ar*H*), 7.47-7.39 (6H, m, 6 × Ar*H*), 7.37-7.35 (1H, m, Ar*H*), 7.19 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.58 (1H, d, *J* 8.0, ArCH=C*H*Br), 5.10 (2H, s, OCH_2Ph); δ_C (100 MHz, $CDCl_3$) 157.5, 136.5, 133.7, 133.2, 132.2, 128.7, 128.1, 127.5, 117.0, 116.6, 114.6, 109.4, 70.4; *m*/*z* HRMS (FI$^+$) 367.9275 ([M$^+$], $C_{14}H_{10}O^{81}Br^{79}Br$ requires 367.9235).

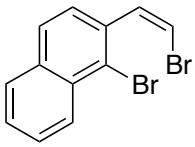
(*Z*)-2-Bromo-1-(2-bromovinyl)-4-methylbenzene, 29



Prepared following general procedure A using potassium *tert*-butoxide (0.67 g, 6.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.62 g, 6.0 mmol, 1.2 eq) and 2-bromo-4-methylbenzaldehyde (1.00 g, 5.0 mmol, 1.0 eq). Column

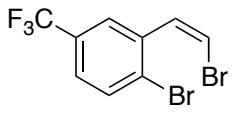
chromatography (100% petroleum ether) afforded alkenyl bromide **29** (0.98 g, 71%, *Z*:*E* 10:1) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3074, 3029, 2921, 1600, 1556, 1481, 1447, 1319, 1220, 1040; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.70 (1H, d, *J* 8.0, Ar*H*), 7.45-7.43 (1H, m, Ar*H*), 7.19 (1H, d, *J* 8.0, ArC*H*=CHBr), 7.17-7.14 (1H, m, Ar*H*), 6.55 (1H, d, *J* 8.0, ArCH=C*H*Br), 2.35 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 140.0, 136.0, 133.1, 130.1, 127.7, 126.7, 123.6, 108.7, 21.0; *m/z* HRMS (FI$^+$) 275.8992 ([M$^+$], $C_9H_8{}^{81}Br^{79}Br$ requires 275.8972). Data in accordance with the literature.[53]

(*Z*)-1-Bromo-2-(2-bromovinyl)naphthalene, 30



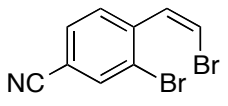
Prepared following general procedure A using potassium *tert*-butoxide (0.52 g, 4.6 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.00 g, 4.6 mmol, 1.2 eq) and 1-bromo-2-naphthaldehyde **22** (0.89 g, 3.8 mmol, 1.0 eq). Column chromatography (100% hexane) yielded *alkenyl bromide* **30** (0.75 g, 63%, *Z*:*E* 5:1) as a white solid: mp 46-48 °C; ν_{max} (neat)/cm^{-1} 3011, 2919, 1621, 1606, 1551, 1422, 1347, 1274, 1157, 1024; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 8.37 (1H, m, Ar*H*), 7.86-7.79 (3H, m, 3 × Ar*H*), 7.61-7.54 (2H, m, 2 × Ar*H*), 7.46 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.68 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 137.2, 134.0, 133.6, 128.2, 127.9, 127.6, 127.3, 127.1, 127.0, 123.7, 110.0, 109.7; *m/z* HRMS (FI$^+$) 311.8975 ([M$^+$], $C_{12}H_8{}^{81}Br^{79}Br$ requires 311.8973).

(*Z*)-1-Bromo-2-(2-bromovinyl)-4-(trifluoromethyl)benzene, 31



Prepared following general procedure A using potassium *tert*-butoxide (0.53 g, 4.7 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.0 g, 4.7 mmol, 1.2 eq) and 2-bromo-5-(trifluoromethyl)benzaldehyde (1.00 g, 3.95 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded *alkenyl bromide* **31** (0.79 g, 61%, *Z*:*E* 10:1) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3080, 3014, 2946, 1604, 1573, 1332, 1213, 1122, 1078, 1028; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 8.04 (1H, ap. s, Ar*H*), 7.74 (1H, ap. d, *J* 8.5, Ar*H*), 7.45 (1H, d, *J* 8.5, Ar*H*), 7.21 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.71 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 136.1, 133.3, 131.2, 129.6 (q, J_{CF} 33.0), 127.5 (m, 2 × C), 126.0 (m), 123.5 (q, J_{CF} 273.5), 111.1; δ_F (375 MHz, $CDCl_3$) -114.3 (s) {^{1}H}; *m/z* HRMS (FI$^+$) 329.8651 ([M$^+$], $C_9H_5{}^{81}Br{}^{79}BrF_3$ requires 329.8690).

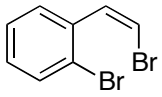
(*Z*)-3-Bromo-4-(2-bromovinyl)benzonitrile, 32



Prepared following general procedure A using potassium *tert*-butoxide (0.8 g, 7.2 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (3.1 g, 7.2 mmol, 1.2 eq) and 3-bromo-4-formylbenzonitrile **23** (1.26 g, 1.29 mmol, 1.0 eq). Column

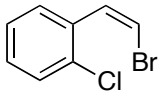
chromatography (10% diethyl ether in petroleum ether) afforded *alkenyl bromide* **32** (0.98 g, 57%, *Z*:*E* >20:1) as a white solid: mp 82-84 °C; ν_{max} (neat)/cm^{-1} 3061, 3035, 3020, 2228, 1619, 1596, 1470, 1312, 1289, 1192, 1093; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.90-7.88 (2H, m, 2 × Ar*H*), 7.65-7.62 (1H, m, Ar*H*), 7.21 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.75 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 140.1, 135.9, 131.1, 131.0, 130.5, 124.0, 117.2, 113.2, 112.2; *m/z* HRMS (FI$^+$) 286.8742 ([M$^+$], $C_9H_5N^{81}Br^{79}Br$ requires 286.8768).

(*Z*)-1-Bromo-2-(2-bromovinyl)benzene, 33



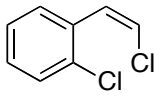
Prepared following general procedure A using potassium *tert*-butoxide (3.65 g, 40.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (14.2 g, 40.0 mmol, 1.2 eq) and 2-bromobenzaldehyde (3.2 mL, 33.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **33** (5.5 g, 64%, *Z*:*E* 10:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3014, 2923, 1617, 1588, 1463, 1428, 1318, 1044; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.81-7.79 (1H, m, Ar*H*), 7.62 (1H, d, *J* 8.0, ArC*H*=CHBr), 7.38-7.34 (1H, m, Ar*H*), 7.24-7.19 (2H, m, 2 × Ar*H*), 6.60 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100MHz, $CDCl_3$) 135.2, 132.7, 132.4, 130.5, 129.6, 126.9, 123.8, 109.4; *m/z* HRMS (FI$^+$) 261.8795 ([M]$^+$, $C_8H_6{}^{81}Br^{79}Br$ requires 261.8816). Data in accordance with the literature.[53]

(*Z*)-1-(2-Bromovinyl)-2-chlorobenzene, 34



Prepared following general procedure A using potassium *tert*-butoxide (1.75 g, 15.6 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (6.79 g, 15.6 mmol, 1.2 eq) and 2-chlorobenzaldehyde (1.2 mL, 10.4 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **34** (1.38 g, 61%, *Z*:*E* 10:1) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3073, 3019, 2924, 1617, 1589, 1521, 1478, 1302, 1178, 1042, 956; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.87-7.84 (1H, m, Ar*H*), 7.44-7.42 (1H, m, Ar*H*), 7.31-7.27 (3H, m, 2 × Ar*H* and C*H*=CHBr), 6.62 (1H, d, *J* 8.0, CH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 133.8, 133.5, 133.3, 130.3, 130.0, 129.4, 126.3, 109.4; *m/z* HRMS (FI$^+$) 217.9314 ([M$^+$], $C_8H_6{}^{81}Br^{35}Cl$ requires 217.9319). Data in accordance with the literature.[53]

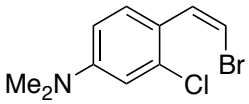
(*Z*)-1-Chloro-2-(2-chlorovinyl)benzene, 35



Prepared following general procedure A using potassium *tert*-butoxide (0.7 g, 6.0 mmol, 1.2 eq), (chloromethyl)triphenylphosphonium chloride (2.1 g, 6.0 mmol, 1.2 eq) and 2-chlorobenzaldehyde (0.6 mL, 5.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **35** (0.55 g, 64%, *Z*:*E* 10:1) as a clear

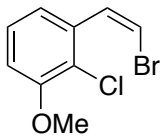
and colourless oil: ν_{max} (neat)/cm^{-1} 3073, 3030, 2946, 1793, 1690, 1468, 1436, 1339, 1126, 1050; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.91-7.89 (1H, m, Ar*H*), 7.44-7.41 (1H, m, Ar*H*), 7.30-7.25 (2H, m, 2 × Ar*H*), 6.93 (1H, d, *J* 8.0, C*H*=CHCl), 6.44 (1H, d, *J* 8.0, CH=C*H*Cl); δ_C (100 MHz, $CDCl_3$) 133.6, 132.1, 130.5, 129.4, 127.0, 126.3, 121.2, 120.0; *m/z* HRMS (FI$^+$) 171.9849 ([M$^+$], $C_8H_6{}^{35}Cl^{35}Cl$ requires 171.9846). Data in accordance with the literature.[53]

(*Z*)-4-(2-Bromovinyl)-3-chloro-*N*,*N*-dimethylaniline, 36



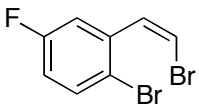
Prepared following general procedure A using potassium *tert*-butoxide (0.9 g, 8.2 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (3.6 g, 8.2 mmol, 1.5 eq) and 2-chloro-4-(dimethylamino)benzaldehyde (1.00 g, 5.46 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded *alkenyl bromide* **36** (0.91 g, 63%, *Z*:*E* 15:1) as a yellow oil: ν_{max} (neat)/cm^{-1} 3076, 2890, 1601, 1544, 1441, 1360, 1222, 1166, 1031; (*Z*)-isomer: δ_H (500 MHz, $CDCl_3$) 7.91 (1H, d, *J* 9.0, Ar*H*), 7.23 (1H, d, *J* 8.0, C*H*=CHBr), 6.71 (1H, d, *J* 2.5, Ar*H*), 6.62 (1H, dd, *J* 9.0 and 2.5, Ar*H*), 6.37 (1H, d, *J* 8.0, CH=C*H*Br), 2.99 (6H, s, ArN(CH_3)$_2$); δ_C (125 MHz, $CDCl_3$) 150.8, 134.9, 130.4, 129.1, 120.3, 112.1, 109.8, 105.2, 40.2; *m/z* HRMS (FI$^+$) 260.9709 ([M$^+$], $C_{10}H_{11}N^{81}Br^{35}Cl$ requires 260.9741).

(*Z*)-1-(2-Bromovinyl)-2-chloro-3-methoxybenzene, 37



Prepared following general procedure A using potassium *tert*-butoxide (1.97 g, 17.6 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (7.67 g, 17.6 mmol, 1.5 eq) and 2-chloro-3-methoxybenzaldehyde (2.00 g, 11.7 mmol, 1.0 eq). Column chromatography (2.5% diethyl ether in petroleum ether) yielded *alkenyl bromide* **37** (2.36 g, 82%, *Z*:*E* 10:1) as a yellow oil: ν_{max}(neat)/cm^{-1} 3009, 2964, 2936, 1610, 1589, 1472, 1321, 1276, 1187, 1110, 1070; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.43 (1H, d, *J* 8.0, Ar*H*), 7.30-7.25 (2H, m, 2 × Ar*H*), 6.94 (1H, d, *J* 8.0, C*H*=CHBr), 6.62 (1H, d, *J* 8.0, CH=C*H*Br), 3.92 (3H, s, ArOCH_3); δ_C (100 MHz, $CDCl_3$) 155.2, 134.9, 133.9, 130.3, 126.7, 122.2, 111.6, 109.6, 56.3; *m/z* HRMS (FI$^+$) 247.9387 ([M$^+$], $C_9H_8{}^{81}Br^{35}ClO$ requires 247.9425).

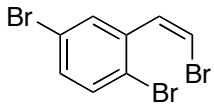
(*Z*)-1-Bromo-2-(2-bromovinyl)-4-fluorobenzene, 38



Prepared following general procedure A using potassium *tert*-butoxide (3.2 g, 29.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (12.5 g, 29.0 mmol, 1.2 eq) and 2-bromo-5-fluorobenzaldehyde (5.0 g, 24.0 mmol, 1.0 eq). Column

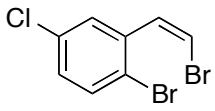
chromatography (100% petroleum ether) afforded alkenyl bromide **38** (4.3 g, 64%, *Z*:*E* 14:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3023, 2926, 1620, 1599, 1576, 1459, 1411, 1320, 1273, 1198, 1033; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.58-7.54 (2H, m, 2 × Ar*H*), 7.17 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.95 (1H, ap. td, *J* 8.5 and 3.0, Ar*H*), 6.65 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 162.5 (d, J_{CF} 235.0), 136.7, 133.8, 131.4, 118.0 (d, J_{CF} 25.0), 117.4, 116.7 (d, J_{CF} 23.0), 110.4 (d, J_{CF} 9.5); δ_F (375 MHz, $CDCl_3$) -62.8 (s) {^{1}H}; *m/z* HRMS (FI$^+$) 279.8698 ([M$^+$], $C_8H_5{}^{81}Br^{79}BrF$ requires 279.8722). Data in accordance with the literature.[53]

(*Z*)-1,4-Dibromo-2-(2-bromovinyl)benzene, 39



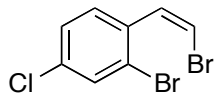
Prepared following general procedure A using potassium *tert*-butoxide (2.6 g, 23.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (10.0 g, 23.0 mmol, 1.2 eq) and 2,5-dibromobenzaldehyde (5.0 g, 19.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) afforded alkenyl bromide **39** (4.15 g, 65%, *Z*:*E* 10:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3006, 2923, 1617, 1544, 1452, 1385, 1318, 1083, 808; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.90 (1H, d, *J* 2.5, Ar*H*), 7.46 (1H, d, *J* 8.5, Ar*H*), 7.33 (1H, dd, *J* 8.5 and 2.5, Ar*H*), 7.14 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.65 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 136.9, 134.0, 133.1, 132.3, 131.2, 122.3, 120.7, 110.7; *m/z* HRMS (FI$^+$) 339.7845 ([M$^+$], $C_8H_5{}^{81}Br^{79}Br^{79}Br$ requires 339.7921). Data in accordance with the literature.[58]

(*Z*)-1-Bromo-2-(2-bromovinyl)-4-chlorobenzene, 40



Prepared following general procedure A using potassium *tert*-butoxide (1.98 g, 17.1 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (7.46 g, 17.1 mmol, 1.5 eq) and 2-bromo-3-chlorobenzaldehyde **20** (2.50 g, 11.4 mmol, 1.0 eq). Column chromatography (100% petroleum ether) afforded alkenyl bromide **40** (2.09 g, 62%, *Z*:*E* 10:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3080, 3017, 2918, 1607, 1579, 1551, 1388, 1316, 1268, 1170, 1029; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* 2.5, Ar*H*), 7.53 (1H, d, *J* 8.5, Ar*H*), 7.19 (1H, dd, *J* 8.5 and 2.5, Ar*H*), 7.14 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.65 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 136.6, 133.7, 133.0, 131.3, 130.3, 129.6, 121.5, 110.6; *m/z* HRMS (FI$^+$) 295.8408 ([M$^+$], $C_8H_5{}^{81}Br^{79}Br^{35}Cl$ requires 295.8425). Data in accordance with the literature.[56]

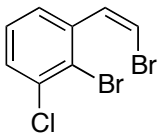
(*Z*)-2-Bromo-1-(2-bromovinyl)-4-chlorobenzene, 41



Prepared following general procedure A using potassium *tert*-butoxide (0.67 g, 6.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.60 g, 6.0 mmol, 1.2 eq) and 2-bromo-4-chlorobenzaldehyde **21** (1.10 g, 5.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) afforded alkenyl bromide **41** (0.77 g, 52%,

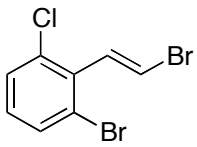
Z:*E* 10:1) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3010, 2987, 1625, 1581, 1547, 1463, 1318, 1102, 1038; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.74 (1H, d, *J* 8.5, Ar*H*), 7.63 (1H, d, *J* 2.0, Ar*H*), 7.34 (1H, dd, *J* 8.5 and 2.0, Ar*H*), 7.15 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.62 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 134.5, 132.3, 131.3, 131.1, 127.3, 124.1, 110.0, 109.8; *m/z* HRMS (FI^+) 295.8495 ([M^+], $C_8H_5{}^{81}Br^{79}Br^{35}Cl$ requires 295.8425). Data in accordance with the literature.[56]

(*Z*)-2-Bromo-1-(2-bromovinyl)-3-chlorobenzene, 42



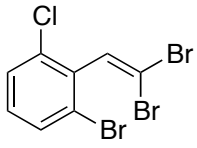
Prepared following general procedure A using potassium *tert*-butoxide (0.77 g, 6.85 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (3.00 g, 6.85 mmol, 1.5 eq) and 2-bromo-3-chlorobenzaldehyde **25** (1.00 g, 4.57 mmol, 1.0 eq). Column chromatography (100% petroleum ether) afforded alkenyl bromide **42** (0.57 g, 42%, *Z*:*E* 10:1) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3015, 2919, 1623, 1576, 1444, 1316, 1154, 1032, 948; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.61-7.59 (1H, m, Ar*H*), 7.46-7.44 (1H, m, Ar*H*), 7.31-7.27 (1H, m, Ar*H*), 7.21 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.63 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 135.2, 132.8, 131.2, 129.8, 128.7, 127.6, 123.6, 110.2; *m/z* HRMS (FI^+) 295.8436 ([M^+], $C_8H_5{}^{81}Br^{79}Br^{35}Cl$ requires 295.8425). Data in accordance with the literature.[56]

(*E*)-1-Bromo-2-(2-bromovinyl)-3-chlorobenzene, 43



Prepared following general procedure A using potassium *tert*-butoxide (0.76 g, 6.75 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (2.94 g, 6.75 mmol, 1.5 eq) and 2-bromo-6-chlorobenzaldehyde **26** (1.00 g, 4.50 mmol, 1.0 eq). Column chromatography (100% petroleum ether) afforded alkenyl bromide **43** (0.74 g, 56%, *E*:*Z* >20:1) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3012, 2980, 1605, 1578, 1377, 1145, 1061; (*E*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.52 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.38 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.13 (1H, d, *J* 14.0, ArC*H*=CHBr), 7.08 (1H, t, *J* 8.0, Ar*H*), 6.89 (1H, d, *J* 14.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 133.9, 132.8, 131.8, 129.4, 129.2, 124.0, 114.5, 111.3; *m/z* HRMS (FI$^+$) 295.8415 ([M$^+$], $C_8H_5{}^{81}Br^{79}Br^{35}Cl$ requires 295.8425). Data in accordance with the literature.[56]

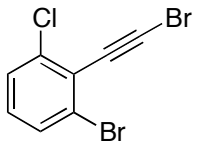
1-Bromo-3-chloro-2-(2,2-dibromovinyl)benzene, 44



A solution of tri*iso*propyl phosphite (7.64 mL, 31.0 mmol, 2.2 eq) in DCM (10 mL) was added over 1 h using a syringe pump to a solution of 2-bromo-6-chlorobenzaldehyde **26** (3.1 g, 14.0 mmol, 1.0 eq) and carbon tetrabromide (7.0 g,

21.0 mmol, 1.5 eq) in DCM (50 mL) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred for 2 h before being cooled to 0 °C and slowly quenched with sat. $NaHCO_{3(aq)}$ (30 mL). The reaction mixture was diluted with water (30 mL). The resulting biphasic mixture was separated and the organic phase washed with brine (2 × 30 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (100% petroleum ether) yielded *tribromide* **44** (3.8 g, 72%) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3018, 2924, 1614, 1573, 1425, 1189, 1082, 968; δ_H (400 MHz, $CDCl_3$) 7.53 (1H, ap. d, *J* 8.0, Ar*H*), 7.40 (1H, ap. d, *J* 8.0, Ar*H*), 7.31 (1H, s, ArC*H*=CBr_2), 7.17 (1H, t, *J* 8.0, Ar*H*); δ_C (100 MHz, $CDCl_3$) 136.1, 134.9, 134.2, 131.1, 130.3, 128.6, 123.8, 96.9; *m/z* HRMS (FI^+) 375.7666 ([M^+], $C_8H_4{}^{81}Br{}^{81}Br{}^{79}Br{}^{35}Cl$ requires 375.7609).

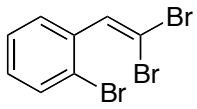
1-Bromo-2-(bromoethynyl)-3-chlorobenzene, 45



Prepared according to a literature procedure.[140] A solution of potassium hydroxide (13.5 g) in water (10 mL) was added drop-wise to a solution of 1-bromo-3-chloro-2-(2,2-dibromovinyl)benzene **44** (1.9 g, 5.0 mmol, 1.0 eq) and benzyltriethylammonium chloride (0.6 g, 2.5 mmol, 0.5 eq) in DCM (20 mL) at 0 °C. The resulting biphasic reaction mixture was stirred rapidly for 1 h at this temperature before being diluted with further DCM (30 mL) and water (40 mL). The mixture was separated and the organic phase washed with brine (2 × 50 mL) before being dried ($MgSO_4$) and

concentrated *in vacuo*. Column chromatography (100% petroleum ether) afforded *bromoalkyne* **45** (1.26 g, 86%) as an orange solid: mp 59-61 °C; ν_{max} (neat)/cm^{-1} 3070, 2924, 2197, 1547, 1436, 1192; δ_H (400 MHz, $CDCl_3$) 7.50 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.36 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.11 (1H, t, *J* 8.0, Ar*H*); δ_C (100 MHz, $CDCl_3$) 137.9, 130.7, 129.7, 128.1, 127.0, 124.7, 76.3, 60.6; *m/z* HRMS (FI^+) 293.8277 ([M^+], $C_8H_3{}^{81}Br^{79}Br^{35}Cl$ requires 293.8268).

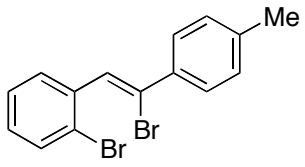
1-Bromo-2-(2,2-dibromovinyl)benzene, 46



A solution of tri*iso*propyl phosphite (6.5 mL, 27.5 mmol, 2.2 eq) in DCM (10 mL) was added over 1 h using a syringe pump to a solution of 2-bromobenzaldehyde (1.46 g, 12.5 mmol, 1.0 eq) and carbon tetrabromide (6.23 g, 18.8 mmol, 1.5 eq) in DCM (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h before being cooled to 0 °C and slowly quenched with sat. $NaHCO_{3(aq)}$ (30 mL). The reaction mixture was diluted with water (30 mL) and the resulting biphasic mixture separated. The organic phase was washed with brine (2 × 50 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (100% petroleum ether) yielded tribromide **46** (3.80 g, 87 %) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3066, 3019, 2953, 1606, 1586, 1463, 1428, 1317, 1277, 1161, 1046; δ_H (400 MHz, $CDCl_3$) 7.62-7.59 (2H, m, 2 × Ar*H*), 7.53 (1H, br. s, ArC*H*=CBr_2), 7.37-7.33 (1H, m, Ar*H*), 7.24-7.20 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 136.7, 136.1,

132.7, 130.4, 129.9, 127.2, 123.1, 93.0; *m/z* HRMS (FI^+) 339.7851 ($[M^+]$, $C_8H_5{}^{81}Br^{79}Br^{79}Br$ requires 339.7921). Data in accordance with the literature.[53]

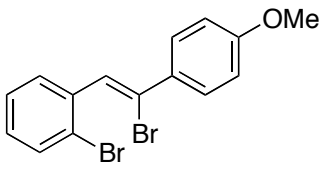
(*Z*)-1-Bromo-2-(2-bromo-2-(*p*-tolyl)vinyl)benzene, 47



Prepared according to a literature procedure.[53] *p*-Tolylboronic acid (0.75 g, 5.5 mmol, 1.1 eq), $Pd_2(dba)_3$ (120 mg, 0.125 mmol, 0.025 eq) and $P(2\text{-fur})_3$ (180 mg, 0.75 mmol, 0.15 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before degassed DME (25 mL), degassed $Na_2CO_{3(aq)}$ (1 M, 10.0 mL, 10.0 mmol, 2.0 eq) and 1-bromo-2-(2,2-dibromovinyl)benzene **46** (1.7 g, 5.0 mmol, 1.0 eq) were added. The reaction mixture was stirred in a pre-heated oil bath at 70 °C for 4 h. After cooling to room temperature, the resulting suspension was partitioned between water (50 mL) and diethyl ether (50 mL). The phases were separated and the aqueous phase extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (100% hexane) yielded alkenyl bromide **47** (1.02 g, 58%, *Z*:*E* >20:1) as an off-white solid: mp 44-46 °C; ν_{max} (neat)/cm^{-1} 3025, 3010, 2919, 1623, 1561, 1462, 1407, 1310, 1183; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 7.5, Ar*H*), 7.64-7.60 (3H, m, 3 × Ar*H*), 7.38 (1H, t, *J* 7.5, Ar*H*), 7.24-7.18 (4H, m, ArC*H*=C and 3 × Ar*H*), 2.41 (3H, s ArCH_3); δ_C (100 MHz, $CDCl_3$) 139.2, 137.3, 137.2, 132.4, 131.0, 129.2, 129.1, 128.7, 127.8, 127.0, 126.9, 124.2,

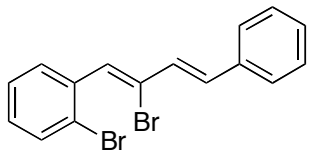
21.2; *m/z* HRMS (FI^+) 351.9297 ([M^+], $C_{15}H_{12}{}^{81}Br^{79}Br$ requires 351.9286). Data in accordance with the literature.[62]

(*Z*)-1-Bromo-2-(2-bromo-2-(4-methoxyphenyl)vinyl)benzene, 48



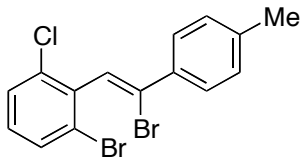
Prepared as for (*Z*)-1-bromo-2-(2-bromo-2-(*p*-tolyl)vinyl)benzene **47** using 4-methoxyphenylboronic acid (0.8 g, 5.5 mmol, 1.1 eq) and 1-bromo-2-(2,2-dibromovinyl)benzene **46** (1.7 g, 5.0 mmol, 1.0 eq). Column chromatography (100% hexane) afforded alkenyl bromide **48** (0.96 g, 52%, *Z*:*E* >20:1) as a yellow solid: mp 75–77 °C; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, d, *J* 8.0, Ar*H*), 7.67 (2H, d, *J* 9.0, 2 × Ar*H*), 7.63 (1H, ap. d, *J* 8.0, Ar*H*), 7.37 (1H, t, *J* 7.5, Ar*H*), 7.21 (1H, d, *J* 8.0, Ar*H*), 7.19 (1H, s, ArC*H*=C), 6.94 (2H, d, *J* 9.0, 2 × Ar*H*), 3.87 (3H, s, ArOCH_3); δ_C (100 MHz, $CDCl_3$) 160.3, 137.3, 132.6, 132.4, 131.1, 129.3, 128.7, 127.9, 126.9, 126.7, 124.2, 113.7, 55.4; *m/z* HRMS (FI^+) 367.9341 ([M^+], $C_{15}H_{12}O^{81}Br^{79}Br$ requires 367.9235). Data in accordance with the literature.[53]

1-Bromo-2-((1*Z*,3*E*)-2-bromo-4-phenylbuta-1,3-dien-1-yl)benzene, 49



Prepared as for (*Z*)-1-bromo-2-(2-bromo-2-(*p*-tolyl)vinyl)benzene **47** using (*E*)-2-phenylvinylboronic acid (0.7 g, 4.6 mmol, 1.1 eq) and 1-bromo-2-(2,2-dibromovinyl)benzene **46** (1.42 g, 4.2 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **49** (1.15 g, 75%, *Z*:*E* >20:1) as a yellow solid: mp 73–75 °C; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.63 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.53 (2H, ap. d, *J* 7.5, 2 × Ar*H*), 7.41-7.31 (4H, m, 4 × Ar*H*), 7.22-7.13 (3H, m, Ar*H*, ArC*H*=CBr and CH=C*H*Ph), 7.00 (1H, d, *J* 15.0, C*H*=CHPh); δ_C (100 MHz, $CDCl_3$) 136.4, 136.2, 135.1, 132.5, 131.5, 131.3, 129.4, 128.2, 128.4, 128.3, 127.2, 126.8, 126.1, 124.3; *m/z* HRMS (FI^+) 363.9294 ([M^+], $C_{16}H_{12}{}^{81}Br^{79}Br$ requires 363.9286). Data in accordance with the literature.[61]

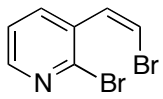
(*Z*)-1-Bromo-2-(2-bromo-2-(*p*-tolyl)vinyl)-3-chlorobenzene, 50



Prepared as for (*Z*)-1-bromo-2-(2-bromo-2-(*p*-tolyl)vinyl)benzene **47** using *p*-tolyl boronic acid (0.8 g, 5.5 mmol, 1.1 eq) and 1-bromo-3-chloro-2-(2,2-

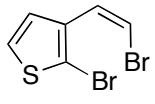
dibromovinyl)benzene **44** (1.88 g, 5.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded *alkenyl bromide* **50** (0.6 g, 30%, *Z*:*E* >20:1) as a yellow solid: mp 79-80 °C; ν_{max} (neat)/cm^{-1} 3025, 2919, 2867, 1609, 1550, 1424, 1378, 1233, 1187, 1123, 1037; δ_H (400 MHz, $CDCl_3$) 7.66-7.64 (2H, m, 2 × Ar*H*), 7.57 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.43 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.25-7.23 (2H, m, 2 × Ar*H*), 7.16 (1H, td, *J* 8.0 and 0.5, Ar*H*), 7.07 (1H, s, ArC*H*=CArBr), 2.42 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 139.6, 137.4, 136.2, 131.7, 131.2, 130.7, 129.6, 129.4, 129.1, 127.7, 126.7, 124.6, 21.3; *m/z* HRMS (FI$^+$) 385.8895 ([M$^+$], $C_{15}H_{11}{}^{81}Br^{79}Br^{35}Cl$ requires 385.8913).

(*Z*)-2-Bromo-3-(2-bromovinyl)pyridine, 51



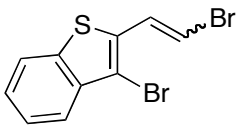
Prepared following general procedure A using potassium *tert*-butoxide (1.80 g, 20.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (7.00 g, 20.0 mmol, 1.2 eq) and 2-bromonicotinaldehyde (3.10 g, 16.5 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **51** (2.78 g, 63%, *Z*:*E* 9:1) as a yellow oil: ν_{max} (neat)/cm^{-1} 3073, 2922, 1682, 1616, 1572, 1550, 1386, 1319, 1185, 1120, 1053; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 8.30 (1H, dd, *J* 4.0 and 2.0, Ar*H*) 8.10 (1H, dd, *J* 4.0 and 2.0, Ar*H*), 7.33-7.29 (1H, m, Ar*H*), 7.16 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.69 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 149.3, 143.1, 138.6, 132.6, 130.3, 122.3, 111.3; *m/z* HRMS (FI$^+$) 262.8731 ([M$^+$], $C_7H_5N^{81}Br^{79}Br$ requires 262.8768). Data in accordance with the literature.[61]

(*Z*)-3-Bromo-2-(2-bromovinyl)thiophene, 52



Prepared following general procedure A using potassium *tert*-butoxide (0.9 g, 7.9 mmol, 1.5 eq), (bromomethyl)triphenylphosphonium bromide (3.4 g, 7.9 mmol, 1.5 eq) and 2-bromonicotinaldehyde (1.0 g, 5.2 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded *alkenyl bromide* **52** (0.90 g, 62%, *Z*:*E* 5:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3084, 2916, 1610, 1589, 1484, 1348, 1247, 1146, 1012; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d, *J* 8.0, ArC*H*=CHBr), 7.41 (1H, d, *J* 5.0, Ar*H*), 7.07 (1H, d, *J* 5.0, Ar*H*), 6.49 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 130.7, 129.5, 126.7, 125.0, 114.3, 106.5; *m*/*z* HRMS (FI$^+$) 267.8387 ([M$^+$], $C_6H_4S^{81}Br^{79}Br$ requires 267.8380).

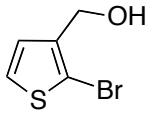
3-Bromo-2-(2-bromovinyl)benzo[*b*]thiophene, 53



Prepared following general procedure A using potassium *tert*-butoxide (0.6 g, 5.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.0 mmol, 1.2 eq) and 3-bromobenzo[*b*]thiophene-2-carbaldehyde (1.0 g, 4.2 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded *alkenyl bromide* **53** (0.80 g, 61%, *Z*:*E* 1:1) as an off-white solid: mp 72-74 °C; ν_{max} (neat)/cm^{-1} 3027, 3005, 2970, 1639,

1555, 1477, 1366, 1313, 1253, 1141, 1066; (*Z*)- and (*E*)-isomers: δ_H (400 MHz, $CDCl_3$) 7.88-7.86 (1H, m, Ar*H*), 7.84-7.82 (1H, m, Ar*H*), 7.80-7.78 (1H, m, Ar*H*), 7.74-7.72 (1H, m, Ar*H*), 7.69 (1H, d, *J* 8.0, ArC*H*=CHBr (*Z*)-isomer), 7.50 (1H, d, *J* 14.0, ArC*H*=CHBr (*E*)-isomer), 7.47-7.40 (4H, m, 4 × Ar*H*), 6.89 (1H, d, *J* 14.0, ArCH=C*H*Br (*E*)-isomer), 6.64 (1H, d, *J* 8.0, ArCH=C*H*Br (*Z*)-isomer); δ_C (100 MHz, $CDCl_3$) 138.2, 138.0, 136.9, 136.5, 134.4, 132.9, 129.6 (2 × C), 126.5, 126.4, 125.8, 125.5, 125.3, 123.5, 123.3, 122.3, 111.9, 110.2, 108.8, 108.4; *m/z* HRMS (FI^+) 317.8399 ($[M^+]$, $C_{10}H_6S^{81}Br^{79}Br$ requires 317.8436).

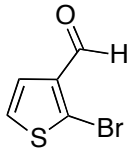
(2-Bromothiophen-3-yl)methanol



2-Bromothiophene-3-carboxylic acid methyl ester (2.00 g, 9.0 mmol, 1.0 eq) was added to a solution of lithium aluminium hydride (0.68 g, 18.0 mmol, 2.0 eq) in THF (40 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, before being warmed to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched *via* drop-wise addition of water (0.5 mL), before $NaOH_{(aq)}$ (5 M, 0.5 mL) and then a further portion of water (1.5 mL) were added. The reaction mixture was filtered through a pad of Celite® and the filtrate concentrated *in vacuo* to yield the desired alcohol (1.62 g, 93%) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3332, 3005, 2930, 1520, 1347, 1155, 1010; δ_H (400 MHz, $CDCl_3$) 7.25 (1H, d, *J* 5.5, Ar*H*), 6.95 (1H, d, *J* 5.5, Ar*H*), 4.76 (2H, s, C*H*$_2$OH), 2.78 (1H, br. s, O*H*); δ_C (100 MHz,

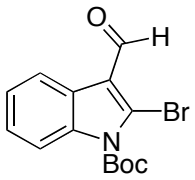
$CDCl_3$) 138.3, 130.1, 125.4, 108.8, 59.0; *m/z* HRMS (FI^+) 193.9256 ([M^+], $C_5H_5OS^{81}Br$ requires 193.9223). Data in accordance with the literature.[141]

2-Bromothiophene-3-carbaldehyde



(2-Bromothiophen-3-yl)methanol (1.00 g, 5.2 mmol, 1.0 eq) was added to a solution of pyridinium chlorochromate (1.24 g, 5.72 mmol, 1.1 eq) in DCM (8 mL) over molecular sieves (4 Å, 700 mg). The resulting mixture was allowed to stir for 16 h at room temperature before being filtered through a pad of Celite®. The pad was washed with DCM (50 mL) and the filtrate concentrated *in vacuo* before column chromatography (10% diethyl ether in petroleum ether) yielded the desired aldehyde (0.56 g, 56%) as an orange oil: ν_{max} (neat)/cm^{-1} 3019, 2945, 1658, 1496, 1415, 1210, 887; δ_H (400 MHz, $CDCl_3$) 9.98 (1H, s, CO*H*), 7.72 (1H, d, *J* 5.0, Ar*H*), 7.15 (1H, d, *J* 5.0, Ar*H*); δ_C (100 MHz, $CDCl_3$) 183.0, 136.9, 134.8, 132.0, 120.3; *m/z* HRMS (FI^+) 191.9061 ([M^+], $C_5H_3OS^{79}Br$ requires 191.9067). Data in accordance with the literature.[142]

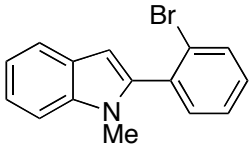
tert-Butyl 2-bromo-3-formyl-1*H*-indole-1-carboxylate, 54



Phosphorous oxybromide (11.1 g, 36.6 mmol, 2.4 eq) in DCM (20 mL) was added drop-wise to a solution of DMF (3.6 mL, 46.0 mmol, 3.0 eq) in DCM (12 mL) at 0 °C. The resulting thick, white mixture was heated to reflux for 15 min before 2-oxindole (2.05 g, 15.4 mmol, 1.0 eq) was added portion-wise. The mixture was allowed to stir for 1 h at reflux. The reaction was allowed to cool, quenched with the addition of crushed ice and allowed for stir for a further 20 min. The resulting biphasic mixture was separated, and the aqueous layer neutralised with solid potassium carbonate. Upon neutralisation, a precipitate appeared. The suspension was filtered and the residue was washed with cold water (50 mL) and cold DCM (50 mL). The solid was then triturated with acetone (50 mL) and filtered. The filtrate was concentrated *in vacuo* and the pale yellow solid obtained was suspended in acetonitrile (15 mL). Di-*tert*-butyl dicarbonate (4.02 g, 5.36 mmol, 1.2 eq), *N*,*N*'-dimethylamino pyridine (0.19 g, 1.52 mmol, 0.1 eq) and triethylamine (2.6 mL, 5.4 mmol, 1.2 eq) were added and the resulting solution allowed to stir for 16 h at room temperature. Water (20 mL) was added and the phases separated. The aqueous phase was extracted with DCM (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and the concentrated *in vacuo*. Column chromatography (5% ethyl acetate in petroleum ether) yielded *aldehyde* **54** (3.10 g, 62%) as a pale yellow solid: mp 120-121 °C; ν_{max} (neat)/cm^{-1} 3014, 2984, 1662, 1441, 1382, 1305, 1133, 1104; δ_H (400 MHz, $CDCl_3$) 10.19 (1H, s, CO*H*), 8.33-8.28 (1H, m, Ar*H*), 8.05-8.00 (1H, m, Ar*H*),

7.38-7.32 (2H, m, 2 × Ar*H*), 1.74 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 187.4, 148.1, 136.6, 125.8, 125.5, 124.8, 122.4, 120.9, 119.8, 114.7, 86.9, 28.1; *m/z* LRMS (ESI$^+$) 673.1 ($^{81}Br^{81}Br$, [(2M+Na)$^+$], 50%), 671.1 ($^{81}Br^{79}Br$, [(2M+Na)$^+$], 100%), 669.1 ($^{79}Br^{79}Br$, [(2M+Na)$^+$], 50%); HRMS (ESI$^+$) 348.0024 ([(M+Na)$^+$], $C_{14}H_{14}O_3N^{81}BrNa$ requires 348.0029).

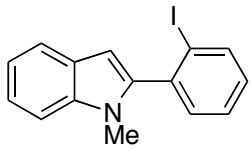
2-(2-Bromophenyl)-1-methyl-1*H*-indole, 55



Prepared according to a literature procedure.[143] 2-Bromoacetophenone (1.31 mL, 10.0 mmol, 1.0 eq) was added to a solution of *N*-methylphenylhydrazine (1.30 mL, 11.0 mmol, 1.1 eq) in phosphoric acid (85%, 5 mL) and the resulting reaction mixture allowed to stir at room temperature for 30 min. Polyphosphoric acid (25.0 g) was added and the viscous solution obtained was heated to 120 °C and stirred for 1 h. After cooling to room temperature, the crude reaction mixture was poured into ice water (150 mL) and resulting aqueous phase extracted with diethyl ether (3 × 150 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% ethyl acetate in petroleum ether) afforded indole **55** (1.24 g, 51%) as a pale yellow solid: mp 87-88 °C; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, dm, *J* 8.0, Ar*H*), 7.70 (1H, dm, *J* 8.0, Ar*H*), 7.46-7.39 (3H, m, 3 × Ar*H*), 7.36-7.28 (2H, m, 2 × Ar*H*), 7.21-7.17 (1H, m, Ar*H*), 6.55 (1H, d, *J* 1.0, C*H*C(Ar)NMe), 3.61 (3H, s, NC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 139.7, 137.3, 134.3, 132.9, 132.8, 130.1, 127.6,

127.2, 125.2, 121.8, 120.7, 119.8, 109.5, 102.1, 30.7; *m/z* LRMS (ESI^+) 288.0 (^{81}Br, [$(M+H)^+$], 100%), 286.0 (^{79}Br, [$(M+H)^+$], 90%). Data in accordance with the literature.[143]

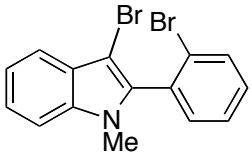
2-(2-Iodophenyl)-1-methyl-1*H*-indole, 56



Prepared according to a literature procedure.[143] 2-Iodoacetophenone (1.43 mL, 10.0 mmol, 1.0 eq) was added to a solution of *N*-methylphenylhydrazine (1.41 mL, 12.0 mmol, 1.2 eq) in phosphoric acid (85%, 5 mL) and the resulting reaction mixture allowed to stir at room temperature for 30 min. Polyphosphoric acid (25.0 g) was added and the viscous solution obtained was heated to 120 °C and stirred for 1 h. After cooling to room temperature, the crude reaction mixture was poured into ice water (150 mL) and resulting aqueous phase extracted with diethyl ether (3 × 150 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% ethyl acetate in petroleum ether) afforded *indole* **56** (1.05 g, 32%) as a pale yellow solid: mp 82-84 °C; ν_{max} (neat)/cm^{-1} 3049, 2962, 2932, 1556, 1427, 1310, 1238, 1130, 1055, 1017; δ_H (400 MHz, $CDCl_3$) 8.00 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.70 (1H, ap. d, *J* 8.0, Ar*H*), 7.46 (1H, td, *J* 7.5 and 1.0, Ar*H*), 7.42-7.40 (1H, m, Ar*H*), 7.39-7.37 (1H, m, Ar*H*), 7.32-7.28 (1H, m, Ar*H*), 7.21-7.14 (2H, m, 2 × Ar*H*), 6.51 (1H, d, *J* 0.5, C*H*C(Ar)NMe), 3.57 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 142.5, 139.0, 138.5, 137.1, 131.9, 130.1, 127.9, 127.6, 121.8, 120.8, 119.8,

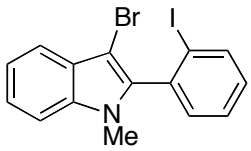
109.6, 101.9, 101.4, 30.8; *m/z* LRMS (ESI^+) 334.0 ([$(M+H)^+$], 100%); HRMS (ESI^+) 334.0087 ([$(M+H)^+$], $C_{15}H_{13}NI$ requires 334.0087).

3-Bromo-2-(2-bromophenyl)-1-methyl-1*H*-indole, 57



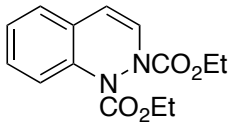
A solution of *N*-bromosuccinimide (370 mg, 2.1 mmol, 1.05 eq) in DMF (2 mL) was added drop-wise to a solution of indole **55** (560 mg, 2.0 mmol, 1.0 eq) in DMF (4 mL) at room temperature. The resulting mixture was allowed to stir for 2 h. After this time, water (15 mL) was added and the resulting aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2.5% ethyl acetate in petroleum ether) afforded *indole* **57** (0.61 g, 84%) as a pale yellow solid: mp 106-107 °C; ν_{max} (neat)/cm^{-1} 3016, 2975, 2954, 1543, 1388, 1134, 1057; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dm, *J* 8.0, Ar*H*), 7.65 (1H, dm, *J* 8.0, Ar*H*), 7.50-7.38 (4H, m, 4 × Ar*H*), 7.34 (1H, td, *J* 8.0 and 1.0, Ar*H*), 7.28-7.24 (1H, m, Ar*H*), 3.59 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 137.1, 136.3, 133.3, 132.9, 132.2, 130.9, 127.4, 126.8, 125.5, 122.9, 120.5, 119.4, 109.7, 93.6, 31.3; *m/z* HRMS (FI^+) 364.9276 ([M^+], $C_{15}H_{11}{}^{81}Br^{79}BrN$, requires 364.9238).

3-Bromo-2-(2-iodophenyl)-1-methyl-1*H*-indole, 58



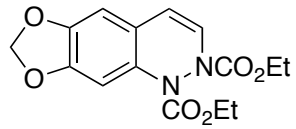
A solution of *N*-bromosuccinimide (430 mg, 2.4 mmol, 1.2 eq) in DMF (2 mL) was added drop-wise to a solution of indole **56** (670 mg, 2.0 mmol, 1.0 eq) in DMF (4 mL) at room temperature. The resulting mixture was allowed to stir for 2 h. After this time, water (15 mL) was added and the resulting aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2% ethyl acetate in petroleum ether) afforded *indole* **58** (0.73 g, 89%) as a pale yellow solid: mp 102-103 °C; ν_{max} (neat)/cm^{-1} 3087, 2967, 2953, 1523, 1367, 1233, 1068; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, ddd, *J* 8.0, 1.0 and 0.5, Ar*H*), 7.66-7.64 (1H, m, Ar*H*), 7.51 (1H, td, *J* 7.5 and 1.0, Ar*H*), 7.41-7.32 (3H, m, 3 × Ar*H*), 7.28-7.20 (2H, m, 2 × Ar*H*), 3.56 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 139.2, 136.5, 136.1, 132.3, 130.8, 128.3, 128.18, 128.15, 126.7, 123.0, 120.5, 119.5, 109.7, 90.6, 31.4; *m/z* LRMS (ESI^+) 435.9 (^{81}Br, [$(M+Na)^+$], 50%), 433.9 (^{79}Br, [$(M+Na)^+$], 50%), 413.9 (^{81}Br, [$(M+H)^+$], 100%), 411.9 (^{79}Br, [$(M+H)^+$], 90%); HRMS (ESI^+) 435.8978 ([$(M+Na)^+$], $C_{15}H_{11}N^{81}BrINa$ requires 435.8992).

Diethyl dihydrocinnoline-1,2-dicarboxylate, 59



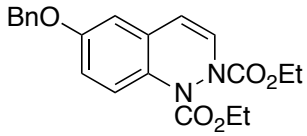
Prepared following general procedure B using (*Z*)-1-chloro-2-(2-bromovinyl)benzene **34** (174 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **59** (130 mg, 59%) as a white solid: mp 59-61 °C; ν_{max} (neat)/cm^{-1} 2985, 2940, 2911, 1737, 1714, 1675, 1630, 1338, 1243, 1045; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.39-7.26 (4H, m, 4 × Ar*H*), 7.16 (1H, d, *J* 7.0, ArCH=C*H*N), 6.31 (1H, d, *J* 7.0, ArC*H*=CHN), 4.25-4.18 (4H, m, 2 × CH_2CH_3), 1.27 (3H, t, *J* 7.0, CH_2CH_3), 1.21 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.4, 152.5, 136.3, 130.1, 128.3, 127.8 (2 × C), 125.8, 125.3, 112.5, 63.9, 63.5, 15.1, 14.9; *m/z* LRMS (ESI^+) 575.3 ([$(2M+Na)^+$], 100%), 299.1 ([$(M+Na)^+$], 20%); HRMS (ESI^+) 299.0999 ([$(M+Na)^+$], $C_{14}H_{16}N_2O_4Na$ requires 299.1002).

Diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate, 60



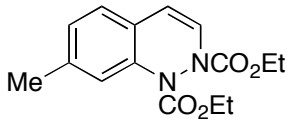
Prepared following general procedure B using 5-bromo-6-(2-bromovinyl)benzo[*d*][1,3]dioxole **27** (246 mg, 0.8 mmol, 1.0 eq). Column chromatography (15% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **60** (234 mg, 91%) as a yellow solid: mp 118-119 °C; ν_{max} (neat)/cm^{-1} 3033, 2995, 2965, 1788, 1661, 1575, 1466, 1254, 1130, 938; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.03 (1H, d, *J* 7.0, ArCH=C*H*N), 6.93 (1H, s, Ar*H*), 6.83 (1H, s, Ar*H*), 6.21 (1H, d, *J* 7.0, ArC*H*=CHN), 6.07 (1H, s, OC*H*H'O), 6.03 (1H, s, OCH*H*'O), 4.24-4.17 (4H, m, 2 × CH_2CH$_3$), 1.26 (3H, t, *J* 7.0, CH$_2$CH_3), 1.21 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.7, 152.6, 147.3, 147.0, 130.4, 128.0, 122.0, 112.8, 106.8, 105.4, 102.5, 63.9, 63.4, 15.1, 14.9; *m/z* LRMS (ESI$^+$) 663.2 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 343.0901 ([(M+Na)$^+$], $C_{15}H_{16}N_2O_6Na$ requires 343.0901).

Diethyl 6-(benzyloxy)dihydrocinnoline-1,2-dicarboxylate, 61



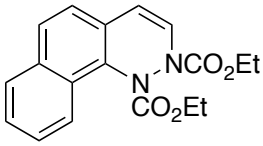
Prepared following general procedure B using (*Z*)-4-(benzyloxy)-1-bromo-2-(2-bromovinyl)benzene **28** (294 mg, 0.8 mmol, 1.0 eq). Column chromatography (10% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **61** (262 mg, 86%) as a yellow gum: ν_{max} (neat)/cm^{-1} 2982, 2935, 2910, 1720, 1622, 1606, 1372, 1238, 1125, 1016; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.47-7.45 (2H, m, 2 × Ar*H*), 7.41-7.38 (2H, m, 2 × Ar*H*), 7.35-7.32 (1H, m, Ar*H*), 7.28 (1H, d, *J* 8.5, Ar*H*), 7.17 (1H, d, *J* 7.0, ArCH=C*H*N), 6.97-6.93 (2H, m, 2 × Ar*H*), 6.24 (1H, d, *J* 7.0, ArC*H*=CHN), 5.14 (2H, s, ArOCH_2Ph), 4.25-4.15 (4H, m, 2 × CH_2CH$_3$), 1.27 (3H, t, *J* 7.0, CH$_2$CH_3), 1.20 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 158.1, 155.8, 152.4, 137.9, 130.3, 129.7, 129.2, 128.9, 128.6, 128.4, 126.4, 115.0, 112.3, 111.9, 70.9, 63.8, 63.5, 15.1, 14.9; *m/z* LRMS (ESI$^+$) 787.3 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 405.1408 ([(M+Na)$^+$], $C_{21}H_{22}N_2O_5Na$ requires 405.1421).

Diethyl 7-methyldihydrocinnoline-1,2-dicarboxylate, 62



Prepared following general procedure B using (*Z*)-2-bromo-1-(2-bromo-vinyl)-4-methylbenzene **29** (140 μl, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **62** (186 mg, 80%) as a yellow solid: mp 61-64 °C; ν_{max} (neat)/cm^{-1} 3010, 2983, 2934, 1732, 1651, 1595, 1400, 1335, 1270, 1129; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.22 (1H, ap. br. s, Ar*H*), 7.14 (1H, d, *J* 7.0, ArCH=C*H*N), 7.10-7.08 (2H, m, 2 × Ar*H*), 6.27 (1H, d, *J* 7.0, ArC*H*=CHN), 4.25-4.18 (4H, m, 2 × CH_2CH$_3$), 2.36 (3H, s, ArCH_3), 1.28-1.20 (6H, m, 2 × CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.4, 152.6, 138.2, 136.4, 129.0, 128.4, 125.7, 125.6, 125.0, 112.6, 63.8, 63.4, 21.6, 15.0, 14.9; *m/z* LRMS (ESI$^+$) 603.2 ([(2M+H)$^+$], 100%), 313.1 ([(M+Na)$^+$], 70%), 291.2 ([(M+H$^+$], 15%); HRMS (ESI$^+$) 313.1158 ([(M+Na)$^+$], $C_{15}H_{18}N_2O_4Na$ requires 313.1164).

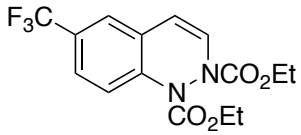
Diethyl benzo[*h*]dihydrocinnoline-1,2-dicarboxylate, 63



Prepared following general procedure B using (*Z*)-1-bromo-2-(2-bromovinyl)naphthalene **30** (250 mg, 0.8 mmol, 1.0 eq). Column chromatography

(5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **63** (190 mg, 73%) as a yellow solid: mp 130-131 °C; ν_{max} (neat)/cm^{-1} 3062, 2987, 2935, 1743, 1730, 1634, 1606, 1590, 1374, 1330, 1231, 1056; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 8.02 (1H, ap. d, *J* 8.5, Ar*H*), 7.93 (1H, ap. d, *J* 7.5, Ar*H*), 7.88 (1H, ap. d, *J* 8.5, Ar*H*), 7.63-7.59 (1H, m, Ar*H*), 7.54-7.53 (1H, m, Ar*H*), 7.46 (1H, ap. d, *J* 8.5, Ar*H*), 7.34 (1H, d, *J* 7.0, ArCH=C*H*N), 6.47 (1H, d, *J* 7.0, ArC*H*=CHN), 4.29-4.10 (4H, m, 2 × CH_2CH$_3$), 1.30 (3H, t, *J* 7.0, CH$_2$CH_3), 1.11 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 156.3, 152.4, 133.9, 131.0, 130.8, 129.2, 128.6, 128.4, 127.5, 126.8, 125.9, 124.2, 123.8, 112.3, 63.9, 63.6, 15.0, 14.9; *m/z* LRMS (ESI$^+$) 675.3 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 349.1153 ([(M+Na)$^+$], $C_{18}H_{18}N_2O_4Na$ requires 349.1159).

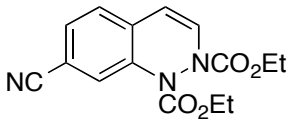
Diethyl 6-(trifluoromethyl)dihydrocinnoline-1,2-dicarboxylate, 64



Prepared following general procedure B using (*Z*)-1-bromo-2-(2-bromovinyl)-4-(trifluoromethyl)benzene **31** (264 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **64** (217 mg, 79%) as a yellow solid: mp 78-80 °C; ν_{max} (neat)/cm^{-1} 3052, 2991, 2943, 1739, 1725, 1621, 1579, 1317, 1203, 1114, 1047; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.67-7.65 (2H, m, 2 × Ar*H*), 7.60-7.58 (1H, m, Ar*H*), 7.28 (1H, d, *J* 7.0, ArCH=C*H*N), 6.45 (1H, d, *J* 7.0, ArC*H*=CHN), 4.27-4.20 (4H, m, 2 × CH_2CH$_3$),

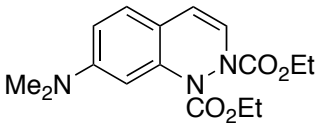
1.27-1.23 (3H, t, *J* 7.0, CH_2CH_3), 1.23 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.9, 152.3, 139.2, 131.8, 128.7, 128.6 (q, J_{CF} 32.0), 126.1, 125.0 (q, J_{CF} 3.5), 124.8 (q, J_{CF} 273.5), 122.8 (q, J_{CF} 4.0), 111.7, 64.3, 63.8, 15.0, 14.9; δ_F (375 MHz, $CDCl_3$) -61.0 (s) {^{1}H}; *m/z* LRMS (ESI^+) 711.2 ([$(2M+Na)^+$], 100%), 367.1 ([$(M+Na)^+$], 60%); HRMS (ESI^+) 367.0871 ([$(M+Na)^+$], $C_{15}H_{15}F_3N_2O_4Na$ requires 367.0876).

Diethyl 7-cyanodihydrocinnoline-1,2-dicarboxylate, 65



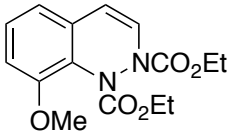
Prepared following general procedure B using (*Z*)-3-bromo-4-(2-bromovinyl)benzonitrile **32** (100 mg, 0.34 mmol, 1.0 eq). Column chromatography (10% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **65** (67 mg, 64%) as a white solid: mp 91-93 °C; ν_{max} (neat)/cm^{-1} 2950, 2935, 2228, 1732, 1630, 1593, 1399, 1295, 1094; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.76-7.75 (1H, m, Ar*H*), 7.69 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.46 (1H, d, *J* 8.0, Ar*H*), 7.37 (1H, d, *J* 7.5, ArCH=C*H*N), 6.39 (1H, d, *J* 7.5, ArC*H*=CHN), 4.28-4.21 (4H, m, 2 × CH_2CH_3), 1.28 (3H, t, *J* 7.0, CH_2CH_3), 1.22 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.1, 152.1, 136.1, 133.2, 132.6, 131.8, 128.8, 126.8, 118.9, 111.0, 110.6, 64.5, 63.9, 15.0, 14.8; *m/z* LRMS (ESI^+) 625.2 ([$(2M+Na)^+$], 100%); HRMS (ESI^+) found 324.0953 ([$(M+Na)^+$], $C_{15}H_{15}N_3O_4Na$ requires 324.0955).

Diethyl 7-(dimethylamino)dihydrocinnoline-1,2-dicarboxylate, 66



Prepared following general procedure B using (*Z*)-1-bromo-2-(2-bromovinyl)-3-chlorobenzene **36** (210 mg, 0.8 mmol, 1.0 eq). Column chromatography (10% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **66** (155 mg, 61%) as a yellow solid: mp 77-79 °C; ν_{max} (neat)/cm^{-1} 3062, 2990, 2908, 1741, 1618, 1550, 1372, 1240, 1130, 1020; δ_H (500 MHz, $C_6D_5CD_3$, 90 °C) 7.06 (1H, d, *J* 8.5, Ar*H*), 6.87 (1H, d, *J* 7.0, ArCH=C*H*N), 6.75 (1H, d, *J* 2.5, Ar*H*), 6.64 (1H, dd, *J* 8.5 and 2.5, Ar*H*), 6.18 (1H, d, *J* 7.0, ArC*H*=CHN), 4.23-4.16 (4H, m, 2 × CH_2CH$_3$), 2.95 (6H, s, N(CH_3)$_2$), 1.26 (3H, t, *J* 7.0, CH$_2$CH_3), 1.22 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $C_6D_5CD_3$, 90 °C) 155.4, 152.9, 151.1, 137.8, 126.5, 125.5, 116.2, 113.3, 111.6, 109.2, 63.6, 63.1, 41.3, 15.1, 14.9; *m/z* LRMS (ESI$^+$) 661.2 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 342.1413 ([(M+Na)$^+$], $C_{16}H_{21}N_3O_4Na$ requires 342.1424).

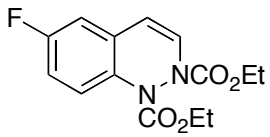
Diethyl 8-methoxydihydrocinnoline-1,2-dicarboxylate, 67



Prepared following general procedure B using (*Z*)-1-(2-bromovinyl)-2-chloro-3-methoxybenzene **37** (198 mg, 0.8 mmol, 1.0 eq). Column chromatography (10%

acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **67** (151 mg, 62%) as a yellow solid: mp 92-93 °C: ν_{max}(neat)/cm^{-1} 3006, 2989, 2942, 1744, 1704, 1621, 1601, 1571, 1332, 1262, 1044, 1009; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.26-7.23 (1H, m, Ar*H*), 7.18 (1H, d, *J* 7.0, ArCH=C*H*N), 7.02 (1H, dd, *J* 8.5 and 1.0, Ar*H*), 6.84 (1H, dd, *J* 7.5 and 1.0, Ar*H*), 6.25 (1H, d, *J* 7.0, ArC*H*=CHN), 4.24-4.07 (4H, m, 2 × CH_2CH$_3$), 3.86 (3H, s, ArOCH_3), 1.26 (3H, t, *J* 7.0, CH$_2$CH_3), 1.16 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.0, 152.2, 150.6, 128.8, 127.9, 127.3, 123.5, 116.2, 112.2, 110.2, 61.9, 61.6, 55.5, 13.3, 13.2; *m/z* LRMS (ESI$^+$) 635.3 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 329.1105 ([(M+Na)$^+$], $C_{15}H_{18}N_2O_5Na$ requires 329.1108).

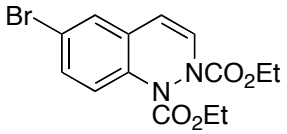
Diethyl 6-fluorodihydrocinnoline-1,2-dicarboxylate, 68



Prepared following general procedure B using 1-bromo-2-(2-bromo-vinyl)-4-fluoro-benzene **38** (235 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **68** (99 mg, 85%) as a yellow solid: mp 65-66 °C; ν_{max} (neat)/cm^{-1} 2984, 2912, 1731, 1627, 1586, 1486, 1398, 1283, 1139; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.41-7.38 (1H, m, Ar*H*), 7.25 (1H, d, *J* 7.5, ArC*H*=CHN), 7.14-7.11 (2H, m, 2 × Ar*H*), 6.30 (1H, d, *J* 7.5, ArCH=C*H*N), 4.27-4.19 (4H, m, 2 × CH_2CH$_3$), 1.29-1.19 (6H, m, 2 × CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 161.5 (d, J_{CF} 243.5), 155.6, 152.3, 132.3 (d, J_{CF} 2.5), 131.2, 129.9

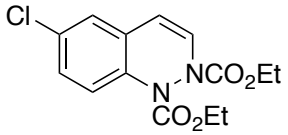
(d, J_{CF} 9.5), 127.3 (d, J_{CF} 9.0), 114.8 (d, J_{CF} 23.5), 112.1 (d, J_{CF} 24.5), 111.5 (d, J_{CF} 2.0), 64.0, 63.6, 15.0, 14.9; δ_F (375 MHz, $CDCl_3$) -114.7 (s) $\{^1H\}$; *m/z* LRMS (ESI^+) 611.2 ([$(2M+Na)^+$], 100%), 317.1 ([$(M+Na)^+$], 75%); HRMS (ESI^+) 317.0905 ([$(M+Na)^+$], $C_{14}H_{15}FN_2O_4Na$ requires 317.0908).

Diethyl 6-bromodihydrocinnoline-1,2-dicarboxylate, 69



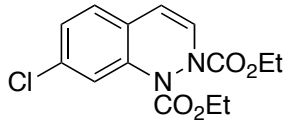
Prepared following general procedure B using (*Z*)-1,4-dibromo-2-(2-bromovinyl)benzene **39** (284 mg, 0.4 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **69** (93 mg, 65%) as a yellow solid: mp 82-84 °C; ν_{max} (neat)/cm^{-1} 2983, 2970, 1738, 1645, 1595, 1445, 1302, 1250, 1129, 1020; δ_H (250 MHz, $(CD_3)_2SO$, 90 °C) 7.48-7.44 (2H, m, 2 × Ar*H*), 7.31-7.28 (1H, m, Ar*H*), 7.22 (1H, d, *J* 7.0, ArCH=C*H*N), 6.29 (1H, d, *J* 7.0, ArC*H*=CHN), 4.27-4.13 (4H, m, 2 × CH_2CH_3), 1.27-1.16 (6H, m, 2 × CH_2CH_3); δ_C (62.5 MHz, $(CD_3)_2SO$, 90 °C) 155.2, 152.3, 135.3, 131.3, 130.9, 130.0, 128.3, 127.3, 120.4, 111.2, 64.1, 63.7, 15.0, 14.9; *m/z* LRMS (ESI^+) 735.1 ($^{81}Br^{81}Br$, [$(2M+Na)^+$], 50%), 733.1 ($^{81}Br^{79}Br$, [$(2M+Na)^+$], 100%), 731.1 ($^{79}Br^{79}Br$, [$(2M+Na)^+$], 60%), 379.1 (^{81}Br, [$(M+Na)^+$], 25%), 377.1 (^{79}Br, [$(M+Na)^+$], 25%); HRMS (ESI^+) 379.0086 ([$(M+Na)^+$], $C_{14}H_{15}{}^{81}BrN_2O_4Na$ requires 379.0088).

Diethyl 6-chlorodihydrocinnoline-1,2-dicarboxylate, 70



Prepared following general procedure B using (*Z*)-1-bromo-2-(2-bromovinyl)-4-chlorobenzene **40** (237 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **70** (193 mg, 78%) as a yellow solid: mp 71-73 °C; ν_{max} (neat)/cm^{-1} 3112, 2966, 1736, 1620, 1579, 1303, 1252, 1084; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.44 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.33 (1H, t, *J* 8.0, Ar*H*), 7.29-7.25 (2H, m, Ar*H* and ArCH=C*H*N), 6.35 (1H, d, *J* 7.0, ArC*H*=CHN), 4.28-4.14 (4H, m, 2 × CH_2CH$_3$), 1.28 (3H, t, *J* 7.0, CH$_2$CH_3), 1.19 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.3, 152.2, 132.9, 131.4, 130.8, 130.0, 129.6, 129.3, 124.5, 111.4, 64.2, 63.6, 15.0, 14.9; *m/z* LRMS (ESI$^+$) 643.2 (^{35}Cl^{35}Cl, [(2M+Na)$^+$], 100%), 333.1 (^{35}Cl, [(M+Na)$^+$], 30%); HRMS (ESI$^+$) 333.0610 ([(M+Na)$^+$], $C_{14}H_{15}{}^{35}ClN_2O_4Na$ requires 333.0613).

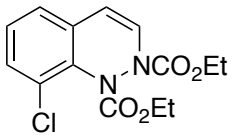
Diethyl 7-chlorodihydrocinnoline-1,2-dicarboxylate, 71



Prepared following general procedure B using (*Z*)-2-bromo-1-(2-bromovinyl)-4-chlorobenzene **41** (237 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone

in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **71** (202 mg, 81%) as a yellow solid: mp 80-81 °C; ν_{max} (neat)/cm^{-1} 3003, 2984, 1730, 1622, 1557, 1373, 1242, 1128, 1050; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.42-7.29 (3H, m, 3 × Ar*H*), 7.18 (1H, d, *J* 7.0, ArCH=C*H*N), 6.33 (1H, d, *J* 7.0, ArC*H*=CHN), 4.25-4.21 (4H, m, 2 × C*H*$_2$CH$_3$), 1.27 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.23 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.1, 152.4, 137.1, 132.3, 130.5, 127.9, 127.3, 126.8, 125.1, 111.8, 64.2, 63.7, 15.0, 14.9; *m/z* LRMS (ESI$^+$) 335.1 (^{37}Cl, [(M+Na)$^+$], 40%), 333.1 (^{35}Cl, [(M+Na)$^+$], 100%); HRMS (ESI$^+$) 333.0612 ([(M+Na)$^+$], $C_{14}H_{15}{}^{35}ClN_2O_4Na$ requires 333.0613).

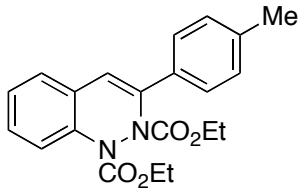
Diethyl 8-chlorodihydrocinnoline-1,2-dicarboxylate, 72



Prepared following general procedure B using (*Z*)-2-bromo-1-(2-bromovinyl)-3-chlorobenzene **42** (119 mg, 0.4 mmol, 1.0 eq). Column chromatography (10% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **72** (80 mg, 65%) as a yellow solid: mp 83-85 °C; ν_{max} (neat)/cm^{-1} 3084, 2985, 2937, 1744, 1731, 1645, 1615, 1426, 1316, 1168, 1030; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.43 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.34-7.31 (1H, m, Ar*H*), 7.29-7.26 (2H, m, Ar*H* and ArCH=C*H*N), 6.36 (1H, d, *J* 7.0, ArC*H*=CHN), 4.28-4.14 (4H, m, 2 × C*H*$_2$CH$_3$), 1.28 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.19 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.3, 152.3, 132.9, 131.4, 130.8, 130.0, 129.6, 129.3, 124.5, 111.4, 64.2, 63.6, 15.0, 14.8; *m/z*

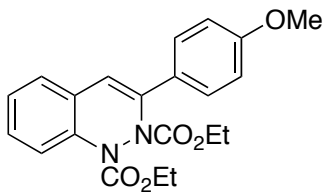
LRMS (ESI$^+$) 643.2 (^{35}Cl, ^{35}Cl, [(2M+Na)$^+$], 50%), 335.1 (^{37}Cl, [(M+Na)$^+$], 10%), 333.1 (^{35}Cl, [(M+Na)$^+$], 50%); HRMS (ESI$^+$) 333.0611 ([(M+Na)$^+$], $C_{14}H_{15}{}^{35}ClN_2O_4Na$ requires 333.0613).

Diethyl 3-(*p*-tolyl)dihydrocinnoline-1,2-dicarboxylate, 73



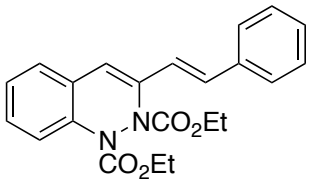
Prepared following general procedure B using (*Z*)-1-bromo-2-(2-bromo-2-(p-tolyl)vinyl)benzene **47** (141 mg, 0.4 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **73** (64 mg, 77%) as a white solid: mp 116-118 °C; ν_{max} (neat)/cm^{-1} 3015, 2995, 1730, 1658, 1516, 1458, 1316, 1171, 1053; δ_H (250 MHz, $(CD_3)_2SO$, 90 °C) 7.64 (2H, d, *J* 8.0, 2 × Ar*H*), 7.53 (1H, ap. d, *J* 8.0, Ar*H*), 7.41 (1H, td, *J* 7.5 and 1.5, Ar*H*), 7.35-7.29 (2H, m, 2 × Ar*H*), 7.25 (2H, d, *J* 8.0, 2 × Ar*H*), 6.96 (1H, s, ArC*H*=C), 4.31-4.20 (2H, m, CH_2CH$_3$), 4.02-3.93 (2H, m, CH_2CH$_3$), 2.35 (3H, s, ArCH_3), 1.27 (3H, t, *J* 7.0, CH$_2$CH_3), 0.95 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (62.5 MHz, $(CD_3)_2SO$, 90 °C) 154.6, 154.4, 141.9, 139.0, 137.1, 133.4, 129.8, 128.5, 127.7, 126.9, 126.8, 126.4, 123.7, 113.9, 63.6, 63.3, 21.6, 15.0, 14.6; *m/z* LRMS (ESI$^+$) 755.3 ([(2M+Na)$^+$], 100%), 389.2 ([(M+Na)$^+$], 100%); HRMS (ESI$^+$) 389.1467 ([(M+Na)$^+$], $C_{21}H_{22}N_2O_4Na$ requires 389.1472).

Diethyl 3-(4-methoxyphenyl)dihydrocinnoline-1,2-dicarboxylate, 74



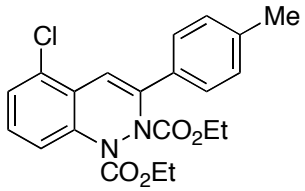
Prepared following general procedure B using (Z)-1-bromo-2-(2-bromo-2-(4-methoxyphenyl)vinyl)benzene **48** (295 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **74** (195 mg, 64%) as a white solid: mp 117-119 °C; ν_{max} (neat) / cm^{-1} 2983, 2936, 2910, 1731, 1609, 1577, 1314, 1251, 1053; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.70 (2H, d, *J* 9.0, 2 × Ar*H*), 7.53 (1H, ap. d, *J* 8.0, Ar*H*), 7.43 (1H, dd, *J* 7.5 and 1.5, Ar*H*), 7.35 (1H, td, *J* 7.5 and 1.5, Ar*H*), 7.29 (1H, td, *J* 7.5 and 1.5, Ar*H*), 7.02 (2H, d, *J* 9.0, 2 × Ar*H*), 6.90 (1H, s, ArC*H*=CArN), 4.32-4.25 (2H, m, C$H_2$$CH_3$), 4.04-3.98 (2H, m, C$H_2$$CH_3$), 3.84 (3H, s, ArOC$H_3$), 1.29 (3H, t, *J* 7.0, CH_2CH_3), 0.98 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 160.9, 154.6, 154.5, 141.8, 137.0, 128.7, 128.3, 128.0, 127.9, 127.0, 126.7, 123.7, 115.0, 112.9, 63.6, 63.3, 56.3, 15.0, 14.7; *m/z* LRMS (ESI^+) 787.4 ([$(2M+Na)^+$], 100%), 405.2 ([$(M+Na)^+$], 10%); HRMS (ESI^+) 405.1405 ([$(M+Na)^+$], $C_{21}H_{22}N_2O_5Na$ requires 405.1421).

(*E*)-Diethyl 3-styryldihydrocinnoline-1,2-dicarboxylate, 75



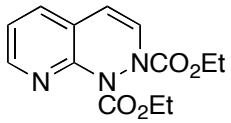
Prepared following general procedure B using 1-bromo-2-(-2-bromo-4-phenylbuta-1,3-dien-1-yl)benzene **49** (291 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **75** (215 mg, 71%) as a white solid: mp 80-82 °C; ν_{max}(neat) / cm^{-1} 3030, 2967, 2921, 1728, 1629, 1578, 1373, 1205, 1093; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.55-7.53 (3H, m, 3 × Ar*H*), 7.42-7.39 (3H, m, 3 × Ar*H* and ArC*H*=CHPh), 7.38-7.31 (2H, m, Ar*H* and ArCH=C*H*Ph), 7.29-7.26 (1H, m, Ar*H*), 7.01-6.98 (2H, m, 2 × Ar*H*), 6.81 (1H, s, ArC*H*=C), 4.27-4.07 (4H, m, 2 × C$H_2$$CH_3$), 1.27 (3H, t, *J* 7.0, CH_2CH_3), 1.13 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.9, 154.2, 140.5, 137.4, 137.3, 132.6, 129.7, 129.0, 128.8, 127.5, 127.4, 127.1, 126.9, 124.4, 123.7, 117.4, 63.53, 63.46, 15.0, 14.0; *m/z* LRMS (ESI$^+$) 779.4 ([(2M+Na)$^+$], 100%), 401.2 ([(M+Na)$^+$], 10%); HRMS (ESI$^+$) 401.1474 ([(M+Na)$^+$], $C_{22}H_{22}N_2O_4Na$ requires 401.1472).

Diethyl 5-chloro-3-(*p*-tolyl)dihydrocinnoline-1,2-dicarboxylate, 76



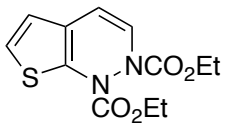
Prepared following general procedure B using (*Z*)-1-bromo-2-(2-bromo-2-(*p*-tolyl)vinyl)-3-chlorobenzene **50** (177 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **76** (134 mg, 73%) as a white solid: mp 133-134 °C; ν_{max}(neat) / cm^{-1} 3033, 2980, 2963, 1721, 1618, 1559, 1510, 1297, 1143, 1061, 951; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.68 (2H, d, *J* 8.0, 2 × Ar*H*), 7.54-7.52 (1H, m, Ar*H*), 7.43-7.38 (2H, m, 2 × Ar*H*), 7.29 (2H, d, *J* 8.0, 2 × Ar*H*), 7.00 (1H, s, ArC*H*=C), 4.34-4.25 (2H, m, CH_2CH_3), 4.06-3.98 (2H, m, CH_2CH_3), 2.39 (3H, s, $ArCH_3$), 1.30 (3H, t, *J* 7.0, CH_2CH_3), 0.98 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.2, 143.8, 139.8, 138.3, 132.9, 131.7, 130.6, 130.0, 129.3, 127.6, 126.8, 126.0, 123.0, 109.9, 64.1, 63.6, 21.7, 15.0, 14.6; *m/z* LRMS (ESI^+) 827.3 (^{37}Cl, [$(2M+Na)^+$], 20%), 823.3 (^{35}Cl, [$(2M+Na)^+$], 100%); HRMS (ESI^+) 423.1082 ([$(M+Na)^+$], $C_{21}H_{21}N_2O_4{}^{35}ClNa$ requires 423.1082).

Diethyl pyrido[2,3-c]dihydropyridazine-1,2-dicarboxylate, 77



Prepared following general procedure B using (*Z*)-2-bromo-3-(2-bromovinyl)pyridine **51** (210 mg, 0.8 mmol, 1.0 eq). Column chromatography (10% acetone in petroleum ether) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **77** (141 mg, 64%) as a yellow solid: mp 73-75°C; ν_{max} (neat)/cm^{-1} 3054, 2984, 2938, 1743, 1622, 1587, 1427, 1303, 1243, 1095, 1018; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 8.36 (1H, dd, *J* 5.0 and 2.0, Ar*H*), 7.74 (1H, dd, *J* 7.5 and 2.0, Ar*H*), 7.36-7.33 (1H, m, Ar*H*), 7.28 (1H, d, *J* 7.0, ArCH=C*H*N), 6.32 (1H, d, *J* 7.0, ArC*H*=CHN), 4.27 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 4.17 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 1.28 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.18 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.3, 152.4, 148.3, 147.9, 134.3, 131.3, 124.2, 123.5, 110.2, 64.0, 63.7, 15.0, 14.9; *m/z* LRMS (ESI$^+$) 300.1 ([(M+Na)$^+$], 100%); HRMS (ESI$^+$) 300.0960 ([(M+Na)$^+$], $C_{13}H_{15}N_3O_4Na$ requires 300.0955).

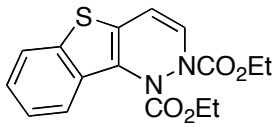
Diethyl thieno[2,3-*c*]dihydropyridazine-1,2-dicarboxylate, 78



Prepared following general procedure B using (*Z*)-3-bromo-2-(2-bromovinyl)thiophene **52** (291 mg, 0.8 mmol, 1.0 eq). Column chromatography (5%

acetone in petroleum ether) yielded *diethyl dihydropyridazine-1,2-dicarboxylate* **78** (120 mg, 53%) as a yellow oil: ν_{max}(neat) / cm^{-1} 3097, 2983, 2935, 1726, 1596, 1525, 1296, 1185, 1075, 917; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.47 (1H, d, *J* 5.5, Ar*H*), 7.13 (1H, d, *J* 5.5, Ar*H*), 6.93 (1H, d, *J* 7.0, ArCH=C*H*N), 6.44 (1H, d, *J* 7.0, ArC*H*=CHN), 4.25-4.19 (4H, m, 2 × CH_2CH$_3$), 1.28-1.22 (6H, m, 2 × CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.9, 153.0, 136.2, 125.8, 125.3, 125.0, 123.7, 109.1, 63.9, 63.5, 15.1, 14.9; *m/z* LRMS (ESI^+) 587.2 ([(2M+Na)$^+$], 100%); HRMS (ESI^+) 305.0575 ([(M+Na)$^+$], $C_{12}H_{14}N_2O_4SNa$ requires 305.0566).

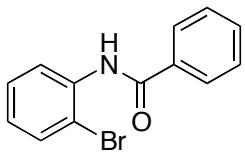
Diethyl benzo[4,5]thieno[3,2-*c*]dihydropyridazine-1,2-dicarboxylate, 79



Prepared following general procedure B using 3-bromo-2-(2-bromovinyl)benzo[*b*]thiophene **53** (254 mg, 0.8 mmol, 1.0 eq). Column chromatography (5% acetone in petroleum ether) yielded *diethyl dihydropyridazine-1,2-dicarboxylate* **79** (97 mg, 36%) as a yellow solid: mp 154-155 °C; ν_{max}(neat)/cm^{-1} 3002, 2970, 1745, 1592, 1520, 1385, 1235, 1172, 1067; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.94-7.92 (1H, m, Ar*H*), 7.74-7.72 (1H, m, Ar*H*), 7.48-7.45 (1H, m, Ar*H*), 7.40-7.38 (1H, m, Ar*H*), 7.20 (1H, d, *J* 7.0, ArCH=C*H*N), 6.53 (1H, d, *J* 7.0, ArC*H*=CHN), 4.29-4.16 (4H, m, 2 × CH_2CH$_3$), 1.28 (3H, t, *J* 7.0, CH$_2$CH_3), 1.18 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.9, 152.7, 138.0, 133.8, 129.5, 128.9, 127.7, 125.8, 125.6, 123.8, 122.6, 108.4, 64.2, 63.7, 15.0, 14.9; *m/z* LRMS

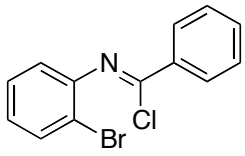
(ESI^+) 687.2 ([$(2M+Na)^+$], 100%); HRMS (ESI^+) 355.0718 ([$(M+Na)^+$], $C_{16}H_{16}N_2O_4SNa$ requires 355.0723).

_N_-(2-Bromophenyl)benzamide, 80



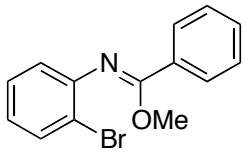
Prepared according to a literature procedure.[54] Benzoyl chloride (2.3 mL, 20.0 mmol, 1.6 eq) was added drop-wise to a solution of 2-bromoaniline (2.0 g, 12.0 mmol, 1.0 eq) and triethylamine (1.9 mL, 13.2 mmol, 1.1 eq) in THF (40 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 3 h before the reaction was quenched with brine (60 mL). The resulting aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethanol afforded benzamide **80** (1.5 g, 45%) as a white solid: ν_{max} (neat)/cm^{-1} 3273, 3058, 2986, 1650, 1577, 1515, 1430, 1263, 1161, 1042; δ_H (400 MHz, $CDCl_3$) 8.48 (1H, dd, *J* 8.5 and 1.5, Ar*H*), 8.40 (1H, br. s, N*H*), 7.88-7.85 (2H, m, 2 × Ar*H*), 7.53-7.49 (2H, m, 2 × Ar*H*), 7.47-7.42 (2H, m, 2 × Ar*H*), 7.32-7.28 (1H, m, Ar*H*), 6.96-6.92 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 165.3, 135.8, 134.6, 132.3, 132.2, 129.0, 128.6, 127.1, 125.3, 121.8, 113.8; *m/z* LRMS (ESI^+) 300.0 (^{81}Br, [$(M+Na)^+$], 100%), 298.0 (^{79}Br, [$(M+Na)^+$], 90%). Data in accordance with the literature.[54]

(*Z*)-*N*-(2-Bromophenyl)benzimidoyl chloride, 81



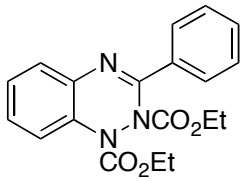
Prepared according to a literature procedure.[54] *N*-(2-Bromophenyl)benzamide **80** (1.0 g, 3.7 mmol, 1.0 eq) and phosphorous pentachloride (0.9 g, 4.1 mmol, 1.1 eq) were suspended in DCM (10 mL). The reaction mixture was heated at reflux for 24 h. After cooling to room temperature, the resulting solution was stirred and heated at 50 °C under reduced pressure until ^{31}P NMR confirmed the complete removal of all phosphorous trichloride. This afforded benzimidoyl chloride **81** (1.0 g, 94%) as a yellow oil: ν_{max} (neat)/cm^{-1} 3061, 1648, 1580, 1488, 1435, 1297, 1186, 1075; δ_H (400 MHz, $CDCl_3$) 8.14-8.11 (2H, m, 2 × Ar*H*), 7.55 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.50-7.46 (1H, m, Ar*H*), 7.42-7.38 (2H, m, 2 × Ar*H*), 7.25 (1H, td, *J* 7.5 and 1.5, Ar*H*), 6.97 (1H, td, *J* 7.5 and 1.5, Ar*H*), 6.88 (1H, dd, *J* 8.0 and 1.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 146.7, 146.0, 135.0, 132.9, 132.5, 129.7, 128.6, 127.9, 126.1, 121.2, 114.7; *m*/*z* HRMS (FI$^+$) 294.9597 ([M$^+$], $C_{13}H_9N_2{}^{81}Br^{35}Cl$ requires 294.9585). Data in accordance with the literature.[54]

(*Z*)-Methyl *N*-(2-bromophenyl)benzimidate, 82



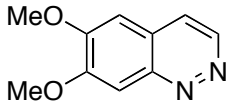
Prepared according to a literature procedure.[54] 2-Bromoaniline (2.0 g, 12.0 mmol, 1.0 eq), trimethyl orthobenzoate (2.3 mL, 13.0 mmol, 1.1 eq) and *p*-toluenesulfonic acid (cat.) were suspended in toluene (60 mL). The reaction mixture was heated at reflux for 3 h with the aid of Dean-Stark apparatus. After cooling to room temperature, the resulting solution was concentrated *in vacuo* and the residue partitioned between diethyl ether (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL). The organic phase was separated and washed with a further portion of sat. $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL) before being dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (5% ethyl acetate in petroleum ether) afforded benzimidate **82** (2.8 g, 83%, single isomer) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3055, 2986, 2945, 1664, 1433, 1276, 1111, 1025; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.25-7.19 (3H, m, 3 × Ar*H*), 7.15-7.11 (2H, m, 2 × Ar*H*), 6.97 (1H, td, *J* 7.5 and 1.5, Ar*H*), 6.72 (1H, td, *J* 7.5 and 1.5, Ar*H*), 6.53 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 3.94 (3H, s, O*C*H_3); δ_C (100 MHz, $CDCl_3$) 159.9, 147.2, 132.8, 131.3, 130.2, 128.7, 128.1, 128.0, 123.9, 122.5, 116.4, 54.5; *m/z* LRMS (ESI^+) 292.0 (^{81}Br, [$(M+H)^+$], 100%), 290.0 (^{79}Br, [$(M+H)^+$], 90%). Data in accordance with the literature.[54]

Diethyl 3-phenylbenzo[*e*][1,2,4]triazine-1,2-dicarboxylate, 83



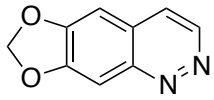
Prepared following general procedure B using (*Z*)-methyl *N*-(2-bromophenyl)benzimidate **82** (232 mg, 0.8 mmol, 1.0 eq). However, the reaction mixture was subjected to microwave irradiation for 2 h at 135 °C**.** Column chromatography (5-10% acetone in petroleum ether) yielded *diethyl benzotriazine-1,2-dicarboxylate* **83** (120 mg, 43%) as a yellow gum: ν_{max} (neat)/cm^{-1} 2970, 2914, 1711, 1613, 1566, 1384, 1223, 1052; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 8.08-8.06 (2H, m, 2 × Ar*H*), 7.62-7.51 (5H, m, 5 × Ar*H*), 7.42-7.36 (2H, m, 2 × Ar*H*), 4.35-4.27 (2H, m, C*H*$_2$CH$_3$), 4.12-4.02 (2H, m, C*H*$_2$CH$_3$), 1.30 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 0.98 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 153.8, 153.0, 152.7, 136.3, 134.3, 132.2, 132.1, 128.9, 128.7, 127.9, 127.2, 125.8, 123.3, 63.8 (2 × C), 14.5, 14.1; *m/z* LRMS (ESI$^+$) 376.1 ([(M+Na)$^+$], 100%), 354.1 ([(M+H)$^+$], 80%); HRMS (ESI$^+$) 376.1260 ([(M+Na)$^+$], $C_{19}H_{19}N_3O_4Na$ requires 376.1268).

General Procedure C for the synthesis of cinnolines, as exemplified by the preparation of 6,7-dimethoxycinnoline, 2



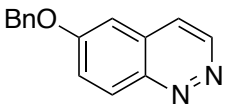
Sodium hydroxide (5 M, 0.4 mL, 1.7 mmol, 5.0 eq) was added drop-wise to a solution of diethyl 6,7-dimethoxydihydrocinnoline-1,2-dicarboxylate **10** (100 mg, 0.3 mmol, 1.0 eq) in ethanol (1.5 mL). The resulting solution, left open to air, was heated at 70 °C for 16 h. After cooling to room temperature, the reaction mixture was partitioned between water (15 mL) and DCM (15 mL). The organic phase was separated and the aqueous phase extracted with DCM (2 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield *cinnoline* **2** (54 mg, 94%) as a yellow solid: mp 119-122 °C; ν_{max} (neat)/cm^{-1} 3013, 2945, 1620, 1505, 1433, 1303, 1218, 1134; δ_H (400 MHz, CD_3OD) 9.04 (1H, d, *J* 5.5, CHC*H*N), 8.00 (1H, d, *J* 5.5, C*H*CHN), 7.63 (1H, s, Ar*H*), 7.27 (1H, s, Ar*H*), 4.08 (3H, s, ArOCH_3), 4.04 (3H, s, ArOCH_3); δ_C (100 MHz, CD_3OD) 156.0, 155.9, 150.1, 145.1, 126.2, 123.9, 106.2, 104.2, 57.0, 56.9; *m/z* LRMS (ESI^+) 403.2 ([(2M+Na)$^+$], 100%), 213.1 ([(M+Na)$^+$], 20%), 191.1 ([(M+H)$^+$], 10%); HRMS (ESI^+) 191.0815 ([(M+H)$^+$], $C_{10}H_{11}N_2O_2$ requires 191.0821).

[1,3]Dioxolo[4,5-*g*]cinnoline, 84



Prepared following general procedure C using diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **60** (100 mg, 0.3 mmol, 1.0 eq). Aqueous work-up yielded *cinnoline* **84** (53 mg, 98%) as a yellow solid: mp 140-142 °C; ν_{max}(neat)/ cm^{-1} 3016, 2969, 2910, 1464, 1280, 1199, 1029, 922; δ_H (400 MHz, CD_3OD) 9.01 (1H, d, *J* 6.0, CHC*H*N), 7.95 (1H, d, *J* 6.0, C*H*CHN), 7.52 (1H, s, Ar*H*), 7.18 (1H, s, Ar*H*), 6.25 (2H, s, OCH_2O); δ_C (100 MHz, CD_3OD) 153.0, 152.7, 150.2, 144.3, 127.0, 123.7, 103.6, 103.0, 100.7; *m/z* LRMS (ESI^+) 371.1 ([(2M+Na)$^+$], 100%), 197.0 ([(M+Na)$^+$], 50%), 175.1 ([(M+H)$^+$], 20%); HRMS (ESI^+) 197.0327 ([(M+Na)$^+$], $C_9H_6O_2N_2Na$ requires 197.0321).

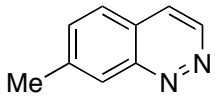
6-(Benzyloxy)cinnoline, 85



Prepared following general procedure C using diethyl 6-(benzyloxy)dihydrocinnoline-1,2-dicarboxylate **61** (130 mg, 0.3 mmol, 1.0 eq). Aqueous work-up yielded *cinnoline* **85** (65 mg, 81%) as a yellow solid: mp 93-95 °C; ν_{max}(neat)/cm^{-1} 3039, 3002, 3962, 1581, 1452, 1192, 993; δ_H (400 MHz, CD_3OD) 9.01 (1H, d, *J* 6.0, CHC*H*N), 8.22 (1H, d, *J* 9.0, Ar*H*), 7.95 (1H, d, *J* 6.0, C*H*CHN), 7.55-7.53 (1H, m, Ar*H*), 7.41 (2H, d, *J* 7.5, 2 × Ar*H*), 7.32-7.23 (4H, m, 4 × Ar*H*), 5.19 (2H, s, ArOCH_2Ph); δ_C (100

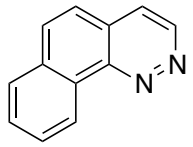
MHz, CD_3OD) 162.1, 149.2, 146.1, 137.4, 131.7, 130.6, 129.7, 129.4, 128.9, 127.2, 124.5, 105.2, 71.9; *m/z* LRMS (ESI^+) 495.2 ([$(2M+Na)^+$], 100%), 259.1 ([$(M+Na)^+$], 20%); HRMS (ESI^+) 259.0838 ([$(M+Na)^+$], $C_{15}H_{12}ON_2Na$ requires 259.0842).

7-Methylcinnoline, 86



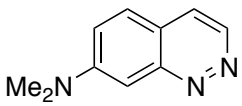
Prepared following general procedure C using diethyl 7-methyldihydrocinnoline-1,2-dicarboxylate **62** (100 mg, 0.3 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **86** (43 mg, 88%) as a yellow solid: mp 101-103 °C; ν_{max} (neat)/cm^{-1} 3046, 2946, 2922, 1628, 1440, 1291, 1103; δ_H (400 MHz, CD_3OD) 9.20 (1H, d, *J* 6.0, CHC*H*N), 8.14-8.13 (1H, m, Ar*H*), 8.10 (1H, dd, *J* 6.0 and 1.0, C*H*CHN), 7.86 (1H, d, *J* 8.5, Ar*H*), 7.68 (1H, dd, *J* 8.5 and 1.5, Ar*H*), 2.61 (3H, s, CH_3); δ_C (100 MHz, CD_3OD) 151.1, 144.7, 142.8, 134.4, 126.9, 126.8, 125.5, 124.2, 21.1; *m/z* LRMS (ESI^+) 311.2 ([$(2M+Na)^+$], 100%), 167.1 ([$(M+Na)^+$], 60%), 145.1 ([$(M+H)^+$], 50%); HRMS (ESI^+) 167.0579 ([$(M+Na)^+$], $C_9H_8N_2Na$ requires 167.0580).

Benzo[*h*]cinnoline, 87



Prepared following general procedure C using diethyl benzo[*h*]dihydrocinnoline-1,2-dicarboxylate **63** (110 mg, 0.3 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **87** (45 mg, 73%) as a yellow solid: mp 60-62 °C; ν_{max}(neat) / cm^{-1} 3048, 2996, 2920, 1579, 1367, 1160; δ_H (400 MHz, CD_3OD) 9.45-9.43 (1H, m, Ar*H*), 9.39 (1H, d, *J* 5.5, CHC*H*N), 8.16 (1H, d, *J* 5.5, C*H*CHN), 8.10 (1H, d, *J* 9.0, Ar*H*), 8.05-8.03 (1H, m, Ar*H*), 7.87-7.86 (2H, m, 2 × Ar*H*), 7.77 (1H, d, *J* 9.0, Ar*H*); δ_C (100 MHz, CD_3OD) 153.6, 149.0, 147.3, 134.2, 133.8, 130.1, 129.7, 128.8, 127.2, 124.4, 123.8, 123.6; *m/z* LRMS (ESI^+) 203.1 ([$(M+Na)^+$], 100%), 181.7 ([$(M+H)^+$], 40%); HRMS (ESI^+) 203.0582 ([$(M+Na)^+$], $C_{12}H_8N_2Na$ requires 203.0580). Data in accordance with the literature.[144]

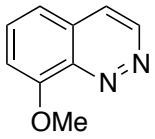
***N*,*N*-Dimethylcinnolin-6-amine, 90**



Prepared following general procedure C using diethyl 7-(dimethylamino)dihydrocinnoline-1,2-dicarboxylate **66** (196 mg, 0.3 mmol, 1.0 eq). Aqueous work-up yielded *cinnoline* **90** (47 mg, 90%) as a yellow solid: mp 97-98 °C; ν_{max} (neat) / cm^{-1} 3027, 2921, 1617, 1437, 1261, 1107, 967; δ_H (400 MHz, CD_3OD)

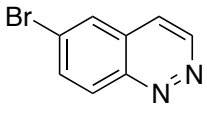
8.90 (1H, d, *J* 5.5, CHC*H*N), 7.85 (1H, dd, *J* 5.5 and 1.0, C*H*CHN), 7.72 (1H, d, *J* 9.5, Ar*H*), 7.50 (1H, ddd, *J* 9.5, 2.5 and 1.0, Ar*H*), 7.15 (1H, d, *J* 2.5, Ar*H*), 3.12 (6H, s, ArN(CH_3)$_2$); δ_C (100 MHz, CD_3OD) 152.7, 152.4, 142.1, 127.6, 124.1, 122.5, 120.8, 101.7, 39.3; *m/z* LRMS (ESI$^+$) 174.1 ([(M+Na)$^+$], 100%); HRMS (ESI$^+$) 174.1019 ([M+H]$^+$, $C_{10}H_{12}N_3$ requires 174.1026).

8-Methoxycinnoline, 91



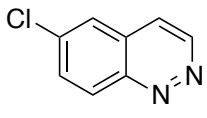
Prepared following general procedure C using diethyl 8-methoxydihydrocinnoline-1,2-dicarboxylate **67** (138 mg, 0.5 mmol, 1.0 eq). Aqueous work-up yielded *cinnoline* **91** (54 mg, 75%) as a yellow solid: mp 94-95 °C; ν_{max}(neat) / cm^{-1} 3004, 2972, 2940, 1616, 1490, 1420, 1301, 1126; δ_H (400 MHz, CD_3OD) 9.27 (1H, d, *J* 6.0, CHC*H*N), 8.09 (1H, d, *J* 6.0, C*H*CHN), 7.75 (1H, ddd, *J* 8.5, 8.0 and 1.0, Ar*H*), 7.47 (1H, dd, *J* 8.5 and 1.0, Ar*H*), 7.28 (1H, ap. d, *J* 8.0, Ar*H*), 4.13 (3H, s, ArOCH_3); δ_C (100 MHz, CD_3OD) 155.7, 145.8, 143.5, 132.9, 128.4, 124.0, 118.2, 109.2, 55.8; *m/z* LRMS (ESI$^+$) 183.1 ([(M+Na)$^+$], 100%); HRMS (ESI$^+$) 183.0527 ([M+Na]$^+$, $C_9H_8N_2ONa$ requires 183.0529).

6-Bromocinnoline, 93



Prepared following general procedure C using diethyl 6-bromodihydrocinnoline-1,2-dicarboxylate **69** (200 mg, 0.6 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **93** (76 mg, 65%) as a yellow solid: mp 110-112 °C; ν_{max}(neat) / cm^{-1} 3057, 2922, 1577, 1363, 1167, 1053; δ_H (400 MHz, CD_3OD) 9.33 (1H, d, *J* 6.0, CHC*H*N), 8.37 (1H, dd, *J* 9.0, Ar*H*), 8.29 (1H, d, *J* 2.0 and 1.0, Ar*H*), 8.15 (1H, dd, *J* 6.0 and 1.0, C*H*CHN), 8.06 (1H, dd, *J* 9.0 and 2.0, Ar*H*); δ_C (100 MHz, CD_3OD) 149.4, 145.7, 135.3, 130.8, 129.5, 128.1, 126.5, 123.2; *m/z* LRMS (ESI^+) 233.0 (^{81}Br, [$(M+Na)^+$], 95%), 231.0 (^{79}Br, [$(M+Na)^+$], 100%); HRMS (ESI^+) 230.9530 ([$(M+Na)^+$], $C_8H_5{}^{79}BrN_2Na$ requires 230.9528). Data in accordance with the literature.[85]

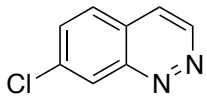
6-Chlorocinnoline, 94



Prepared following general procedure C using diethyl 6-chlorodihydrocinnoline-1,2-dicarboxylate **70** (84 mg, 0.3 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **94** (31 mg, 70%) as a yellow solid: mp 99-101 °C; ν_{max} (neat) / cm^{-1} 3054, 1665, 1579, 1399, 1115, 1069; δ_H (500 MHz, CD_3OD) 9.33 (1H, d, *J* 6.0, CHC*H*N), 8.43 (1H, d, *J* 9.0, Ar*H*), 8.14 (1H, dd, *J* 6.0 and 1.0, C*H*CHN), 8.07 (1H, dd, *J* 2.0 and 1.0, Ar*H*), 7.92 (1H, dd, *J* 9.0 and

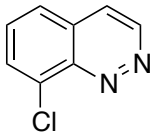
2.0, Ar*H*); δ_C (125 MHz, CD_3OD) 150.3, 146.7, 138.9, 133.7, 132.0, 128.7, 126.9, 124.4; *m/z* LRMS (ESI^+) 189.0 (^{37}Cl, [$(M+Na)^+$], 30%), 187.0 (^{35}Cl, [$(M+Na)^+$], 100%); HRMS (ESI^+) 187.0040 ([$(M+Na)^+$], $C_8H_5{}^{35}ClN_2Na$ requires 187.0033). Data in accordance with the literature.[85]

7-Chlorocinnoline, 95



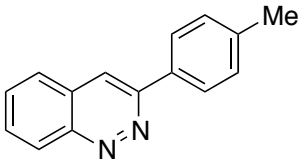
Prepared following general procedure C using diethyl 7-chlorodihydrocinnoline-1,2-dicarboxylate **71** (106 mg, 0.3 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **95** (38 mg, 68%) as a yellow solid: mp 84-85 °C; ν_{max} (neat) / cm^{-1} 3049, 3015, 2919, 1625, 1581, 1397, 1247, 1130; δ_H (400 MHz, CD_3OD) 9.33 (1H, d, *J* 6.0, CHC*H*N), 8.41-8.39 (1H, m, Ar*H*), 8.19-8.17 (1H, m, C*H*CHN), 8.02 (1H, d, *J* 9.0, Ar*H*), 7.81 (1H, dd, *J* 9.0 and 2.0, Ar*H*); δ_C (100 MHz, CD_3OD) 150.9, 145.6, 137.1, 132.8, 129.3, 127.4, 125.5, 124.2; *m/z* LRMS (ESI^+) 189.0 (^{37}Cl, [$(M+Na)^+$], 30%), 187.0 (^{35}Cl, [$(M+Na)^+$], 100%); HRMS (ESI^+) 187.0033 ([$(M+Na)^+$], $C_8H_5{}^{35}ClN_2Na$ requires 187.0033).

8-Chlorocinnoline, 96



Prepared following general procedure C using diethyl 8-chlorodihydrocinnoline-1,2-dicarboxylate **72** (125 mg, 0.4 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **96** (36 mg, 56%) as a yellow solid: mp 78-80 °C; ν_{max} (neat) / cm^{-1} 3052, 3011, 2981, 1674, 1419, 1283, 1218, 1096; δ_H (500 MHz, CD_3OD) 9.44 (1H, d, *J* 6.0, CHC*H*N), 8.26 (1H, d, *J* 6.0, C*H*CHN), 8.09 (1H, dd, *J* 7.5 and 1.0, Ar*H*), 8.01 (1H, dd, *J* 8.5 and 1.0, Ar*H*), 7.85-7.82 (1H, m, Ar*H*); δ_C (125 MHz, CD_3OD) 148.1, 147.1, 135.0, 133.0, 132.7, 129.8, 127.7, 125.3; *m/z* LRMS (ESI^+) 189.0 (^{37}Cl, [$(M+Na)^+$], 30%), 187.0 (^{35}Cl, [$(M+Na)^+$], 100%); HRMS (ESI^+) 187.0035 ([$(M+Na)^+$], $C_8H_5{}^{35}ClN_2Na$ requires 187.0033).

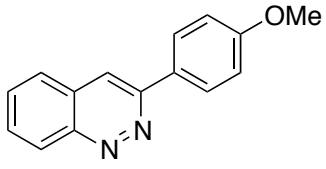
3-(*p*-Tolyl)cinnoline, 97



Prepared following general procedure C using diethyl 3-(*p*-tolyl)dihydrocinnoline-1,2-dicarboxylate **73** (70 mg, 0.2 mmol, 1.0 eq). Column chromatography (5% acetone and 2.5% triethylamine in petroleum ether) yielded cinnoline **97** (27 mg, 64%) as a yellow solid: mp 101-103 °C; ν_{max}(neat) / cm^{-1} 3026, 3007, 2970, 1366,

1216, 967; δ_H (400 MHz, CD_3OD) 8.45 (1H, s, C*H*C(Ar)N), 8.42 (1H, ap. d, *J* 8.5, Ar*H*), 8.09 (2H, d, *J* 8.5, 2 × Ar*H*), 8.03-8.01 (1H, m, Ar*H*), 7.91-7.87 (1H, m, Ar*H*), 7.84-7.80 (1H, m, Ar*H*), 7.37 (2H, d, *J* 8.5, 2 × Ar*H*), 2.42 (3H, s, ArCH_3); δ_C (100 MHz, CD_3OD) 154.2, 149.8, 140.0, 134.1, 131.9, 131.1, 129.8, 128.6, 127.6, 127.5, 127.2, 120.0, 20.3; *m/z* LRMS (ESI^+) 463.2 ([$(2M+Na)^+$], 100%), 243.1 ([$(M+Na)^+$], 10%); HRMS (ESI^+) 243.0894 ([$M+Na]^+$, $C_{15}H_{12}N_2Na$ requires 243.0893). Data in accordance with the literature.[88]

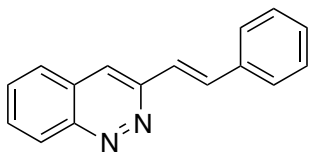
3-(4-Methoxyphenyl)cinnoline, 98



Prepared following general procedure C using diethyl 3-(4-methoxyphenyl)dihydrocinnoline-1,2-dicarboxylate **74** (100 mg, 0.2 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded cinnoline **98** (62 mg, 65%) as a yellow solid: mp 105-106 °C; ν_{max} (neat) / cm^{-1} 3062, 3037, 2997, 1365, 1205, 1097; δ_H (400 MHz, CD_3OD) 8.38-8.36 (2H, m, Ar*H* and C*H*C(Ar)N), 8.12 (2H, d, *J* 9.0, 2 × Ar*H*), 7.97-7.94 (1H, m, Ar*H*), 7.86-7.82 (1H, m, Ar*H*), 7.79-7.76 (1H, m, Ar*H*), 7.06 (2H, d, *J* 9.0, 2 × Ar*H*), 3.86 (3H, s, ArOCH_3); δ_C (100 MHz, CD_3OD) 161.5, 153.9, 149.5, 131.8, 130.8, 129.2, 128.6, 128.5, 127.6, 127.5, 119.3, 114.5, 54.9; *m/z* LRMS (ESI^+) 495.2 ([$(2M+Na)^+$], 100%);

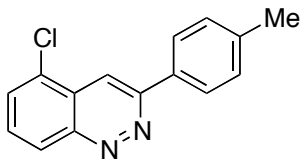
HRMS (ESI$^+$) 259.0839 ([(M+Na)$^+$], $C_{15}H_{12}ON_2Na$ requires 259.0842). Data in accordance with the literature.[88]

(*E*)-3-Styrylcinnoline, 99



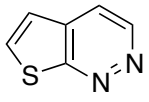
Prepared following general procedure C using (*E*)-diethyl 3-styryldihydrocinnoline-1,2-dicarboxylate **75** (46 mg, 0.1 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **99** (19 mg, 68%) as a yellow solid: mp 114-115 °C; ν_{max} (neat) / cm^{-1} 3024, 2970, 2924, 1637, 1579, 1312, 1217, 1029; δ_H (400 MHz, $(CD_3)_2CO$) 8.50-8.47 (1H, m, Ar*H*), 8.17 (1H, s, C*H*C(Alk)N), 8.10 (1H, d, *J* 16.0, ArC*H*=CHPh), 8.02-8.00 (1H, m, Ar*H*), 7.92-7.88 (1H, m, Ar*H*), 7.86-7.82 (1H, m, Ar*H*), 7.78-7.76 (2H, m, Ar*H*), 7.68 (1H, d, *J* 16.0, ArCH=C*H*Ph), 7.48-7.44 (2H, m, 2 × Ar*H*), 7.39-7.35 (1H, m, Ar*H*); δ_C (100 MHz, $(CD_3)_2CO$) 153.8, 152.5, 150.1, 137.2, 133.6, 131.7, 130.6, 129.9, 129.2, 128.9, 127.6, 126.6, 126.2, 119.7; *m/z* LRMS (ESI$^+$) 487.2 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 255.0895 ([(M+Na)$^+$], $C_{16}H_{12}N_2Na$ requires 255.0893).

5-Chloro-3-(*p*-tolyl)cinnoline, 100



Prepared following general procedure C using diethyl 5-chloro-3-(*p*-tolyl)dihydrocinnoline-1,2-dicarboxylate **76** (23 mg, 0.1 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **100** (10 mg, 68%) as a dark orange solid: mp 115-116 °C; ν_{max} (neat)/cm^{-1} 3027, 2921, 1508, 1378, 1215, 1049; δ_H (500 MHz, CD_3OD) 8.58 (1H, s, C*H*C(Ar)N), 8.44 (1H, ap. d, *J* 8.5 Ar*H*), 8.15 (2H, d, *J* 8.0, 2 × Ar*H*), 7.96 (1H, dd, *J* 7.5 and 1.0, Ar*H*), 7.89-7.85 (1H, m, Ar*H*), 7.41 (2H, d, *J* 8.0, 2 × Ar*H*), 2.68 (3H, s, ArCH_3); δ_C (125 MHz, CD_3OD) 156.0, 151.0, 141.6, 134.7, 132.6, 132.0, 131.9, 131.0, 129.3, 128.4, 126.8, 116.8, 21.4; *m/z* LRMS (ESI$^+$) 531.2 ($^{35}Cl^{35}Cl$, [(2M+Na)$^+$], 100%), 277.1 (^{35}Cl, [(M+Na)$^+$], 20%), 255.1 (^{35}Cl, [(M+H)$^+$], 10%); HRMS (ESI$^+$) 277.0503 ([(M+Na)$^+$], $C_{15}H_{11}N_2{}^{35}ClNa$ requires 277.0503).

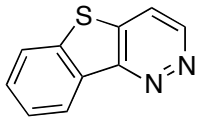
Thieno[2,3-*c*]pyridazine, 102



Prepared following general procedure C using diethyl thieno[2,3-*c*]dihydropyridazine-1,2-dicarboxylate **78** (100 mg, 0.4 mmol, 1.0 eq). Column chromatography (20% acetone and 2.5% triethylamine in petroleum ether) yielded *pyridazine* **102** (27 mg, 58%) as a pale yellow solid: mp 87-89 °C; ν_{max} (neat) / cm^{-1}

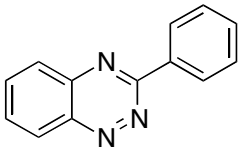
3016, 2970, 1396, 1173, 1067, 1029; δ_H (400 MHz, CD_3OD) 8.97 (1H, d, *J* 5.5, CHC*H*N), 8.29 (1H, dd, *J* 5.5 and 1.0, C*H*CHN), 8.11 (1H, d, *J* 5.5, SC*H*CH), 7.73 (1H, dd, *J* 5.5 and 1.0, SCHC*H*); δ_C (100 MHz, CD_3OD) 161.0, 144.7, 139.7, 136.4, 124.0, 123.0; HRMS (FI^+) 136.0096 ([M^+], $C_6H_4N_2S$ requires 136.0095).

Benzo[4,5]thieno[3,2-*c*]pyridazine, 103



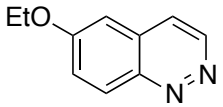
Prepared following general procedure C using diethyl benzo*[4,5]*thieno*[3,2-c]*dihydropyridazine-1,2-dicarboxylate **79** (160 mg, 0.5 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *pyridazine* **103** (42 mg, 47%) as a pale orange solid: mp 131-133 °C; ν_{max} (neat) / cm^{-1} 3052, 2979, 2961, 1621, 1316, 1183, 1079; δ_H (500 MHz, CD_3OD) 9.15 (1H, d, *J* 5.5, CHC*H*N), 8.67 (1H, ddd, *J* 8.0, 1.5 and 1.0, Ar*H*), 8.33 (1H, d, *J* 5.5, C*H*CHN), 8.03 (1H, dt, *J* 8.0 and 1.0, Ar*H*), 7.77-7.73 (1H, m, Ar*H*), 7.70-7.66 (1H, m, Ar*H*); δ_C (125 MHz, CD_3OD) 157.0, 147.2, 141.4, 141.0, 133.1, 132.0, 127.4, 124.4, 124.3, 122.9; *m/z* LRMS (ESI^+) 395.1 ([$(2M+Na)^+$], 10%), 209.0 ([$(M+Na)^+$], 100%); HRMS (ESI^+) 209.0138 ([$(M+Na)^+$], $C_{10}H_6N_2SNa$ requires 209.0144).

3-Phenylbenzo[*e*][1,2,4]triazine, 104



Prepared following general procedure C using diethyl 3-phenylbenzo[*e*][1,2,4]triazine-1,2-dicarboxylate **83** (130 mg, 0.4 mmol, 1.0 eq). Column chromatography (5% ethyl acetate in petroleum ether) afforded triazine **104** (50 mg, 61%) as a deep yellow solid: mp 122-123 °C; ν_{max} (neat)/cm^{-1} 3016, 2970, 2946, 1544, 1368, 1228, 1216; δ_H (500 MHz, $(CD_3)_2SO$) 8.68-8.66 (2H, m, 2 × Ar*H*), 8.61-8.59 (1H, m, Ar*H*), 8.19-8.17 (2H, m, 2 × Ar*H*), 8.04-8.01 (1H, m, Ar*H*), 7.68-7.65 (3H, m, 3 × Ar*H*); δ_C (125 MHz, $(CD_3)_2SO$) 158.8, 146.1, 140.3, 136.7, 135.2, 131.7, 131.2, 129.18, 129.17, 128.8, 128.3; *m/z* LRMS (ESI$^+$) 208.1 ([(M+H)$^+$], 100%). Data in accordance with the literature.[145]

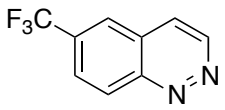
6-Ethoxycinnoline, 105



Prepared following general procedure C using diethyl 6-fluorodihydrocinnoline-1,2-dicarboxylate **68** (100 mg, 0.3 mmol, 1.0 eq). Aqueous work-up yielded *cinnoline* **105** (49 mg, 83%) as a yellow solid: mp 80-82 °C; ν_{max} (neat) / cm^{-1} 2982, 2970, 2934, 1619, 1439, 1205, 1110, 1037; δ_H (500 MHz, $(CD_3)_2SO$) 9.19 (1H, d, *J* 6.0, CHC*H*N), 8.31 (1H, d, *J* 9.5, Ar*H*), 8.02 (1H, d, *J* 6.0, C*H*CHN), 7.53-7.51 (1H, m, Ar*H*), 7.31

(1H, ap. s, Ar*H*), 4.19 (2H, q, *J* 7.0, ArOC*H*$_2$CH$_3$), 1.40 (3H, t, *J* 7.0, ArOCH$_2$C*H*$_3$); δ_C (125 MHz, (CD$_3$)$_2$SO) 159.6, 147.4, 145.1, 130.7, 127.8, 124.8, 121.7, 103.7, 64.1, 14.3; *m/z* LRMS (ESI$^+$) 371.2 ([(2M+Na)$^+$], 100%), 197.1 ([(M+Na)$^+$], 40%), 175.1 ([(M+H)$^+$], 10%); HRMS (ESI$^+$) 197.0680 ([(M+Na)$^+$], $C_{10}H_{10}ON_2Na$ requires 197.0685).

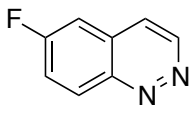
6-(Trifluoromethyl)cinnoline, 88



Sodium hydroxide (5 M, 0.4 mL, 1.7 mmol, 5.0 eq) was added drop-wise to a solution of diethyl 6-(trifluoromethyl)dihydrocinnoline-1,2-dicarboxylate **64** (150 mg, 0.4 mmol, 1.0 eq) in ethanol (1.3 mL). The reaction mixture was allowed to stir, left open to air, at room temperature for 36 h. After this time, the resulting suspension was partitioned between water (15 mL) and DCM (15 mL). The organic phase was separated and the aqueous phase extracted with DCM (2 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **88** (33 mg, 42%) as a dark yellow solid: mp 101-103 °C; ν_{max} (neat) / cm^{-1} 3043, 3006, 2964, 1325, 1117, 1059; δ_H (400 MHz, CD$_3$OD) 9.49 (1H, d, *J* 6.0, CHC*H*N), 8.68 (1H, d, *J* 9.0, Ar*H*), 8.52 (1H, m, Ar*H*), 8.39 (1H, dd, *J* 6.0 and 1.0, C*H*CHN), 8.17 (1H, dd, *J* 9.0 and 2.0, Ar*H*); δ_C (100 MHz, CD$_3$OD) 152.0, 147.4, 133.8 (q, J_{CF} 33.0), 131.9, 127.9 (q, J_{CF} 3.0), 127.2, 127.1 (q, J_{CF} 4.5), 126.1, 124.9 (q,

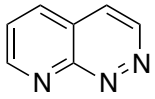
J_{CF} 272.0); δ_F (375 MHz, $CDCl_3$) -64.8 (s) {^{1}H}; HRMS (FI$^+$) 198.0401 ([M$^+$], $C_9H_5F_3N_2$ requires 198.0405).

6-Fluorocinnoline, 92



Prepared as for 6-(trifluoromethyl)cinnoline **88** using diethyl 6-fluorodihydrocinnoline-1,2-dicarboxylate **68** (118 mg, 0.4 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded cinnoline **92** (22 mg, 37%) as a yellow solid: mp 105-107 °C; ν_{max} 3042, 3006, 2987, 2951, 1682, 1460, 1236, 1079; δ_H (400 MHz, CD_3OD) 9.29 (1H, dd, *J* 6.0 and 1.0, C*H*CHN), 8.57-8.53 (1H, m, Ar*H*), 8.21 (1H, d, *J* 6.0, CHC*H*N), 7.84-7.79 (1H, m, Ar*H*), 7.73 (1H, dd, *J* 8.5 and 2.5, Ar*H*); δ_C (100 MHz, CD_3OD) 163.6 (d, J_{CF} 262.0), 145.3, 132.8, 132.7, 128.7 (d, J_{CF} 11.0), 124.0 (d, J_{CF} 6.5), 122.6, 109.9 (d, J_{CF} 22.5); δ_F (375 MHz, CD_3OD) -116.5 (s) {^{1}H}; *m/z* LRMS (ESI$^+$) 171.0 ([(M+Na)$^+$], 100%); HRMS (ESI$^+$) 171.0330 ([(M+Na)$^+$], $C_8H_5FN_2Na$ requires 171.0329). Data in accordance with the literature.[85]

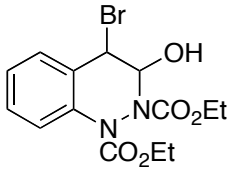
Pyrido[2,3-*c*]pyridazine, 101



Prepared as for 6-(trifluoromethyl)cinnoline **88** using diethyl pyrido[2,3-c]dihydropyridazine-1,2-dicarboxylate **77** (111 mg, 0.4 mmol, 1.0 eq). Column

chromatography (20% acetone and 2.5% triethylamine in petroleum ether) yielded *cinnoline* **101** (26 mg, 51%) as a yellow solid: mp 117-118 °C; ν_{max} (neat) / cm^{-1} 3004, 2969, 1583, 1379, 1088; δ_H (500 MHz, CD_3OD) 9.51 (1H, d, *J* 5.5, CHC*H*N), 9.33 (1H, dd, *J* 4.0 and 2.0, Ar*H*), 8.59 (1H, dd, *J* 8.5 and 2.0, Ar*H*), 8.35 (1H, d, *J* 5.5, C*H*CHN), 7.92 (1H, dd, *J* 8.5 and 4.0, Ar*H*); δ_C (125 MHz, CD_3OD) 158.8, 157.6, 147.8, 138.7, 128.3, 126.7, 124.0; *m/z* LRMS (ESI^+) 154.0 ([$(M+Na)^+$], 100%); HRMS (ESI^+) 154.0370 ([$(M+Na)^+$], $C_7H_5N_3Na$ requires 154.0376).

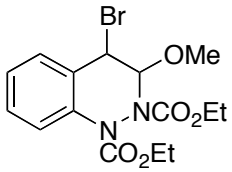
Diethyl 4-bromo-3-hydroxy-3,4-dihydrocinnoline-1,2-dicarboxylate, 106



N-Bromosuccinimde (131 mg, 0.75 mmol, 1.5 eq) and diethyl dihydrocinnoline-1,2-dicarboxylate **59** (138 mg, 0.5 mmol, 1.0 eq) were suspended in DCM (2 mL) and the resulting reaction mixture was allowed to stir at room temperature for 1 h. The resulting suspension was diluted with DCM (20 mL) and water (20 mL). The resulting biphasic mixture was separated and the aqueous phase extracted with DCM (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10-20% acetone in petroleum ether) afforded *bromohydrin* **106** (120 mg, 64%) as a white solid: mp 46-47 °C; ν_{max} (neat)/cm^{-1} 3400, 2983, 2936, 1698, 1583, 1416, 1371, 1306, 1204, 1025; δ_H (500 MHz, $(CD_3)_2SO$) 7.60-7.55 (2H, br. m, Ar*H* and O*H*), 7.43 (1H, ap. t, *J* 7.0, Ar*H*), 7.34 (1H, td, *J* 7.0

and 1.5, Ar*H*), 7.22-7.18 (1H, m, Ar*H*), 6.15 and 6.07 (1H, 2 × s, C*H*OH), 5.45 (1H, s, C*H*Br), 4.25-4.10 (4H, m, 2 × CH_2CH$_3$), 1.26-1.19 (6H, m, 2 × CH$_2$CH_3); *m/z* LRMS (ESI$^+$) 771.1 (^{81}Br^{81}Br, [(2M+Na)$^+$], 50%), 769.1 (^{81}Br^{79}Br, [(2M+Na)$^+$], 100%), 767.1 (^{79}Br^{79}Br, [(2M+Na)$^+$], 40%); HRMS (ESI$^+$) found 397.0192 ([(M+Na)$^+$], $C_{14}H_{17}{}^{81}BrN_2O_5Na$ requires 397.0193). Incomplete characterisation data due to low stability of the molecule at elevated temperatures.

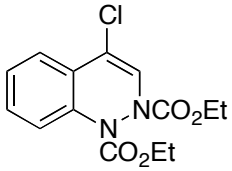
Diethyl 4-bromo-3-methoxy-3,4-dihydrocinnoline-1,2-dicarboxylate, 107



N-Bromosuccinimde (670 mg, 3.8 mmol, 1.5 eq) and diethyl dihydrocinnoline-1,2-dicarboxylate **59** (690 mg, 2.5 mmol, 1.0 eq) were suspended in DCM (10 mL) and the resulting reaction mixture was allowed to stir at room temperature for 1 h. Methanol (5 mL) was then slowly added and the reaction allowed to stir for a further 30 min. Water (20 mL) was added and the organic phase separated. The aqueous was extracted with DCM (2 × 20 mL) and the organic phases combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford *bromide* **107** (850 mg, 88%) as a pale yellow solid: mp 86-88 °C; ν_{max} (neat)/cm^{-1} 3003, 2986, 2968, 1604, 1509, 1465, 1408, 1369, 1287, 1173; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.66 (1H, ap. d, *J* 8.5, Ar*H*), 7.46-7.43 (1H, m, Ar*H*), 7.37-7.33 (1H, m, Ar*H*), 7.22-7.19 (1H, m, Ar*H*), 5.89 (1H, s, C*H*OMe), 5.52 (1H, s, C*H*Br), 4.27-4.22 (4H, m, 2 × CH_2CH$_3$), 3.50 (3H, s, OCH_3),

1.29-1.25 (6H, m, 2 × CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.9, 154.6, 137.4, 135.6, 132.1, 129.4, 127.9, 125.9, 123.0, 122.5, 63.8, 58.0, 57.0, 15.1, 14.9; *m/z* HRMS (FI^+) 389.0337 ($[M^+]$, $C_{15}H_{19}{}^{81}BrO_5N_2$ requires 389.0350).

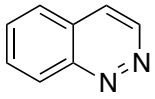
Diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate, 109



N-Chlorosuccinimde (800 mg, 6.0 mmol, 1.2 eq) and diethyl dihydrocinnoline-1,2-dicarboxylate **59** (1.38 g, 5.0 mmol, 1.0 eq) were suspended in DMF (10 mL) and heated at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was partitioned between water (40 mL) and ethyl acetate (40 mL). The organic phase was separated and washed with water (3 × 40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (5-25% ethyl acetate in hexane) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **109** (1.35 g, 87%) as a white solid: mp 93-94 °C; ν_{max} (neat)/cm^{-1} 2983, 2938, 2910, 1751, 1735, 1623, 1601, 1568, 1369, 1242, 1052; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.54-7.52 (1H, m, Ar*H*), 7.50-7.46 (2H, m, 2 × Ar*H*), 7.44-7.41 (2H, m, Ar*H* and C=C*H*N), 4.27-4.20 (4H, m, 2 × CH_2CH_3), 1.27 (3H, t, *J* 7.0, CH_2CH_3), 1.22 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 154.9, 152.1, 136.3, 130.3, 128.1, 127.9, 126.1, 125.4, 123.5, 118.3, 64.3, 64.0, 15.0, 14.9; *m/z* LRMS (ESI^+) 643.1 (^{35}Cl, $[(2M+Na)^+]$, 100%), 335.1 (^{37}Cl, $[(M+Na)^+]$, 30%),

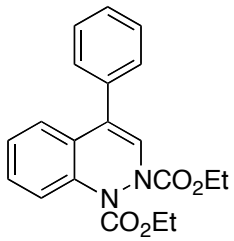
333.1 (^{35}Cl, [(M+Na)$^+$], 60%), 311.1 (^{35}Cl, [(M+H)$^+$], 30%); HRMS (ESI$^+$) 333.0617 ([(M+Na)$^+$], $C_{14}H_{15}{}^{35}ClN_2O_4Na$ requires 333.0613).

Cinnoline, 110



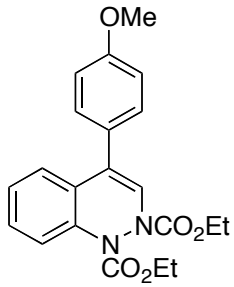
Prepared following general procedure C using diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** (156 mg, 0.5 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in petroleum ether) yielded cinnoline **110** (36 mg, 54%) as an off-white solid: ν_{max} (neat) / cm^{-1} 3059, 1581, 1392, 1292, 1091; δ_H (400 MHz, $CDCl_3$) 9.29 (1H, d, *J* 6.0, ArCHC*H*N), 8.52-8.50 (1H, m, Ar*H*), 7.85-7.80 (3H, m, 2 × Ar*H* and C*H*CHN), 7.75-7.71 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 150.8, 145.0, 131.2, 130.7, 129.8, 126.6, 126.0, 122.6; *m/z* LRMS (ESI$^+$) 153.0 ([(M+Na)$^+$], 100%); HRMS (ESI$^+$) 153.0424 ([(M+Na)$^+$], $C_8H_6N_2Na$ requires 153.0423). Data in accordance with the literature.[85]

General Procedure D for the synthesis of 4-aryl diethyl dihydrocinnoline-1,2-dicarboxylates, exemplified by the preparation of diethyl 4-phenyldihydrocinnoline-1,2-dicarboxylate, 111



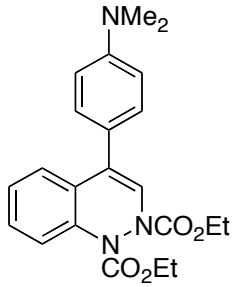
Phenyl boronic acid (92 mg, 0.75 mmol, 1.5 eq), diethyl 4-chlorodihydrocinnoline-1,2-dicarboxylate **109** (155 mg, 0.50 mmol, 1.0 eq), $Pd(OAc)_2$ (6 mg, 0.025 mmol, 0.05 eq), XPhos (24 mg, 0.05 mmol, 0.1 eq) and Cs_2CO_3 (326 mg, 1.0 mmol, 2.0 eq) were combined in a reaction vial. The vessel was evacuated and filled with nitrogen three times before toluene (1 mL) was added and the resulting suspension heated at 100 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL), filtered through a pad of Celite® and concentrated in *vacuo*. Column chromatography (5-25% ethyl acetate in hexane) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **111** (160 mg, 91%) as a white solid: mp 95-97 °C; ν_{max} (neat)/cm^{-1} 2987, 2977, 2959, 1749, 1726, 1601, 1565, 1372, 1269, 1058; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.50-7.39 (7H, m, 7 × ArH), 7.30-7.27 (1H, m, ArH), 7.20 (1H, s, C=C*H*N), 7.11-7.09 (1H, m, ArH), 4.29-4.21 (4H, m, 2 × CH_2CH$_3$), 1.30 (3H, t, *J* 7.0, CH$_2$CH_3), 1.23 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.4, 152.6, 136.8, 135.5, 129.7, 129.6, 128.99, 128.96, 128.4, 127.7, 127.0, 126.1, 125.7, 125.0, 64.0, 63.6, 15.1, 14.9; *m/z* LRMS (ESI$^+$) 727.3 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) 375.1320 ([(M+Na)$^+$], $C_{20}H_{20}N_2NaO_4$ requires 375.1315).

Diethyl 4-(4-methoxyphenyl)dihydrocinnoline-1,2-dicarboxylate, 112



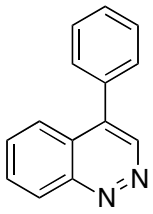
Prepared following general procedure D using 4-methoxyphenylboronic acid (114 mg, 0.75 mmol, 1.5 eq). Column chromatography (5-25% ethyl acetate in hexane) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **112** (170 mg, 89%) as a white solid: mp 119-121 °C; ν_{max} (neat)/cm^{-1} 2978, 2960, 2935, 1740, 1704, 1629, 1610, 1567, 1347, 1216, 1035; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.49-7.47 (1H, m, Ar*H*), 7.41-7.38 (1H, m, Ar*H*), 7.32 (2H, d, *J* 8.5, 2 × Ar*H*), 7.29-7.26 (1H, m, Ar*H*), 7.14 (1H, s, C=C*H*N), 7.11-7.10 (1H, m, Ar*H*), 7.04 (2H, d, *J* 8.5, 2 × Ar*H*), 4.28-4.20 (4H, m, 2 × CH_2CH$_3$), 3.84 (3H, s, ArOCH_3), 1.29 (3H, t, *J* 7.0, CH$_2$CH_3), 1.23 (3H, t, *J* 7.0, CH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 160.3, 155.3, 152.7, 136.8, 130.8, 128.9, 128.6, 127.7, 127.6, 126.3, 125.8, 125.6, 125.0, 115.4, 63.9, 63.6, 56.2, 15.1, 14.9; *m/z* LRMS (ESI$^+$) 787.3 ([(2M+Na)$^+$], 100%); HRMS (ESI$^+$) found 405.1416 ([(M+Na)$^+$], $C_{21}H_{22}N_2NaO_5$ requires 405.1421).

Diethyl 4-(4-(dimethylamino)phenyl)dihydrocinnoline-1,2-dicarboxylate, 113



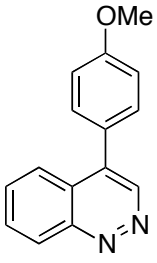
Prepared following general procedure D using 4-(dimethylamino)phenylboronic acid (124 mg, 1.5 mmol, 1.5 eq). Column chromatography (5-25% ethyl acetate in hexane) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **113** (161 mg, 82%) as a white solid: mp 109-110 °C; ν_{max} (neat)/cm^{-1} 3076, 2980, 2934, 1717, 1610, 1567, 1552, 1372, 1252, 1053; δ_H (500 MHz, $C_6D_5CD_3$, 90 °C) 7.48-7.46 (1H, m, Ar*H*), 7.40-7.37 (1H, m, Ar*H*), 7.29-7.26 (1H, m, Ar*H*), 7.21 (2H, d, *J* 9.0, 2 × Ar*H*), 7.17-7.16 (1H, m, Ar*H*), 7.07 (1H, s, C=C*H*N), 6.81 (2H, d, *J* 9.0, 2 × Ar*H*), 4.27-4.21 (4H, m, 2 × C*H*$_2$CH$_3$), 2.97 (6H, s, ArN(C*H*$_3$)$_2$), 1.29 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.23 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $C_6D_5CD_3$, 90 °C) 155.4, 152.8, 151.3, 136.9, 130.2, 128.8, 128.7, 127.5, 126.5, 125.5, 125.3, 125.2, 122.8, 113.4, 63.9, 63.5, 41.2, 15.1, 15.0; *m/z* LRMS (ESI$^+$) 813.4 ([(2M+Na)$^+$], 100%), 418.2 ([(M+Na)$^+$], 20%); HRMS (ESI$^+$) found 418.1735 ([(M+Na)$^+$], $C_{22}H_{25}N_3NaO_4$ requires 418.1737).

4-Phenylcinnoline



Prepared following general procedure C using diethyl 4-phenyldihydrocinnoline-1,2-dicarboxylate **111** (164 mg, 0.4 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in hexane) yielded the desired *cinnoline* (92 mg, 74%) as a yellow solid: mp 156-157 °C; ν_{max} (neat)/cm^{-1} 3056, 2970, 1519, 1443, 1379, 1137; δ_H (500 MHz, CD_3OD) 9.27 (1H, s, C(Ph)C*H*N), 8.55-8.53 (1H, m, Ar*H*), 8.09-8.07 (1H, m, Ar*H*), 8.02-7.99 (1H, m, Ar*H*), 7.90-7.87 (1H, m, Ar*H*), 7.66-7.62 (5H, m, 5 × Ar*H*); δ_C (125 MHz, CD_3OD) 151.7, 145.5, 138.2, 135.2, 133.3, 132.6, 131.1, 130.7, 130.3, 130.2, 126.2, 125.9; *m/z* LRMS (ESI$^+$) 435.1 ([(2M+Na)$^+$], 100%), 229.1 ([(M+Na)$^+$], 30%); HRMS (ESI$^+$) 229.0736 ([(M+Na)$^+$], $C_{14}H_{10}N_2Na$ requires 229.0736).

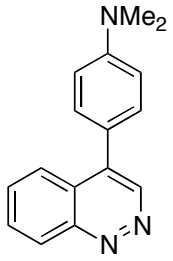
4-(4-Methoxyphenyl)cinnoline, 114



Prepared following general procedure C using diethyl 4-(4-methoxy)phenyldihydrocinnoline-1,2-dicarboxylate **112** (210 mg, 0.6 mmol, 1.0 eq).

Column chromatography (10% acetone and 2.5% triethylamine in hexane) yielded *cinnoline* **114** (83 mg, 82%) as a yellow solid: mp 172-173 °C; ν_{max} (neat)/cm^{-1} 3012, 2999, 2962, 1608, 1575, 1400, 1292, 1137; δ_H (500 MHz, CD_3OD) 9.22 (1H, s, C(Ar)C*H*N), 8.49-8.47 (1H, m, Ar*H*), 8.12-8.09 (1H, m, Ar*H*), 7.98-7.95 (1H, m, Ar*H*), 7.87-7.84 (1H, m, Ar*H*), 7.60-7.57 (2H, m, 2 × Ar*H*), 7.18-7.16 (2H, m, 2 × Ar*H*), 3.92 (3H, s, ArOCH_3); δ_C (125 MHz, CD_3OD) 162.5, 151.7, 145.5, 138.0, 133.0, 132.5, 132.4, 130.1, 127.1, 126.3, 126.0, 115.8, 56.0; *m/z* LRMS (ESI$^+$) 495.2 ([(2M+Na)$^+$], 100%), 237.1 ([(M+H)$^+$], 20%); HRMS (ESI$^+$) 259.0845 ([(M+Na)$^+$], $C_{15}H_{12}N_2NaO$ requires 259.0842).

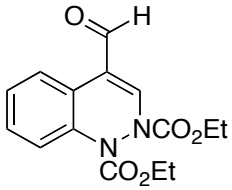
4-(Cinnolin-4-yl)-*N*,*N*-dimethylaniline, 115



Prepared following general procedure C using diethyl 4-(4-(dimethylamino)phenyl dihydrocinnoline-1,2-dicarboxylate **113** (133 mg, 0.3 mmol, 1.0 eq). Column chromatography (10% acetone and 2.5% triethylamine in hexane) yielded *cinnoline* **115** (64 mg, 75%) as a bright orange solid: mp 182-184 °C; ν_{max} (neat)/cm^{-1} 2983, 2970, 2919, 1606, 1564, 1249, 1184, 1064; δ_H (500 MHz, CD_3OD) 9.22 (1H, s, C(Ar)C*H*N), 8.47-8.45 (1H, m, Ar*H*), 8.24-8.22 (1H, m, Ar*H*), 7.97-7.95 (1H, m, Ar*H*), 7.87-7.85 (1H, m, Ar*H*), 7.57-7.55 (2H, m, 2 × Ar*H*), 6.99-6.97 (2H, m, 2 × Ar*H*), 3.09 (6H, s, ArN(CH_3)$_2$); δ_C (125 MHz, CD_3OD) 153.0, 151.7, 145.4, 138.8,

132.6, 132.3, 132.2, 129.9, 126.4, 126.3, 121.8, 113.7, 40.4; *m/z* LRMS (ESI^+) 521.2 ([(2M+Na)$^+$], 100%), 250.1 ([(M+H)$^+$], 30%); HRMS (ESI^+) 250.1341 ([(M+H)$^+$], $C_{16}H_{16}N_3$ requires 250.1339).

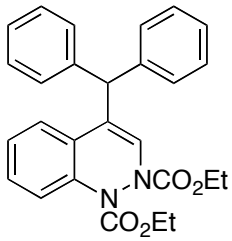
Diethyl 4-formyldihydrocinnoline-1,2-dicarboxylate, 116



Phosphorous oxychloride (0.5 mL, 5.0 mmol, 5.0 eq) was added drop-wise to DMF (4 mL) at 0 °C. The solution was allowed to stir for 20 min at this temperature before diethyl dihydrocinnoline-1,2-dicarboxylate **59** (276 mg, 1.0 mmol, 1.0 eq) was added drop-wise as a solution in DMF (1 mL). The resulting mixture was allowed to warm to room temperature and then heated at 80 °C for 16 h. After cooling to room temperature the reaction mixture was poured onto ice-cold water (40 mL) and the product extracted with DCM (2 × 40 mL). The combined organic phases were washed with water (3 × 40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (0-30% ethyl acetate in hexane) yielded *aldehyde* **116** (249 mg, 82%) as a pale yellow solid: mp 85-86 °C; ν_{max} (neat)/cm^{-1} 3072, 3010, 2989, 1728, 1671, 1607, 1567, 1367, 1222, 1016; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 9.71 (1H, s, CO*H*), 8.32 (1H, s, C=C*H*N), 8.17-8.16 (1H, m, Ar*H*), 7.44-7.43 (2H, m, 2 × Ar*H*), 7.40-7.37 (1H, m, Ar*H*), 4.38-4.36 (2H, m, C*H*$_2$CH$_3$), 4.21-4.19 (2H, m, C*H*$_2$CH$_3$), 1.34 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.20 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90

°C) 189.9, 155.4, 151.1, 147.1, 135.2, 129.3, 128.4, 126.0, 125.1, 124.9, 120.9, 64.9, 64.5, 14.9, 14.8; *m/z* LRMS (ESI^+) 631.2 ([$(2M+Na)^+$], 100%), 327.1 ([$(M+Na)^+$], 40%), 305.1 ([$(M+H)^+$], 20%); HRMS (ESI^+) 327.0947 ([$(M+Na)^+$], $C_{15}H_{16}N_2NaO_5$ requires 327.0951).

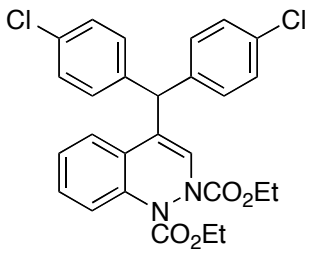
General Procedure E for the synthesis of 4-alkyl diethyl dihydrocinnoline-1,2-dicarboxylates, exemplified by the preparation of diethyl 4-benzhydryldihydrocinnoline-1,2-dicarboxylate, 117



Diphenylmethanol (138 mg, 0.8 mmol, 1.5 eq), *p*-toluenesulfonic acid (10 mg, 0.1 mmol, 0.1 eq) and diethyl dihydrocinnoline-1,2-dicarboxylate **59** (138 mg, 0.5 mmol, 1.0 eq) were suspended in toluene (1 mL). The resulting solution was heated to 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL). The resulting biphasic mixture was separated and the aqueous phase extracted with diethyl ether (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (5-10% acetone in petroleum ether) afforded *diethyl dihydrocinnoline-1,2-dicarboxylate* **117** (190 mg, 86%) as a pale yellow solid: mp 73-75 °C; ν_{max} (neat)/cm^{-1} 3026, 2981, 1718, 1600, 1452, 1244, 1214, 1053; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.39-7.36 (4H, m, 4 × Ar*H*), 7.32-7.26 (4H, m, 4 × Ar*H*),

7.22-7.17 (6H, m, 6 × Ar*H*), 6.41 (1H, s, C=C*H*N), 5.70 (1H, s, Ph_2CH), 4.26-4.13 (4H, m, 2 × CH_2CH_3), 1.23-1.18 (6H, m, 2 × CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.4, 152.1, 142.2, 141.6, 136.4, 129.6, 129.1 (2 × C), 128.94, 128.89, 128.4, 128.1, 127.28, 127.25, 127.1, 126.3, 125.1, 123.6, 63.6, 63.0, 49.8, 14.60, 14.58; *m/z* LRMS (ESI^+) 465.2 ([$(M+Na)^+$], 20%), 443.2 ([$(M+H)^+$], 100%); HRMS (ESI^+) 465.1776 ([$(M+Na)^+$], $C_{27}H_{26}N_2O_4Na$ requires 465.1785).

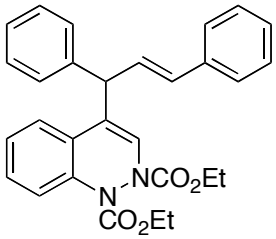
Diethyl 4-(bis(4-chlorophenyl)methyl)dihydrocinnoline-1,2-dicarboxylate, 118



Prepared following general procedure E using 4,4'-dichlorobenzhydrol (190 mg, 0.8 mmol, 1.5 eq). Column chromatography (5-10% acetone in petroleum ether) afforded *diethyl dihydrocinnoline-1,2-dicarboxylate* **118** (211 mg, 83%) as a light pink solid: mp 79-81 °C; ν_{max} (neat)/cm^{-1} 3004, 2980, 1720, 1630, 1488, 1281, 1173, 1053; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.44-7.30 (7H, m, 7 × Ar*H*), 7.23-7.18 (5H, m, 5 × Ar*H*), 6.41 (1H, s, C=C*H*N), 5.77 (1H, s, Ar_2CH), 4.26-4.16 (4H, m, 2 × CH_2CH_3), 1.23-1.19 (6H, m, 2 × CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 149.6, 146.4, 135.1, 134.4, 130.7, 126.6, 126.5, 125.6, 125.1, 123.5, 123.4, 123.3, 122.6, 122.3, 121.6, 119.9, 119.4, 117.9, 58.0, 57.4, 42.6, 8.88, 8.86; *m/z* LRMS (ESI^+) 535.2 ($^{37}Cl^{35}Cl$,

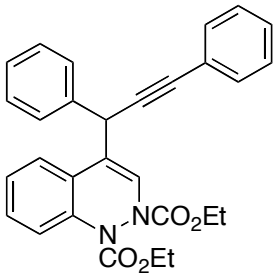
[(M+Na)$^+$], 60%), 533.2 ($^{35}Cl^{35}Cl$, [(M+Na)$^+$], 100%); HRMS (ESI$^+$) 533.0999 ([(M+Na)$^+$], $C_{27}H_{24}{}^{35}Cl^{35}ClN_2O_4Na$ requires 533.1005).

(*E*)-Diethyl 4-(1,3-diphenylallyl)dihydrocinnoline-1,2-dicarboxylate, 119



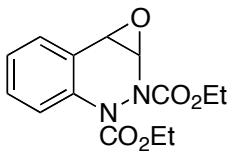
Prepared following general procedure E using 1,3-diphenyl-2-propen-1-ol (158 mg, 0.75 mmol, 1.5 eq). Column chromatography (5-10% acetone in petroleum ether) afforded *diethyl dihydrocinnoline-1,2-dicarboxylate* **119** (147 mg, 63%) as a yellow solid: mp 63-64 °C; ν_{max} (neat)/cm^{-1} 3026, 2980, 1719, 1630, 1568, 1485, 1286, 1129, 1028; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.46-7.18 (14H, m, 14 × Ar*H*), 7.15 and 6.81 (1H, 2 × s, C=C*H*N), 6.68-6.62 (1H, m, PhCHC*H*=CHPh), 6.53 and 6.36 (1H, 2 × d, *J* 16.0, PhCHCH=C*H*Ph), 5.12 and 5.07 (1H, 2 × d, *J* 7.0, PhC*H*CH=CHPh), 4.27-4.18 (4H, m, 2 × C*H*$_2$CH$_3$), 1.26-1.19 (6H, m, 2 × CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 149.7, 146.6, 136.5, 135.6, 131.6, 131.0, 130.7, 126.5, 125.2, 123.4, 123.3, 123.2, 122.6, 122.4, 122.2, 121.6, 121.5, 121.3, 121.1, 120.9, 119.4, 118.0, 57.8, 57.4, 41.6, 41.5, 9.0, 8.9; *m/z* LRMS (ESI$^+$) 469.3 ([(M+H)$^+$], 100%); HRMS (ESI$^+$) found 491.1925 ([(M+Na)$^+$], $C_{29}H_{28}N_2O_4Na$ requires 491.1941).

Diethyl 4-(1,3-diphenylprop-2-yn-1-yl)dihydrocinnoline-1,2-dicarboxylate, 120



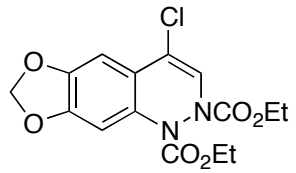
Prepared following general procedure E using 1,3-diphenyl-2-propyn-1-ol (158 μL, 0.75 mmol, 1.5 eq). Column chromatography (5-10% acetone in petroleum ether) afforded *diethyl dihydrocinnoline-1,2-dicarboxylate* **120** (165 mg, 71%) as a pale orange solid: mp 59-61 °C; ν_{max} (neat)/cm^{-1} 3060, 2981, 1721, 1599, 1373, 1242, 1051; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.64-7.19 (14H, m, 14 × Ar*H*), 5.61 and 5.51 (1H, 2 × s, C=C*H*N), 4.29-4.17 (4H, m, 2 × C*H*$_2$CH$_3$), 1.30-1.25 (3H, m, CH$_2$C*H*$_3$), 1.20-1.16 (3H, m, CH$_2$C*H*$_3$); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 149.6, 146.5, 134.5, 133.2, 130.7, 126.0, 123.4, 123.3, 122.6, 122.3, 122.2, 122.1, 122.0, 121.9, 121.5, 121.4, 119.5, 119.4, 117.8, 117.2, 84.1, 83.7, 80.5, 79.6, 57.9, 57.4, 8.9, 8.8; *m/z* LRMS (ESI$^+$) 489.2 ([(M+Na)$^+$], 40%), 467.3 ([(M+H)$^+$], 100%); HRMS (ESI$^+$) found 489.1781 ([(M+Na)$^+$], $C_{29}H_{26}N_2O_4Na$ requires 489.1785).

Diethyl oxireno[2,3-*c*]dihydrocinnoline-2,3(1a*H*,7b*H*)-dicarboxylate, 121



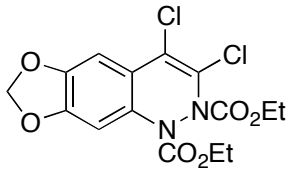
Oxone (1.5 g, 5.0 mmol, 2.5 eq) in water (6 mL) was added drop-wise to a vigourously stirring solution of diethyl dihydrocinnoline-1,2-dicarboxylate **59** (560 mg, 2.0 mmol, 1.0 eq) in a 3:2:2 mixture of acetone, DCM and sat. $NaHCO_{3(aq)}$ (9 mL, 6 mL and 6 mL respectively) at 0 °C and left open to air. The resulting biphasic mixture was stirred at this temperature for 30 min before being allowed to warm to room temperature and stirred for a further 1 h. The reaction was partitioned between DCM (30 mL) and water (30 mL). The resulting biphasic mixture was separated and the aqueous layer extracted with a further volume of DCM (30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford *epoxide* **121** (580 mg, quant.) as a colourless gum: ν_{max} (neat)/cm^{-1} 3055, 2983, 1724, 1612, 1372, 1289, 1238, 1046; δ_H (200 MHz, $CDCl_3$) 7.45-7.41 (3H, m, 3 × Ar*H*), 7.30-7.22 (1H, m, Ar*H*), 5.95 (1H, d, *J* 3.0, ArCHOC*H*N), 4.31-4.18 (4H, m, 2 × C*H*$_2$CH$_3$), 3.97 (1H, d, *J* 3.0, ArC*H*OCHN), 1.34-1.26 (6H, m, 2 × CH$_2$C*H*$_3$); *m/z* LRMS (ESI^+) 607.2 ([$(2M+Na)^+$], 100%); HRMS (ESI^+) found 315.0943 ([$(M+Na)^+$], $C_{14}H_{16}N_2NaO_5$ requires 315.0951). Incomplete characterisation data due to low stability of the molecule at elevated temperatures.

Diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate, 123



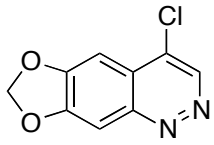
N-Chlorosuccinimde (280 mg, 2.1 mmol, 1.05 eq) and diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **60** (640 mg, 2.0 mmol, 1.0 eq) were suspended in DMF (4 mL) and heated at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (20 mL). The organic phase was separated and washed with water (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2% ethyl acetate and 48% petroleum ether in DCM) yielded *diethyl dihydrocinnoline-1,2-dicarboxylate* **123** (582 mg, 82%) as an off-white solid: mp 98-100 °C; ν_{max} (neat)/cm^{-1} 3002, 2987, 2913, 1750, 1731, 1683, 1627, 1589, 1479, 1372, 1177; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.28 (1H, s, CClC*H*N), 7.03 (1H, s, Ar*H*), 7.00 (1H, s, Ar*H*), 6.14 (1H, d, *J* 0.5, OC*H*H'O), 6.10 (1H, d, *J* 0.5, OCH*H'*O), 4.27-4.19 (4H, m, 2 × CH_2CH_3), 1.27 (3H, t, *J* 7.0, CH_2CH_3), 1.23 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 155.2, 152.3, 148.8, 147.4, 130.9, 125.7, 120.4, 118.6, 106.8 (2 × C), 103.1, 64.3, 63.9, 15.0, 14.9; *m/z* LRMS (ESI^+) 733.1 ($^{37}Cl^{35}Cl$, $[(2M+Na)^+]$, 60%), 731.1 ($^{35}Cl^{35}Cl$, $[(2M+Na)^+]$, 100%), 377.0 (^{35}Cl, $[(M+Na)^+]$, 20%); HRMS (ESI^+) 377.0515 ($[(M+Na)^+]$, $C_{15}H_{15}{}^{35}ClN_2NaO_6$ requires 377.0511).

Diethyl 3,4-dichloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate, 124



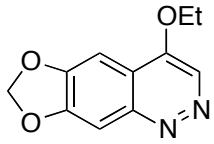
N-Chlorosuccinimde (334 mg, 2.5 mmol, 2.5 eq) and diethyl [1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **60** (320 mg, 1.0 mmol, 1.0 eq) were suspended in DMF (2 mL) and heated at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (20 mL). The organic phase was separated and washed with water (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2% ethyl acetate and 48% petroleum ether in DCM) afforded *diethyl dihydrocinnoline-1,2-dicarboxylate* **124** (303 mg, 78%) as an off-white solid: mp 143-144 °C; ν_{max} (neat)/cm^{-1} 2989, 2971, 2935, 1743, 1725, 1626, 1588, 1370, 1215, 1030; δ_H (500 MHz, $(CD_3)_2SO$, 90 °C) 7.13 (1H, s, Ar*H*), 7.08 (1H, s, Ar*H*), 6.16 (1H, d, *J* 1.0, OC*H*H'O), 6.13 (1H, d, *J* 1.0, OCH*H*'O), 4.29-4.22 (4H, m, 2 × CH_2CH_3), 1.27 (3H, t, *J* 7.0, CH_2CH_3), 1.23 (3H, t, *J* 7.0, CH_2CH_3); δ_C (125 MHz, $(CD_3)_2SO$, 90 °C) 153.3, 153.2, 149.1, 146.8, 131.7, 123.9, 122.9, 118.8, 105.0, 104.2, 103.1, 64.6, 64.1, 14.6, 14.5; *m/z* LRMS (ESI^+) 413.0 ($^{37}Cl^{35}Cl$, [$(M+Na)^+$], 60%), 411.0 ($^{35}Cl^{35}Cl$, [$(M+Na)^+$], 100%); HRMS (ESI^+) found 411.0117 ([$(M+Na)^+$], $C_{15}H_{14}{}^{35}Cl^{35}ClN_2NaO_6$ requires 411.0121).

4-Chloro-[1,3]dioxolo[4,5-*g*]cinnoline, 125



Prepared following general procedure C using diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **123** (106 mg, 0.3 mmol, 1.0 eq) and sodium hydroxide (5 M, 0.15 mL, 0.75 mmol, 2.5 eq). Column chromatography (10% acetone and 2.5% triethylamine in hexane) yielded minor product *cinnoline* **125** (8 mg, 13%) as a yellow solid: mp 167-169 °C; ν_{max} (neat)/cm^{-1} 3036, 2962, 2929, 1545, 1421, 1202, 1028; δ_H (500 MHz, $(CD_3)_2CO$) 9.64 (1H, s, CClC*H*N), 8.14 (1H, s, Ar*H*), 7.88 (1H, s, Ar*H*), 6.87 (2H, s, OCH_2O); δ_C (125 MHz, $(CD_3)_2CO$) 153.1, 152.7, 150.3, 143.5, 132.4, 123.4, 104.2, 103.6, 96.8; *m/z* LRMS (ESI$^+$) 233.0 (^{37}Cl, [(M+Na)$^+$], 45%), 231.0 (^{35}Cl, [(M+Na)$^+$], 100%); HRMS (ESI$^+$) found 230.9940 ([(M+Na)$^+$], $C_9H_5{}^{35}ClN_2NaO_2$ requires 230.9932).

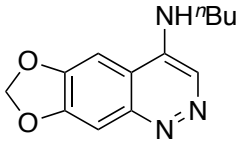
4-Ethoxy-[1,3]dioxolo[4,5-*g*]cinnoline, 126



Prepared following general procedure C using diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **123** (106 mg, 0.3 mmol, 1.0 eq) and sodium hydroxide (5 M, 0.3 mL, 1.5 mmol, 5.0 eq). Column chromatography (10% acetone

and 2.5% triethylamine in hexane) yielded minor product *cinnoline* **126** (7 mg, 11%) as a yellow solid: mp 159-161 °C; ν_{max} (neat)/cm^{-1} 3016, 2970, 2946, 1436, 1368, 1215, 1092; δ_H (500 MHz, $(CD_3)_2SO$) 8.99 (1H, s, C(OEt)C*H*N), 7.63 (1H, s, Ar*H*), 7.33 (1H, s, Ar*H*), 6.30 (2H, s, OCH_2O), 4.41 (2H, q, *J* 7.0, OCH_2CH$_3$), 1.47 (3H, t, *J* 7.0, OCH$_2$CH_3); δ_C (125 MHz, $(CD_3)_2SO$) 151.4, 151.2, 150.3, 149.1, 129.8, 115.4, 103.4, 102.8, 95.0, 64.7, 14.4; *m/z* LRMS (ESI$^+$) 219.1 ([(M+H)$^+$], 100%); HRMS (ESI$^+$) found 219.0767 ([(M+H)$^+$], $C_{11}H_{11}N_2O_3$ requires 219.0764).

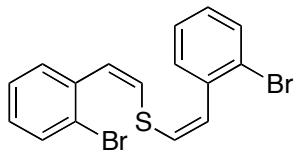
_N_-Butyl-[1,3]dioxolo[4,5-*g*]cinnolin-4-amine, 122



Diethyl 4-chloro-[1,3]dioxolo[4,5-*g*]dihydrocinnoline-1,2-dicarboxylate **123** (106 mg, 0.3 mmol, 1.0 eq), BrettPhos pre-catalyst (24 mg, 0.03 mmol, 0.1 eq) and NaO^{t}Bu (43 mg, 0.45 mmol, 1.5 eq) were combined in a reaction vial. The vessel was evacuated and filled with nitrogen three times before dioxane (1 mL) was added. *n*-Butylamine (44 μL, 0.45 mmol, 1.5 eq) was added and the resulting suspension heated at 70 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL), filtered through a pad of Celite® and concentrated *in vacuo*. The resulting crude was dissolved in ethanol (3 mL) before sodium hydroxide (5 M, 0.3 mL, 1.5 mmol, 5.0 eq) was added and the resulting solution heated at 70 °C for 16 h. After cooling to room temperature, the reaction mixture was partitioned between water (15 mL) and DCM (15 mL). The organic phase was separated and the aqueous

phase extracted with DCM (2 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2% methanol in ethyl acetate) yielded cinnoline **122** (46 mg, 62%) as a dark yellow solid: mp 201-203 °C; ν_{max} (neat)/cm^{-1} 3224, 3012, 2954, 1613, 1578, 1461, 1283, 1035; δ_H (500 MHz, $(CD_3)_2SO$) 8.47 (1H, s, C(NH^{n}Bu)C*H*N), 7.66 (1H, s, Ar*H*), 7.39 (1H, s, Ar*H*), 6.96 (1H, br t, *J* 5.5, N*H*^{n}Bu), 6.22 (2H, s, OCH_2O), 3.35-3.31 (2H, m, NCH_2), 1.66-1.63 (2H, m, CH_2), 1.45-1.38 (2H, m, CH_2), 0.94 (3H, t, *J* 7.5, CH_3); δ_C (125 MHz, $(CD_3)_2SO$) 150.2, 148.5, 147.1, 139.9, 127.8, 111.9, 103.7, 102.2, 96.3, 41.7, 30.3, 19.7, 13.8; *m/z* LRMS (ESI^+) 513.2 ([(2M+Na)$^+$], 100%), 491.2 ([(2M+H)$^+$], 60%), 246.1 ([(M+H)$^+$], 90%); HRMS (ESI^+) 246.1242 ([(M+Na)$^+$], $C_{13}H_{15}N_3O_2$ requires 246.1237). Data in accordance with the literature.[116]

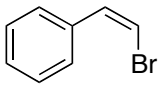
Bis((*Z*)-2-bromostyryl)sulfane, 127



Thiourea (76 mg, 1.0 mmol, 2.0 eq),), $Pd_2(dba)_2$ (12 mg, 0.013 mmol, 0.025 eq), DPEPhos (20 mg, 0.038 mmol, 0.075 eq) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before dioxane (1.5 mL) and (*Z*)-1-bromo-2-(2-bromovinyl)benzene **33** (75 μL, 0.5 mmol, 1.0 eq) were added and the resulting suspension heated at 90 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL), filtered through a pad of Celite® and concentrated *in vacuo*. Column

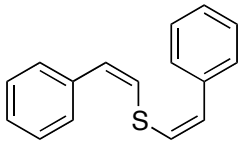
chromatography (100% petroleum ether) afforded *thioether* **127** (79 mg, 80%, *Z*,*Z*:*Z*,*E* 10:1) as a white solid: mp 87-88 °C; ν_{max} (neat)/cm^{-1} 3033, 2921, 1691, 1591, 1557, 1429, 1364, 1022; (*Z*,*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.61-7.58 (4H, m, 4 × Ar*H*), 7.33 (2H, td, *J* 7.5 and 1.0, 2 × Ar*H*), 7.12 (2H, td, *J* 8.0 and 1.5, 2 × Ar*H*), 6.76 (2H, d, *J* 10.5, 2 × ArC*H*=CHS), 6.53 (2H, d, *J* 10.5, 2 × ArCH=C*H*S); δ_C (100 MHz, $CDCl_3$) 135.8, 132.8, 129.6, 128.8, 127.8, 127.2, 126.5, 123.9; *m/z* LRMS (ESI$^+$) 420.9 ($^{81}Br^{81}Br$, [(M+Na)$^+$], 50%), 418.9 ($^{81}Br^{79}Br$, [M+Na)$^+$], 100%), 416.9 ($^{79}Br^{79}Br$, [(M+Na)$^+$], 50%); HRMS (ESI$^+$) 418.8913 ([(M+Na)$^+$], $C_{16}H_{12}{}^{81}Br^{79}BrSNa$ requires 418.8898).

(*Z*)-(2-Bromovinyl)benzene, 128



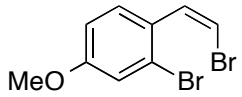
Prepared following general procedure A using potassium *tert*-butoxide (4.04 g, 36.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (15.7 g, 36.0 mmol, 1.2 eq) and benzaldehyde (3.0 mL, 30.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **128** (3.1 g, 56%, *Z*:*E* 10:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3016, 2970, 2946, 1612, 1544, 1489, 1367, 1228; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.76-7.74 (2H, m, 2 × Ar*H*), 7.46-7.35 (3H, m, 3 × Ar*H*), 7.12 (1H, d, *J* 8.0, ArC*H*=CHBr), 6.48 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 137.2, 135.0, 132.4, 129.0, 128.4, 128.3, 126.2, 106.4; *m/z* HRMS (FI$^+$) 183.9714 ([M$^+$], $C_8H_7{}^{81}Br$ requires 183.9711). Data in accordance with the literature.[101]

Di((*Z*)-styryl)sulfane, 129



Prepared as for bis((*Z*)-2-bromostyryl)sulfane **127** in a competition experiment using (*Z*)-(2-bromovinyl)benzene (130 μL, 1.0 mmol, 2.0 eq), bromobenzene (107 μL, 1.0 mmol, 2.0 eq) and thiourea (38 mg, 0.5 mmol, 1.0 eq). Column chromatography afforded the sole product thioether **129** (91 mg, 76%, *Z*,*Z*:*Z*,*E* 10:1) as a colourless oil: ν_{max} (neat)/cm^{-1} 3055, 3022, 2970, 1682, 1592, 1489, 1359, 1314, 1205, 1027; (*Z*,*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.54 (4H, ap. d, *J* 7.5, 4 × Ar*H*), 7.44 (4H, ap. t, *J* 7.5, 4 × Ar*H*), 7.31 (2H, ap. d, *J* 7.5, 2 × Ar*H*), 6.59 (2H, d, *J* 10.5, 2 × ArC*H*=CHS), 6.42 (2H, *J* 10.5, × ArCH=C*H*S); δ_C (100 MHz, $CDCl_3$) 136.3, 128.8, 128.5, 127.2, 126.9, 126.1; *m*/*z* HRMS (FI$^+$) 238.0820 ([M$^+$], $C_{16}H_{14}O_2S$; requires 238.0816). Data in accordance with the literature.[126]

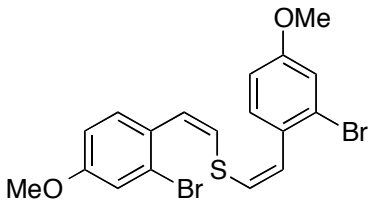
(*Z*)-2-Bromo-1-(2-bromovinyl)-4-methoxybenzene, 130



Prepared following general procedure A using potassium *tert*-butoxide (670 mg, 6.0 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.62 g, 6.0 mmol, 1.2 eq) and 2-bromo-4-methoxybenzaldehyde (1.0 g, 5.0 mmol, 1.0 eq). Column

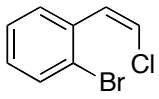
chromatography (100% petroleum ether) yielded *alkenyl bromide* **130** (770 mg, 53%, *Z*:*E* 10:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3015, 3005, 2970, 1596, 1538, 1481, 1436, 1370, 1286; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.80 (1H, d, *J* 8.5, Ar*H*), 7.18-7.16 (2H, m, Ar*H* and ArC*H*=CHBr), 6.90 (1H, dd, *J* 8.5 and 2.5, Ar*H*), 6.50 (1H, d, *J* 8.0, ArCH=C*H*Br), 3.82 (3H, s, ArOCH_3); δ_C (100 MHz, $CDCl_3$) 159.8, 131.6, 131.0, 127.3, 124.5, 117.8, 113.0, 107.8, 55.6; *m/z* HRMS (FI$^+$) 291.8922 ([M$^+$], $C_9H_8O^{81}Br^{79}Br$ requires 291.8867).

Bis((*Z*)-2-bromo-4-methoxystyryl)sulfane, 131



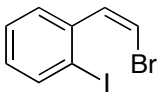
Prepared as for bis((*Z*)-2-bromostyryl)sulfane **127** using (*Z*)-2-bromo-1-(2-bromovinyl)-4-methoxybenzene **130** (87 μL, 0.5 mmol, 1.0 eq). Column chromatography (5% Diethyl ether in petroleum ether) yielded *thioether* **131** (78 mg, 68%, *Z*,*Z*:*Z*,*E* >20:1) as a white solid: mp 98-100 °C; ν_{max} (neat)/cm^{-1} 3012, 2970, 2906, 1667, 1595, 1508, 1481, 1375, 1237, 1101; δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.5, 2 × Ar*H*), 7.15 (2H, d, *J* 2.5, 2 × Ar*H*), 6.89 (2H, dd, *J* 8.5 and 2.5, 2 × Ar*H*), 6.69 (2H, d, *J* 10.5, 2 × ArC*H*=CHS), 6.40 (2H, d, *J* 10.5, 2 × ArCH=C*H*S), 3.81 (6H, s, 2 × OCH_3); δ_C (100 MHz, $CDCl_3$) 159.1, 130.2, 128.3, 126.1, 125.9, 124.4, 118.1, 113.1, 55.6; *m/z* HRMS (FI$^+$) 455.9233 ([M$^+$], $C_{18}H_{16}O_2S^{81}Br^{79}Br$, requires 455.9218).

(*Z*)-1-Bromo-2-(2-chlorovinyl)benzene, 132



Prepared following general procedure A using potassium *tert*-butoxide (1.4 g, 12.0 mmol, 1.2 eq), (chloromethyl)triphenylphosphonium chloride (4.2 g, 12.0 mmol, 1.2 eq) and 2-bromobenzaldehyde (1.2 mL, 10.0 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **132** (1.5 g, 68%, *Z*:*E* 5:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3027, 2944, 1689, 1605, 1561, 1463, 1337, 1278; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.87 (1H, ap. d, *J* 7.5, Ar*H*), 7.63 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.38-7.34 (1H, m, Ar*H*), 7.21-7.17 (1H, m, Ar*H*), 6.89 (1H, d, *J* 8.0, ArC*H*=CHCl), 6.43 (1H, d, *J* 8.0, ArCH=C*H*Cl); δ_C (100 MHz, $CDCl_3$) 134.9, 133.9, 132.7, 130.7, 129.5, 129.0, 127.0, 119.9; *m*/*z* HRMS (FI$^+$) 217.9333 ([M$^+$], $C_8H_6{}^{81}Br^{35}Cl$ requires 217.9319). Data in accordance with the literature.[53]

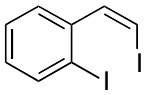
(*Z*)-1-(2-Bromovinyl)-2-iodobenzene, 133



Prepared following general procedure A using potassium *tert*-butoxide (580 mg, 5.2 mmol, 1.2 eq), (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.2 mmol, 1.2 eq) and 2-iodobenzaldehyde (1.0 g, 4.3 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded alkenyl bromide **133** (960 mg, 72%, *Z*:*E* 10:1) as a

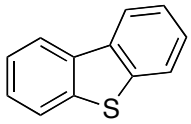
pale yellow oil: ν_{max} (neat)/cm^{-1} 3063, 3004, 1581, 1557, 1431, 1313, 1217, 1160; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.91 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.70 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.42-7.38 (1H, m, Ar*H*), 7.11 (1H, d, *J* 8.0, ArC*H*=CHBr), 7.06-7.02 (1H, m, Ar*H*), 6.59 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_C (100 MHz, $CDCl_3$) 140.8, 139.1, 138.8, 136.6, 130.1, 129.7, 127.8, 109.4; *m/z* HRMS (FI$^+$) 309.8680 ([M$^+$], $C_8H_6{}^{81}BrI$ requires 309.8677). Data in accordance with the literature.[146]

(*Z*)-1-Iodo-2-(2-iodovinyl)benzene, 134



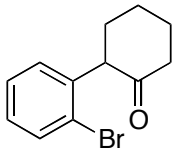
Prepared following general procedure A using potassium *tert*-butoxide (580 mg, 5.2 mmol, 1.2 eq), (iodomethyl)triphenylphosphonium iodide (2.76 g, 5.2 mmol, 1.2 eq) and 2-iodobenzaldehyde (1.0 g, 4.3 mmol, 1.0 eq). Column chromatography (100% petroleum ether) yielded *alkenyl iodide* **134** (1.3 g, 85%, *Z*:*E* 10:1) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3055, 2984, 1556, 1482, 1430, 1295, 1143; (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 7.90 (1H, ap. d, *J* 8.0, Ar*H*), 7.57 (1H, ap. d, *J* 7.5, Ar*H*), 7.43-7.39 (1H, m, Ar*H*), 7.25 (1H, d, *J* 8.5, ArC*H*=CHI), 7.08-7.04 (1H, m, Ar*H*), 6.74 (1H, d, *J* 8.5, ArCH=C*H*I); δ_C (100 MHz, $CDCl_3$) 148.4, 143.1, 141.3, 139.1, 129.8, 127.8, 99.0, 84.2; *m/z* HRMS (FI$^+$) 355.8553 ([M$^+$], $C_8H_6I_2$ requires 355.8559).

Dibenzo[*b*,*d*]thiophene, 135



Prepared as for bis((*Z*)-2-bromostyryl)sulfane **127** using 2,2'-diiodo-1,1'-biphenyl (203 mg, 0.5 mmol, 1.0 eq). Column chromatography (100% petroleum ether) afforded benzothiophene **135** (86 mg, 93%) as a white solid: ν_{max} (neat)/cm^{-1} 3050, 3017, 2970, 1677, 1511, 1455, 1366, 1264, 1130; δ_H (400 MHz, $CDCl_3$) 8.21-8.17 (2H, m, 2 × Ar*H*), 7.91-7.87 (2H, m, 2 × Ar*H*), 7.51-7.47 (4H, m, 4 × Ar*H*); δ_C (100 MHz, $CDCl_3$) 139.4, 135.5, 126.7, 124.4, 122.8, 121.6; *m*/*z* HRMS (FI$^+$) 184.0352 ([M$^+$], $C_{12}H_8S$ requires 184.0347). Data in accordance with the literature.[147]

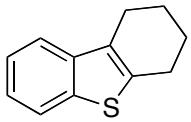
2-(2-Bromophenyl)cyclohexanone, 136



Prepared according to a literature procedure.[68] Caesium carbonate (9.1 g, 28.0 mmol, 2.3 eq), $Pd_2(dba)_3$ (58 mg, 0.06 mmol, 0.005 eq) and Xantphos (88 mg, 0.15 mmol, 0.012 eq) were combined in a reaction flask. The vessel was evacuated and filled with nitrogen three times before dioxane (13 mL) was added. 1-Bromo-2-iodobenzene (1.6 mL, 12.7 mmol, 1.0 eq) and cyclohexanone (2.7 mL, 25.5 mmol, 2.0 eq) were also added and the resulting suspension heated at 80 °C for 24 h. After cooling to room

temperature, the reaction mixture was partitioned between diethyl ether (50 mL) and water (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (10% diethyl ether in petroleum ether) yielded ketone **136** (1.9 g, 58%) as a white solid: mp 57-58 °C; ν_{max} (neat)/cm^{-1} 2920, 2910, 1709, 1566, 1462, 1377, 1281, 1196, 1121, 1070; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.39-7.07 (3H, m, 3 × Ar*H*), 4.12 (1H, dd, *J* 12.0 and 5.0, COC*H*Ar), 2.62-2.52 (2H, m, CH_2), 2.35-2.15 (2H, m, CH_2), 2.11-1.71 (4H, m, 2 × CH_2); δ_C (100 MHz, $CDCl_3$) 208.3, 137.8, 132.1, 128.9, 127.8, 126.8, 124.6, 56.0, 41.8, 33.6, 27.1, 25.1; *m/z* HRMS (FI^+) 252.0151 ([M^+], $C_{12}H_{13}O^{79}Br$ requires 252.0150). Data in accordance with the literature.[68]

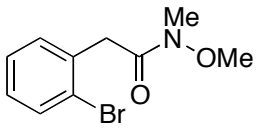
1,2,3,4-Tetrahydrodibenzo[*b*,*d*]thiophene, 137



2-(2-Bromophenyl)cyclohexanone **136** (127 mg, 0.5 mmol, 1.0 eq), sodium sulfide nonahydrate (360 mg, 1.5 mmol, 3.0 eq) and CuI (10 mg, 0.05 mmol, 0.1 eq) were combined in a reaction vial. The mixture was evacuated and filled with nitrogen three times before DMF (1.5 mL) and water (0.5 mL) were added. The reaction mixture was subjected to microwave irradiation for 2 h at 120 °C. After cooling to room temperature, the crude reaction mixture was partitioned between ethyl acetate (10 mL) and brine (10 mL). The organic phase was separated and washed with brine (2 ×

10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (100% petroleum ether) yielded benzothiophene **137** (48 mg, 51%) as a white solid: ν_{max} (neat)/cm^{-1} 3027, 2970, 2927, 1460, 1366, 1216; δ_H (400 MHz, $CDCl_3$) 7.80 (1H, ap. d, *J* 8.0, Ar*H*), 7.61 (1H, ap. d, *J* 8.0, Ar*H*), 7.37 (1H, ap. t, *J* 7.0, Ar*H*), 7.32-7.27 (1H, m, Ar*H*), 2.91-2.88 (2H, m, CH_2), 2.80-2.78 (2H, m, CH_2), 1.97-1.95 (4H, m, 2 × CH_2); δ_C (100 MHz, $CDCl_3$) 139.8, 138.4, 137.0, 129.5, 123.8, 123.5, 122.3, 120.4, 25.7, 23.70, 23.67, 22.4; *m/z* HRMS (FI$^+$) 188.0664 ([M^+], $C_{12}H_{12}S$ requires 188.0660). Data in accordance with the literature.[68]

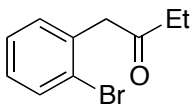
2-(2-Bromophenyl)-*N*-methoxy-*N*-methylacetamide, 138



1,1'-Carbonyldiimidazole (2.2 g, 13.3 mmol, 1.3 eq) was added portion-wise to a solution of 2-bromophenylacetic acid (2.2 g, 10.0 mmol, 1.0 eq) in DCM (30 mL) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and stirred for a further 1 h before *N*,*O*-dimethylhydroxylamine hydrochloride (2.0 g, 20.0 mmol, 2.0 eq) was added portion-wise. The resulting suspension was allowed to stir overnight. The reaction was quenched *via* addition of water (20 mL) and the resulting biphasic mixture separated. The aqueous phase was extracted with DCM (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (25% ethyl acetate in petroleum ether) afforded *Weinreb amide* **138** (2.26 g, 88%) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 3055, 2966, 1661, 1586,

1465, 1378, 1172, 1012; δ_H (400 MHz, $CDCl_3$) 7.56 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.31-7.25 (2H, m, 2 × Ar*H*), 7.14-7.10 (1H, m, Ar*H*), 3.93 (2H, s, COCH_2Ar), 3.71 (3H, s, OCH_3), 3.22 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 171.4, 135.0, 132.7, 131.4, 128.6, 127.5, 125.1, 61.4, 39.7, 32.4; *m/z* LRMS (ESI^+) 282.0 (^{81}Br, [$(M+Na)^+$], 100%), 280.0 (^{79}Br, [$(M+Na)^+$], 100%); HRMS (ESI^+) 281.9920 ([$(M+Na)^+$], $C_{10}H_{12}{}^{81}BrNO_2Na$ requires 281.9923).

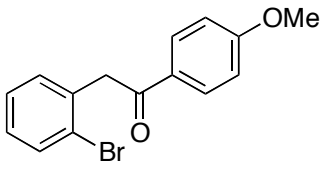
1-(2-Bromophenyl)butan-2-one, 139



Ethylmagnesium chloride (1.9 M in THF, 0.6 mL, 1.2 mmol, 1.2 eq) was added to a solution of 2-(2-bromophenyl)-*N*-methoxy-*N*-methylacetamide **138** (260 mg, 1.0 mmol, 1.0 eq) in THF (5 mL) at -20 °C. The resulting solution was allowed to warm to room temperature and stirred for 1 h. The reaction was then cooled to 0 °C and quenched *via* slow addition of sat. $NH_4Cl_{(aq)}$ (5 mL). The resulting suspension was diluted with water (15 mL) and diethyl ether (15 mL). The resulting biphasic mixture was separated and the aqueous phase extracted with diethyl ether (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (2.5-5% diethyl ether in petroleum ether) afforded *ketone* **139** (141 mg, 62%) as a clear and colourless oil: ν_{max} (neat)/cm^{-1} 3010, 2964, 2944, 1675, 1587, 1467, 1257, 1027; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.28 (1H, td, *J* 7.5 and 1.0, Ar*H*), 7.22 (1H, dd, *J* 7.5 and 2.0, Ar*H*), 7.14 (1H, td, *J* 7.5 and 2.0,

Ar*H*), 3.86 (2H, s, COCH_2Ar), 2.52 (2H, q, *J* 7.5, CH_2CH$_3$), 1.09 (3H, t, *J* 7.5, CH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 207.6, 134.9, 132.8, 131.7, 128.7, 127.6, 125.0, 49.7, 35.8, 7.8; *m/z* LRMS (ESI$^+$) 251.0 (^{81}Br, [(M+Na)$^+$], 100%), 249.0 (^{79}Br, [M+Na)$^+$], 95%); HRMS (ESI$^+$) 250.9871 ([(M+Na)$^+$], $C_{10}H_{11}{}^{81}BrONa$ requires 250.9865).

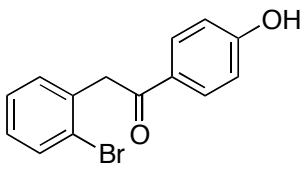
2-(2-Bromophenyl)-1-(4-methoxyphenyl)ethanone, 140



Prepared according to a literature procedure.[148] A solution of 2-bromophenyl acetic acid (4.3 g, 20.0 mmol, 1.0 eq) and thionyl chloride (3.4 mL, 40.0 mmol, 2.0 eq) in toluene (48 mL) was heated at relfux for 2 h. After cooling to room temperature, the resulting reaction mixture was concentrated *in vacuo* and redissolved in DCM (60 mL). Anisole (4.8 mL, 44.0 mmol, 2.2 eq) was added to the solution of the crude acid chloride and the resulting mixture cooled to 0 °C. Aluminium trichloride (3.2 g, 24.0 mmol, 1.2 eq) was added portion-wise, ensuring the reaction temperature remained below 10 °C. The resulting reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by addition of $HCl_{(aq)}$ (1 M, 60 mL). The organic layer was separated and the aqueous layer extracted with DCM (2 × 60 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated in *vacuo* to generate the crude product as a solid. The product was recrystallised from 1:1 MTBE:pentane to afford ketone **140** (3.16 g, 52%) as a white solid: ν_{max} (neat)/cm^{-1} 3015, 2931, 2903, 1666, 1597, 1469, 1333, 1169, 1027; δ_H (400 MHz, $CDCl_3$) 8.05

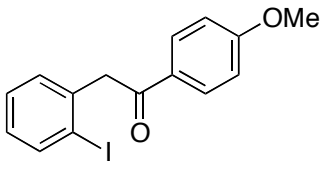
(2H, d, *J* 9.0, 2 × Ar*H*), 7.61-7.59 (1H, m, Ar*H*), 7.31-7.24 (2H, m, 2 × Ar*H*), 7.17-7.13 (1H, m, Ar*H*), 6.97 (2H, d, *J* 9.0, 2 × Ar*H*), 4.42 (2H, s, COCH_2Ar), 3.88 (3H, s, ArOCH_3); δ_C (100 MHz, $CDCl_3$) 194.9, 163.7, 135.3, 132.8, 131.7, 130.7, 129.7, 128.6, 127.5, 125.1, 113.8, 55.5, 45.4; *m/z* LRMS (ESI$^+$) 329.0 (^{81}Br, [(M+Na)$^+$], 100%), 327.0 (^{79}Br, [M+Na)$^+$], 90%), 307.0 (^{81}Br, [(M+H)$^+$], 20%)), 305.0 (^{79}Br, [M+H)$^+$], 20%). Data in accordance with the literature.[148]

2-(2-Bromophenyl)-1-(4-hydroxyphenyl)ethanone, 141



Prepared as for 1,2,3,4-tetrahydrodibenzo[*b*,*d*]thiophene **137** using 2-(2-bromophenyl)-1-(4-methoxyphenyl)ethanone **140** (153 mg, 0.5 mmol, 1.0 eq). Column chromatography (50% diethyl ether in petroleum ether) afforded *phenol* **141** (37 mg, 24%) as a white solid: mp 186-188 °C; ν_{max} (neat)/cm^{-1} 3278, 3020, 2957, 2915, 1656, 1574, 1514, 1487, 1221, 1172; δ_H (400 MHz, $(CD_3)_2CO$) 9.24 (1H, s, O*H*), 8.02 (2H, d, *J* 9.0, 2 × Ar*H*), 7.62-7.60 (1H, m, ArH), 7.37-7.34 (2H, m, 2 × Ar*H*), 7.24-7.20 (1H, m, Ar*H*), 6.98 (2H, d, *J* 9.0, 2 × Ar*H*), 4.50 (2H, s, COCH_2Ar); δ_C (100 MHz, $(CD_3)_2CO$) 194.1, 162.4, 136.7, 132.7, 131.0, 130.8, 129.5, 128.9, 127.9, 125.4, 115.7, 45.5; *m/z* LRMS (ESI$^+$) 315.0 (^{81}Br, [(M+Na)$^+$], 100%), 313.0 (^{79}Br, [M+Na)$^+$], 100%), 293.0 (^{81}Br, [(M+H)$^+$], 15%)), 291.0 (^{79}Br, [M+H)$^+$], 10%); HRMS (ESI$^+$) 314.9817 ([(M+Na)$^+$], $C_{14}H_{11}{}^{81}BrO_2Na$ requires 314.9815).

2-(2-Iodophenyl)-1-(4-methoxyphenyl)ethanone, 142



A solution of 2-iodophenyl acetic acid (1.3 g, 5.0 mmol, 1.0 eq) and thionyl chloride (0.85 mL, 10.0 mmol, 2.0 eq) in toluene (12 mL) was heated at relfux for 2 h. After cooling to room temperature, the resulting reaction mixture was concentrated *in vacuo* and redissolved in DCM (15 mL). Anisole (1.2 mL, 11.0 mmol, 2.2 eq) was added to the solution of the crude acid chloride and the resulting mixture cooled to 0 °C. Aluminium trichloride (800 mg, 6.0 mmol, 1.2 eq) was added portion-wise, ensuring the reaction temperature remained below 10 °C. The resulting reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by addition of $HCl_{(aq)}$ (1 M, 15 mL). The organic layer was separated and the aqueous layer extracted with DCM (2 × 15 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to generate the crude product as a solid. The product was recrystallised from 1:1 MTBE:heptane to afford ketone **142** (1.10 g, 63%) as a white solid: ν_{max} (neat)/cm^{-1} 2969, 2931, 1673, 1598, 1508, 1463, 1320, 1171, 982; δ_H (400 MHz, $CDCl_3$) 8.05 (2H, d, *J* 9.0, 2 × Ar*H*), 7.88 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.32 (1H, td, *J* 8.0 and 1.0, Ar*H*), 7.24 (1H, dd, *J* 7.5 and 1.0, Ar*H*), 6.99-6.96 (3H, m, 3 × Ar*H*), 4.42 (2H, s, COCH_2Ar)), 3.88 (3H, s, ArOCH_3); δ_C (100 MHz, $CDCl_3$) 195.0, 163.7, 139.4, 138.9, 130.9, 130.7, 129.8, 128.7, 128.4, 113.9, 101.5, 55.6, 50.1; *m/z* LRMS (ESI^+) 375.0 ([(M+Na)$^+$], 100%), 353.0 ([(M+H)$^+$], 40%). Data in accordance with the literature.[67]

References

1. Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*. VCH: New York, 2011.
2. Bolm, C.; Beller, M. *Transition Metals for Organic Synthesis*. VCH: New York, 2004; Vols. 1 and 2; Zeni, G.; Larock, R. C. *Chem. Rev.* **2006,** *106*, 464; Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008,** *108*, 3395.
3. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004,** *104*, 2127.
4. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*. 4th Ed.; Blackwell Publishing: Oxford, 2000.
5. Sadig, J. E. R.; Willis, M. C. *Synthesis* **2011,** 1.
6. Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009,** *351*, 3027; Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006,** *4*, 2337; Fischer, C.; Koenig, B., *Beilstein J. Org. Chem.* **2011,** *7*, 59.
7. Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008,** *47*, 6338.
8. Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.
9. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995,** *34*, 1348.
10. Louie, J.; Hartwig, J. F. *Tet. Lett.* **1995,** *36*, 3609.
11. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996,** *118,* 7215.
12. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996,** *118*, 7217.
13. Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000,** *122,* 4618; Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124*, 14844; Shekhar, S.; Ryberg, P.; Hartwig, J. F. *Org. Lett.* **2006,** *8,* 851; Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006,** *128,* 3584.
14. Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. *Tet. Lett.* **1999,** *40*, 3789.
15. Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008,** *130,* 6586.
16. Hartwig, J. F. *Acc. Chem. Res.* **2008,** *41*, 1534.
17. Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011,** *2*, 27.
18. Marion, N.; Navarro, O.; Mei, J. G.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006,** *128,* 4101; Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008,** *41,* 1440.
19. Fleckenstein, C. A.; Plenio, H. *Chem. Soc. Rev.* **2010,** *39,* 694
20. Barluenga, J.; Aznar, F.; Moriel, P.; Valdes, C. *Adv. Synth. Catal.* **2004,** *346,* 1697.
21. Yin, J. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124,* 6043.
22. Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009,** *65,* 6576; Su, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2012,** *51,* 4710.
23. Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007,** *129,* 10354.
24. Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006,** *128,* 10028.
25. Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem. Int. Ed* .**2010,** *49,* 4071.
26. Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011,** *50,* 9943.

27. Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006,** *128*, 10694.
28. Fernandez-Rodriguez, M. A.; Shen, Q. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006,** *128*, 2180.
29. Van den Hoogenband, A.; Lange, J. H. M.; Bronger, R. P. J.; Stoit, A. R.; Terpstra, J. W. *Tet. Lett.* **2010,** *51,* 6877.
30. Yi, J.; Fu, Y.; Xiao, B.; Cui, W.-C.; Guo, Q.-X. *Tet. Lett.* **2011,** *52,* 205.
31. Kuhn, M.; Falk, F. C.; Paradies, J. *Org. Lett.* **2011,** *13*, 4100.
32. Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008,** *108*, 3054; Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003,** *42,* 5400; Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004,** *248*, 2337.
33. Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903,** *36*, 2382.
34. Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906,** *39*, 1691.
35. Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010,** *39,* 10338.
36. Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tet. Lett.* **1999,** *40,* 2657.
37. Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001,** *3,* 4315; Goodbrand, H. B.; Hu, N. X. *J. Org. Chem.* **1999,** *64,* 670.
38. Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010,** *1*, 13.
39. Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem. Eur. J.* **2004,** *10,* 5607.
40. Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008,** *41,* 1450.
41. Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006,** *128,* 8742.
42. Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009,** *131,* 78; Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007,** *26*, 4546.
43. Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132,* 6205.
44. Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001,** *123*, 7727.
45. Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003,** *5,* 3667.
46. Wang, X.; Guram, A.; Ronk, M.; Milne, J. E.; Tedrow, J. S.; Faul, M. M. *Tet. Lett.* **2012,** *53,* 7.
47. Pan, X. H.; Cai, Q.; Ma, D. W. *Org. Lett.* **2004,** *6,* 1809.
48. Ma, D. W.; Cai, Q. *Org. Lett.* **2003,** *5,* 3799.
49. Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002,** *4,* 2803.
50. Zhao, D. B.; Wu, N. J.; Zhang, S. A.; Xi, P. H.; Su, X. Y.; Lan, J. B.; You, J. S. *Angew. Chem. Int. Ed.* **2009,** *48*, 8729.
51. Li, Y.; Nie, C.; Wang, H.; Li, X.; Verpoort, F.; Duan, C. *Eur. J. Org. Chem.* **2011**, 7331.
52. Ball, C. J.; Willis, M. C. *Eur. J. Org. Chem.* **2013**, 425.
53. Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006,** *348*, 851.
54. Sadig, J. E. R.; Foster, R.; Wakenhut, F.; Willis, M. C., *J. Org. Chem.* **2012**, *77*, 9473.
55. Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem. Int. Ed.* **2005,** *44*, 403.
56. Henderson, L. C.; Lindon, M. J.; Willis, M. C. *Tetrahedron* **2010,** *66*, 6632.
57. Hodgkinson, R. C.; Schulz, J.; Willis, M. C. *Tetrahedron* **2009,** *65*, 8940; Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Comm.* **2007**, 4764.

58. Hodgkinson, R. C.; Schulz, J.; Willis, M. C. *Org. Biomol. Chem.* **2009,** *7*, 432.
59. Dong, S.-X.; Zhang, X.-G.; Liu, Q.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Synthesis* **2010**, 1521.
60. Liang, Y.; Meng, T. H.; Zhang, H. J.; Xi, Z. F. *Synlett* **2011**, 911.
61. Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009,** *11*, 583.
62. Dieudonne-Vatran, A.; Azoulay, M.; Florent, J.-C. *Org. Biomol. Chem.* **2012,** *10*, 2683.
63. Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Tet. Lett.* **2007,** *48*, 7578.
64. Li, C.-L.; Zhang, X.-G.; Fang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010,** *75*, 7037.
65. Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006,** *71*, 1802.
66. Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007,** *46*, 7509.
67. Chen, C. Y.; Dormer, P. G. *J. Org. Chem.* **2005,** *70*, 6964.
68. Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004,** *6*, 4755.
69. Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem. Int. Ed.* **2007,** *46*, 2598.
70. Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Chem. Comm.* **2009**, 6744.
71. Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem. Int. Ed.* **2009,** *48*, 4222.
72. Itoh, T.; Mase, T. *Org. Lett.* **2007,** *9*, 3687.
73. Lewgowd, W.; Stanczak, A. *Archiv Der Pharmazie* **2007,** *340*, 65.
74. Hennequin, L. F.; Thomas, A. P.; Johnstone, C.; Stokes, E. S. E.; Ple, P. A.; Lohmann, J. J. M.; Ogilvie, D. J.; Dukes, M.; Wedge, S. R.; Curwen, J. O.; Kendrew, J.; Lambert-van der Brempt, C. *J. Med. Chem.* **1999,** *42*, 5369; Yu, Y. N.; Singh, S. K.; Liu, A.; Li, T. K.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003,** *11*, 1475; Ruchelman, A. L.; Singh, S. K.; Ray, A.; Wu, X. H.; Yang, J. M.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2004,** *12*, 795; Scott, D. A.; Dakin, L. A.; Del Valle, D. J.; Diebold, R. B.; Drew, L.; Gero, T. W.; Ogoe, C. A.; Omer, C. A.; Repik, G.; Thakur, K.; Ye, Q.; Zheng, X. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 1382.
75. Lunniss, C.; Eldred, C.; Aston, N.; Craven, A.; Gohil, K.; Judkins, B.; Keeling, S.; Ranshaw, L.; Robinson, E.; Shipley, T.; Trivedi, N. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 137.
76. Barraja, P.; Diana, P.; Lauria, A.; Passannanti, A.; Almerico, A. M.; Minnei, C.; Longu, S.; Congiu, D.; Musiu, C.; La Colla, P. *Bioorg. Med. Chem.* **1999,** *7*, 1591; Ryu, C. K.; Lee, J. Y. *Bioorg. Med. Chem. Lett.* **2006,** *16*, 1850.
77. Mitsumori, T.; Bendikov, M.; Sedo, J.; Wudl, F. *Chem. Mat.* **2003,** *15*, 3759; Chapoulaud, V. G.; Ple, N.; Turck, A.; Queguiner, G. *Tetrahedron* **2000,** *56*, 5499.
78. Vinogradova, O. V.; Balova, I. A. *Chem. Heterocycl. Compd.* **2008,** *44,* 501.
79. Von Richter, V. *Chem. Ber.* **1883,** *16*, 677.
80. Simpson, J. C. E. *The Chemistry of Heterocyclic Compounds. Condensed Pyridazine and Pyrazine Rings (Cinnolines, Phthalazines and Quinoxalines).* Wiley-Interscience: New York, 1953; Vol. 5.
81. Baumgarten, H. E.; Anderson, C. H. *J. Am. Chem. Soc.* **1958,** *80*, 1981; Kanner, C. B.; Pandit, U. K. *Tetrahedron* **1981,** *37*, 3513; Kiselyov, A. S. *Tet. Lett.* **1995,** *36*, 1383; Kiselyov, A. S.; Dominguez, C. *Tet. Lett.* **1999,** *40*, 5111; Al-Awadi, N. A.; Elnagdi, M. H.; Ibrahim, Y. A.; Kaul, K.; Kumar, A.

Tetrahedron **2001,** *57*, 1609; Shvartsberg, M. S.; Ivanchikova, I. D. *Tet. Lett.* **2000,** *41*, 771; Gomaa, M. A. M. *Tet. Lett.* **2003,** *44*, 3493.
82. Alford, E. J.; Schofield, K. *J. Chem. Soc.* **1952**, 2102.
83. Chen, D.; Yang, C.; Xie, Y.; Ding, J. *Heterocycles* **2009,** *77*, 273; Alhambra, C.; Becker, C.; Blake, T.; Chang, A.; Damewood, J. R., Jr.; Daniels, T.; Dembofsky, B. T.; Gurley, D. A.; Hall, J. E.; Herzog, K. J.; Horchler, C. L.; Ohnmacht, C. J.; Schmiesing, R. J.; Dudley, A.; Ribadeneira, M. D.; Knappenberger, K. S.; Maciag, C.; Stein, M. M.; Chopra, M.; Liu, X. F.; Christian, E. P.; Arriza, J. L.; Chapdelaine, M. J. *Bioorg. Med. Chem.* **2011,** *19*, 2927.
84. Alajarin, M.; Bonillo, B.; Marin-Luna, M.; Vidal, A.; Orenes, R.-A. *J. Org. Chem.* **2009,** *74*, 3558.
85. Kimball, D. B.; Hayes, A. G.; Haley, M. M. *Org. Lett.* **2000,** *2*, 3825.
86. Kimball, D. B.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2002,** *67,* 6395; Kimball, D. B.; Weakley, T. J. R.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002,** *124,* 13463; Kimball, D. B.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002,** *124,* 1572.
87. Zhu, C.; Yamane, M. *Tetrahedron* **2011,** *67,* 4933.
88. Zhang, G.; Miao, J.; Zhao, Y.; Ge, H. *Angew. Chem. Int. Ed.* **2012,** *51,* 8318.
89. Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997,** *62,* 7507; Back, R. A. *Rev. Chem. Intermed.* **1984,** *5,* 3.
90. Marsh, B. J.; Carbery, D. R. *J. Org. Chem.* **2009,** *74*, 3186.
91. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001,** *3,* 3803; Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009,** *74,* 4542; Kim, H.-Y.; Lee, W.-J.; Kang, H.-M.; Cho, C.-G. *Org. Lett.* **2007,** *9,* 3185.
92. Lim, Y. K.; Jung, J. W.; Lee, H.; Cho, C. G. *J. Org. Chem.* **2004,** *69,* 5778.
93. Smith, A. B., III; Foley, M. A.; Dong, S.; Orbin, A. *J. Org. Chem.* **2009,** *74,* 5987.
94. Yuan, Y.-Q.; Guo, S.-R. *Synlett* **2011,** 2750; Bian, M.; Xu, F.; Ma, C. *Synthesis* **2007,** 2951.
95. Ma, F. F.; Peng, Z. Y.; Li, W. F.; Xie, X. M.; Zhang, Z. G., *Synlett* **2011**, 2555-2558.
96. Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*. 4th ed.; Wiley-Interscience: New York, 2007.
97. Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed* .**2006,** *45*, 7079.
98. Bryan, C.; Aurregi, V.; Lautens, M. *Org. Syn.* **2009,** *86*, 36.
99. Guerinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 19.
100. Cody, J.; Fahrni, C. J. *Tetrahedron* **2004,** *60,* 11099.
101. Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998,** *63,* 8965.
102. Fuwa, H.; Goto, T.; Sasaki, M. *Org. Lett.* **2008,** *10,* 2211.
103. Denmark, S. E.; Liu, J. H. *Org. Synth.* **2005**, 42.
104. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001,** *57,* 9225.
105. Gage, J. R.; Evans, D. A. *Org. Synth.* **1993,** 8.
106. Ball, C. J.; Gilmore, J.; Willis, M. C. *Angew. Chem. Int. Ed.* **2012,** *51*, 5718.
107. March, J., *Advanced Organic Chemistry*. 4th ed.; Wiley-Interscience: New York, 1992.

108. Wada, T.; Iwasaki, M.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2010,** *16*, 10671.
109. Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000,** *122*, 4020.
110. Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008,** *41*, 1461.
111. Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008,** *130*, 2926.
112. Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012,** *134*, 10773.
113. Chatterj.A; Biswas, K. M. *J. Org. Chem.* **1973,** *38*, 4002.
114. Frost, C. G.; Hartley, J. P. *Mini-Rev Org. Chem.* **2004,** *1*, 1.
115. Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydr. Res.* **2006,** *341*, 2714.
116. Ruchelman, A. L.; Singh, S. K.; Wu, X. H.; Ray, A.; Yang, J. M.; Li, T. K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 3333.
117. Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004,** *10*, 2983.
118. Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132*, 14073.
119. Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*. Wiley: Chichester, UK 1997.
120. Qin, Z.; Kastrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A.; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007,** *50*, 2682.
121. Drouhet, E.; Dupont, B. *Arzneimittel-Forschung/Drug Research* **1992,** *42*, 705.
122. Hsiao, C. N.; Kolasa, T. *Tet. Lett.* **1992,** *33*, 2629.
123. Gilchrist, T. L. *J. Chem. Soc. Perkin Trans. I* **2001**, 2491; Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003,** *103*, 893.
124. Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Comm.* **2008**, 5529; Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006,** *45*, 4473.
125. Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011,** *111*, 1596.
126. Paradies, J. *Synthesis* **2010,** 947.
127. Kamer, P. C. J.; van Leeuwen, P. W. N.; Reek, J. N. H. *Acc. Chem. Res.* **2001,** *34*, 895.
128. Sahoo, S. K.; Jamir, L.; Guin, S.; Patel, B. K. *Adv. Synth. Catal.* **2010,** *352*, 2538.
129. Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2004,** *10*, 494.
130. Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2005,** *11*, 2276.
131. Kappe, C. O. *Angew. Chem. Int. Ed.* **2004,** *43*, 6250.
132. Fang, Y. Q.; Lautens, M. *Org. Lett.* **2005,** *7*, 3549.
133. Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007,** *9*, 3379; Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007,** *72*, 1510.
134. You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010,** *12*, 3930.
135. Ananikov, V. P.; Hazipov, O. V.; Beletskaya, I. P. *Chem. Asian J.* **2011,** *6*, 306; Xi, Z. F.; Song, Z. Y.; Liu, G. Z.; Liu, X. Z.; Takahashi, T. *J. Org. Chem.* **2006,** *71*, 3154; Xi, Z. F.; Liu, X. Z.; Lu, J. M.; Bao, F. Y.; Fan, H. T.; Li, Z. P.; Takahashi, T. *J. Org. Chem.* **2004,** *69*, 8547.
136. Bredihhin, A.; Maeorg, U. *Org. Lett.* **2007,** *9,* 4975.
137. Vautravers, N. R.; Regent, D. D.; Breit, B. *Chem. Comm.* **2011,** *47*, 6635.

138. Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F. *J. Org. Chem.* **2011,** *76,* 6414.
139. Gohier, F.; Mortier, J. *J. Org. Chem.* **2003,** *68,* 2030.
140. Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008,** *10*, 4275.
141. Navacchia, M. L.; Melucci, M.; Favaretto, L.; Zanelli, A.; Gazzano, M.; Bongini, A.; Barbarella, G. *Org. Lett.* **2008,** *10,* 3665.
142. Christophersen, C.; Begtrup, M.; Ebdrup, S.; Petersen, H.; Vedso, P. *J. Org. Chem.* **2003,** *68,* 9513.
143. So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem. Int. Ed.* **2008,** *47,* 8059.
144. McClintock, S. P.; Zakharov, L. N.; Herges, R.; Haley, M. M. *Chem. Eur. J.* **2011,** *17*, 6798.
145. Guo, H.; Liu, J.; Wang, X.; Huang, G. *Synlett* **2012,** 903.
146. Tietze, L. F.; Nobel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998,** *120,* 8971.
147. Samanta, R.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2011,** *50,* 5217.
148. Bonnamour, J.; Piedrafita, M.; Bolm, C. *Adv. Synth. Catal.* **2010,** *352,* 1577.