New Hydrogen Atom Transfer Methodologies for Synthesis

PhD Thesis

2016 – 2020

Oliver Turner

Industrial Supervisor – Dr. David J Hirst

Academic Supervisor – Prof. John Murphy

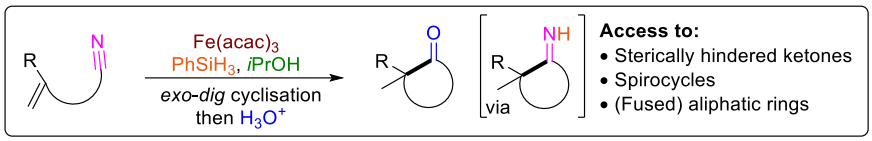
This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:  Date: 26/03/2020

Abstract

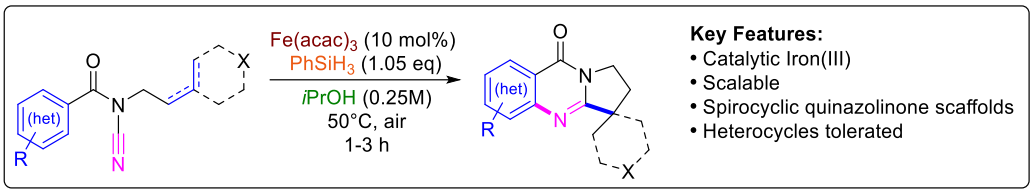
This thesis describes the development of new hydrogen atom transfer (HAT) methodologies, particularly focussed on additions to the C≡N bond (an underutilised radical acceptor). The two main published bodies of work are outlined below in Scheme 1 and 2.

A HAT-mediated intramolecular C-C coupling reaction between alkenes and nitriles, using $PhSiH_3$ and catalytic $Fe(acac)_3$, has been established.[1] This introduces a new strategic bond disconnection for ring-closing reactions, forming ketones via imine intermediates. Of note is the scope of the reaction, including formation of sterically hindered ketones, spirocycles and fused aliphatic systems.



Scheme 1. *Outline of HAT-mediated alkene-nitrile cyclisation methodology.*

Inspired by aspects of the alkene-nitrile project, a radical domino cyclisation reaction of *N*-cyanamide alkenes, mediated by HAT was also developed (Scheme 2).[2] This methodology, using $PhSiH_3$ and catalytic $Fe(acac)_3$, allows for the synthesis of challenging (spiro)quinazolinone scaffolds from simple, tractable (hetero)aryl carboxylic acid and cyanamide building blocks.



Scheme 2. *Outline of HAT-mediated domino cyclisation methodology.*

Further studies, such as exploiting unexpected side-reactions, as well as probing curious mechanistic observations have been made throughout this work. Possible future work is suggested throughout this thesis and hopefully can be pursued in the near future.

Table of Contents

Abbreviations

acac – Acetylacetone

Ac - Acetyl

Ar – Aryl

atm – Atmosphere

AIBN – Azobisisobutyronitrile

BDE – Bond dissociation energy

BINAP – 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

Boc – *tert*-Butyloxycarbonyl

Bn – Benzyl

Bu – Butyl

CIDNP – Chemically induced dynamic nuclear polarisation

Dan – 1,8-Diaminonaphthalene

DCM – Dichloromethane

DIAD – Diisopropyl azodicarboxylate

dibm – Diisobutyrylmethane

DMA – *N,N*-Dimethylacetamide

DMF – *N,N*-Dimethylformamide

dba – Dibenzylideneacetone

dpm – 2,2,6,6-Tetramethyl-3,5-heptanedionato

dppf – 1,1'-Bis(diphenylphosphino)ferrocene

d.r. – Diastereomeric ratio

E – Electrophile

EDG – Electron-donating group

ee – Enantiomeric excess

Et – Ethyl

EtOAc – Ethyl acetate

eq – Equivalents

Eqn – Equation

EWG – Electron-withdrawing group

GSK – GlaxoSmithKline

HAT – Hydrogen atom transfer

Het – Heterocycle

HFAC – Hexafluoroacetylacetone

HFIP – 1,1,1,3,3,3-Hexafluoro-2-propanol

HPLC – High performance liquid chromatography

HRMS – High resolution mass spectrometry

IPAc – Isopropyl acetate

i-Pr – Isopropyl

IR – Infrared spectroscopy

KIE – Kinetic isotope effect

L – Ligand

LCMS – Liquid chromatography mass spectroscopy

LiHMDS – Lithium bis(trimethylsilyl)amide

Lit – Literature

MDAP – Mass directed automated preparative HPLC

Me – Methyl

Mes – Mesitylene (1,3,5-trimethylbenzene)

MH – Metal hydride

MH-HAT – Metal hydride-hydrogen atom transfer

MIDA – 2,2'-(Methylimino)diacetic acid

min – Minutes

M.pt. – Melting point

Nu – Nucleophile

OAc – Acetate

Ph – Phenyl

Pin – Pinacolato

Pr – Propyl

NMR – Nuclear magnetic resonance

RBF – Round-bottomed flask

R.D.S – Rate determining step

Recryst. – Recrystallisation

RT – Room temperature

s – Seconds

S.M. – Starting material

TBHP – *tert*-Butyl hydroperoxide

t-Bu – *tert*-Butyl

TBS – *tert*-Butyldimethylsilyl ether

THF – Tetrahydrofuran

T.M. – Transition Metal

TPPMS – Sodium diphenylphosphinobenzene-3-sulfonate

Ts – Tosyl (*p*-toluenesulfonyl)

Quant. – Quantitative

wt. – Weight

vs. – Versus

Acknowledgements

To Prof. John Murphy, who has been the most supportive, kind and thought-provoking supervisor I could have asked for. You have always made yourself available to discuss anything, no matter how big or small. I feel privileged to have spent the last three and a half years under your tutelage. I would also like to thank you and your group for making me feel so welcome, especially during my time in Glasgow. In particular, to Kenny, Andrew, Norman and Giuseppe.

To Dr. David Hirst, who had the not so easy task of undertaking supervision of me part way through my PhD (and eliminating any bad habits I had picked up!). You have always had my best interests at heart, and I could not have done this without your support, thank you so much.

To Dr. Eric Talbot, who's inspiration and relentless drive provided the foundation of research in this thesis. I am grateful for the year I had under your supervision, I would not be where I am now without it.

To Dr. Vipul Patel, who I admire deeply as a professional and as a person. I owe you for some of the most memorable and fun experiences whilst we shared a lab and an office together in 2S120.

To Harry and Andrea, thank you for the support you continue to provide to all the PhD students on this programme. This would not be the success it is without your tireless efforts. To Laura and Billy, the same can also be said.

Finally, thank you to GSK for providing a fantastic environment to conduct this research in. It has been a thoroughly enjoyable experience and one that I will be forever grateful to have had.

1 – Introduction to Hydrogen Atom Transfer

Hydrogen atom transfer (HAT) is one of the most fundamental and common chemical reactions in organic free radical chemistry. It is defined as the concerted movement of a hydrogen atom (H·) in a single kinetic step from one group to another (Eqn 1).[3]

$$A\text{-}H + B^{\bullet} \rightarrow A^{\bullet} + H\text{-}B \qquad (1)$$

One of the most exploited HAT reactions is the termination of a carbon-centred radical with tributyltin hydride (Bu_3SnH). The $^{\bullet}SnBu_3$ radical can be generated via reaction with azobisisobuyronitrile (AIBN), thermally or photochemically, as shown in Figure 1. Following propagation with a halogenoalkane, the resulting carbon-centred radical may undergo cyclisation according to Baldwin's rules (Figure 1).[4,5]

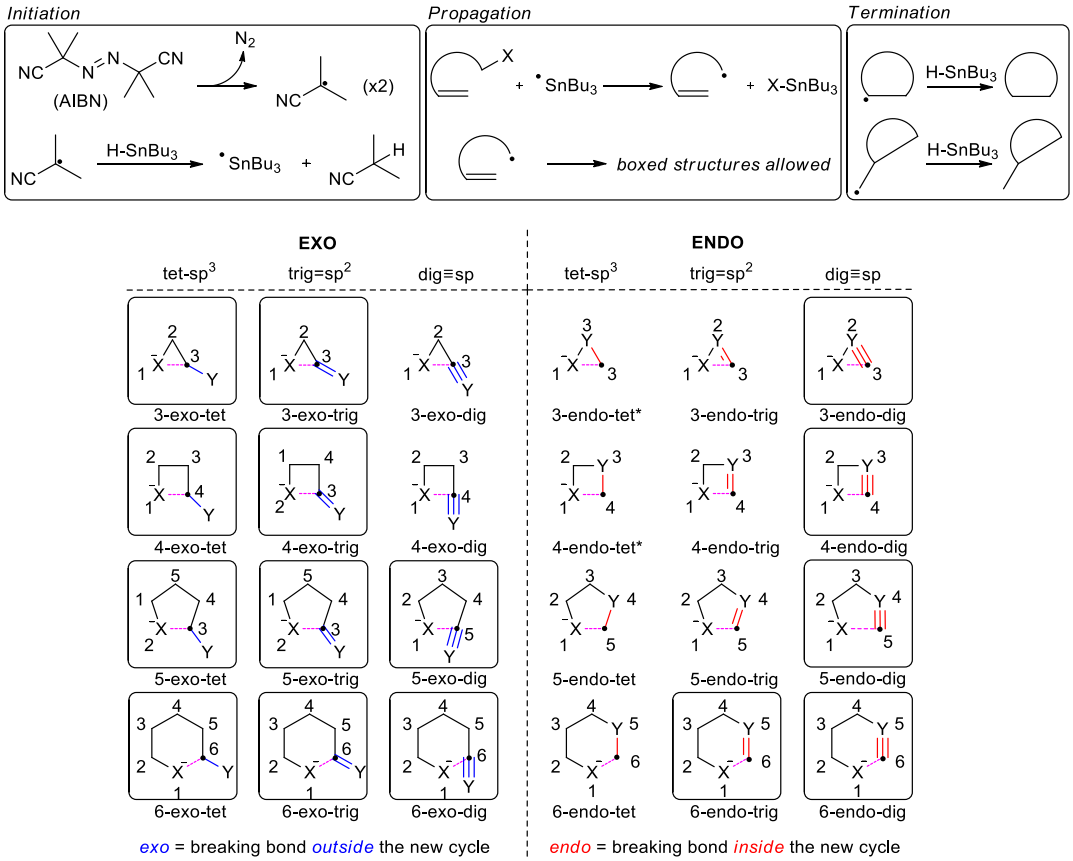


Figure 1. *Patterns of ring closure, for 3- to 6-membered rings, predicted to be favourable by Baldwin. *Denotes no prediction was made.* ***Boxed structures predicted to be allowed.***

However, as the ring-closure rules by Baldwin concern anionic processes, the corresponding radical ring-closures are more tentatively aligned (e.g. radical-*tet*

closure is rarely seen). More recently, a revised version of Baldwin's rules was published by Alabugin which focussed in detail on ring-closures of alkynes (*dig* systems), and found the following trends (Table 1).[6]

Table 1. *Revised Baldwin rules for digonal cyclisations of anions and radicals.*

Anionic		3	4	5	6
Dig	*endo-*	X	X	✓	✓
	exo-	✓	✓	✓✓	✓✓

Radical		3	4	5	6
Dig	*endo-*	X	X	✓	✓
	exo-	✓	✓	✓✓	✓✓

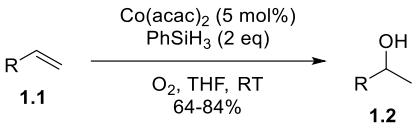
Red squares correspond to disfavoured, yellow squares to borderline/problematic, and green to favoured modes of ring-closure.

Although Bu_3SnH, as shown earlier, is a very capable hydrogen atom donor (BDE = 78 kcal/mol)[7] it suffers from extreme toxicity[8] and the need for specific work-ups to remove the troublesome tin by-products.[9] Various improvements to the use of stoichiometric Bu_3SnH have been developed, some of which are catalytic in tin[10] or use silicon alternatives.[11] Although once a widely used method for carbacycle formation reactions,[12] Bu_3SnH methodology has fallen out of favour in the last century with the emergence of new radical fields such as metal hydride hydrogen atom transfer (MH-HAT).

1.1 – Metal-Hydride Hydrogen Atom Transfer to Alkenes

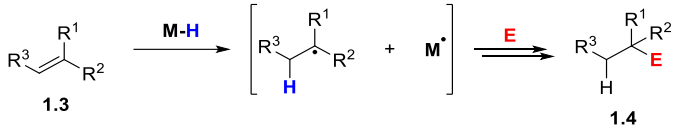
MH-HAT to carbon-carbon double bonds was discovered in the early 1960s when Kwiatek and Seyler considered metal hydrides as catalysts in the hydrogenation of various α,β-unsaturated compounds. They first reported that hydridopentacyano-cobaltate(III), $Co(CN)_5H^{3-}$, could facilitate hydrogenation at room temperature and 1-atm hydrogen pressure.[13,14] However, this interesting finding did not find interest among organic chemists until more than a decade later, when Teruaki Mukaiyama began work in the 1980s on the catalytic hydration of alkenes.[15,16]

The reaction, coined “Mukaiyama hydration of alkenes” (Scheme 3), transforms a terminal alkene (**1.1**) to its corresponding Markovinkov alcohol (**1.2**), in the presence of molecular oxygen, phenylsilane and catalytic amounts of $Co(acac)_2$.[17] The mild conditions and large functional group tolerance of the Mukaiyama hydration has led to its use in the late stages of many natural product syntheses.[18–20]



Scheme 3. *Mukaiyama hydration of alkenes.*

This pioneering work opened up a synthetic toolbox for MH-HAT reactions with alkenes, known as hydrofunctionalisation. Initial C-H bond formation at the least stabilised position, leads to a carbon-centred radical (or organometallic) that can subsequently be trapped by an electrophile (E) (Scheme 4). The addition of hydrogen and a functional group to alkene **1.3** proceeds to the hydrofunctionalised product **1.4** (after redox event) with Markovnikov selectivity and high chemoselectivity.



Scheme 4. *HAT Markovnikov hydrofunctionalisation of alkenes.*

1.1.1 – Hydrofunctionalisation of Alkenes – Reaction scope

The hydrofunctionalisation of alkenes by first row transition metal (T.M.) hydrides has since been extended to forms C-O (hydroperoxidation[21] and hydroalkoxylation[22]); C-N (nitrosation[23], hydrohydrazination[24], hydroazidation[24] and hydroamination[25]); C-C (reductive carbocyclisation[26]/dimerisation[27], hydrocyanation[28], conjugate addition,[29] hydromethylation[29]/styrenylation[30]/arylation[31], reductive coupling[32,33]); C-X (hydrofluorination[34,35]/chlorination[36]/bromination[37]/Iodination[37]); C-H (hydrogenation[38]), C-S and C-Se (hydrochalcogenation[39]) bonds (Figure 2).

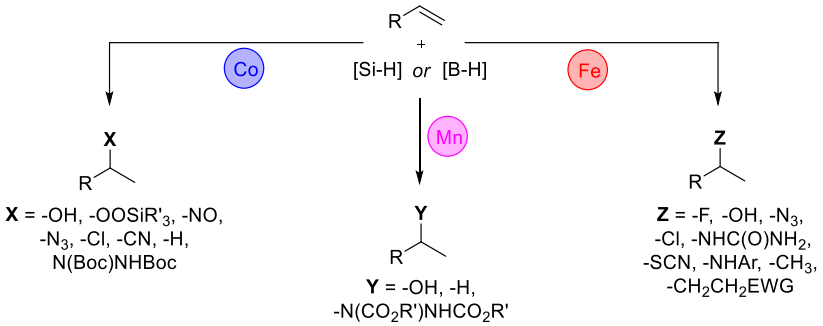


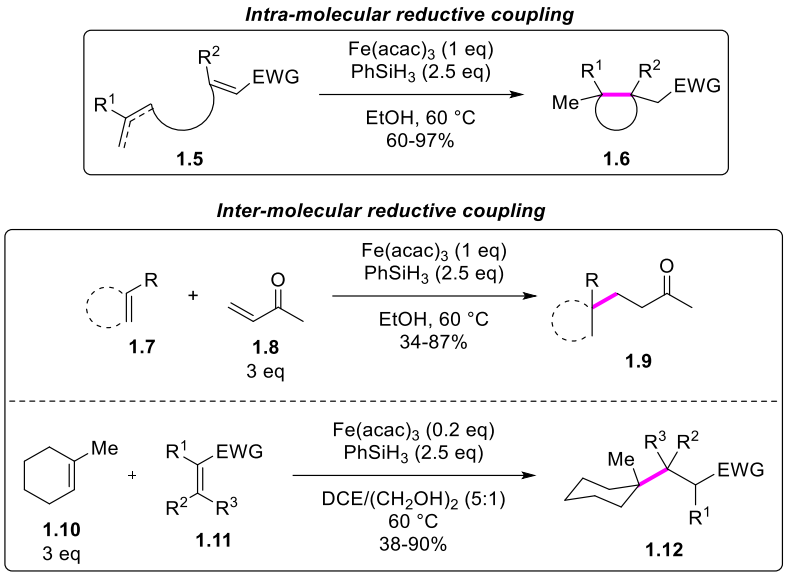
Figure 2. *Hydrofunctionalisation of alkenes by 1st row T.M. hydrides.*

The above transformations have been extensively reviewed (2016)[40], thus only those reactions that provided inspiration to this research or contribute mechanistic insight will be discussed in detail herein.

1.1.2 – Recent Advances in MH-HAT Alkenes

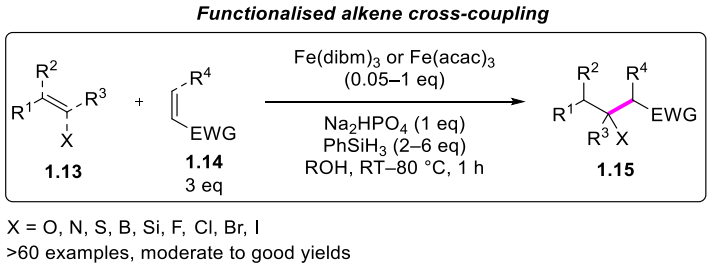
Baran Group

Inspired by previous work in the field of alkene hydrofunctionalisation reactions (Boger[18,34], Carreira[19,24,28,36,41,42] and Mukaiyama[15–17,43]), Baran *et al*. showed that unactivated alkenes (**1.5**, **1.7** and **1.10**) could be coupled directly to electron-deficient alkenes (**1.8** and **1.11**) in both intra- and intermolecular reactions (Scheme 5).[32] Generation of hindered bicyclic systems, vicinal quaternary centres and even cyclopropanes was achieved in good yields. However, reduced yield was reported, in some cases, due to the premature reduction of the donor alkene to the corresponding alkane. This methodology effectively serves as a tin-free version of the Giese reaction.[44]



Scheme 5. *HAT-mediated alkene-alkene reductive coupling reactions.*

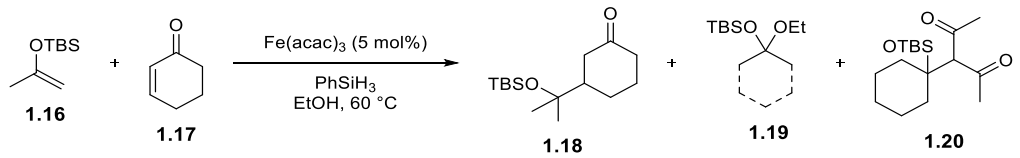
Recently, Baran *et al.* published an expansion to the original alkene cross-coupling methodology, showing that multiple heteroatom-substituted alkenes (**1.13**) were easily coupled to electron-deficient alkenes (**1.14**) to give cross-coupled products **1.15** (Scheme 6).[33] The role of the newly included inorganic base, Na_2HPO_4, was not discussed.



Scheme 6. *HAT-mediated functionalised alkene-alkene cross-coupling reaction.*

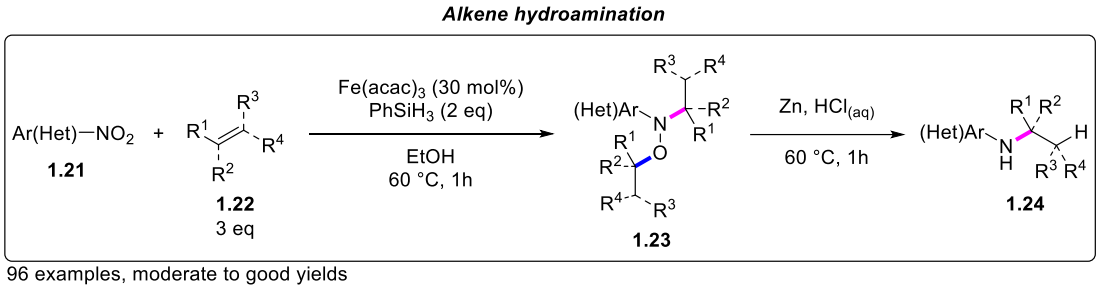
Of particular note is the tolerance to various boron species (BPin, BMIDA and Bdan[45]) which can serve as functional handles for various subsequent metal-catalysed cross-coupling reactions.[46] Also of interest is the use of fluorinated alkenes, allowing access to quaternary fluorinated centres that would be difficult or impossible to access by other means. The power of this methodology lies in the facile exploration of under-developed chemical space, offering a new method for the formation of C-C bonds in the presence of multiple heteroatoms (O, N, S, B, Si, F, Cl , Br, I).

One notable difference in the updated reaction conditions (*cf*. to the earlier methodology)[32] is the use of Fe(dibm)$_3$. The increased steric shield of *dibm* in comparison to *acac* (i.e. methyl vs. isopropyl) is presumed to limit the ability of the iron species to behave as a Lewis acid, thus limiting the formation of the reported side-products (**1.19** and **1.20**), shown below in Scheme 7, during the coupling reaction of **1.16** and **1.17** to form **1.18**.



Scheme 7. *Side-products observed when using Fe(acac)$_3$. The use of Fe(dibm)$_3$ limited the formation of **1.19** and **1.20**, increasing the yield of desired product **1.18**.*

Baran *et al.* extended the HAT methodology to the synthesis of secondary amines (**1.24**) via practical alkene hydroamination with nitro(hetero)arenes (**1.21**) (Scheme 8).[47]



Scheme 8. *HAT-mediated alkene hydroamination reaction.*

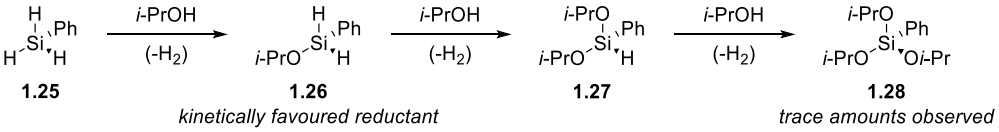
It was proposed the reaction proceeded via initial reduction of the nitro(hetero)arene (**1.21**), which subsequently forms an adduct with the alkyl radical derived from HAT reaction of the donor alkene (**1.22**). Zn-mediated cleavage of the resulting N-O σ bond (**1.23**) liberates the desired hindered secondary amine (**1.24**) in moderate-good yield. More recent work on alkene hydroamination has been carried out by the Thomas group, who reported that an amine-bis(phenolate) iron(III) catalyst showed superior catalytic activity to Fe(acac)$_3$.[48,49]

The latest HAT methodology reported by Baran *et al*. is the hydromethylation of unactivated alkenes (not shown).[29] Mono-, di-, and trisubstituted alkenes can be

hydromethylated in a highly chemoselective fashion. This is of particular use for late-stage functionalisation of drug molecules and has potential application in radioactive labelling.

Shenvi Group

In 2016, Shenvi *et al.* reported the discovery of an outstanding reductant for metal-catalysed radical hydrofunctionalisation reactions.[50] It was revealed that $PhSiH_3$, the reductant of choice for most MH-HAT reactions, was in fact not the kinetically preferred reductant in many of the aforementioned transformations. On inspection of the silane solvolysis distributions (by GC), it was found that Ph(*i*-PrO)SiH_2 (**1.26**) (generated *in situ* from $PhSiH_3$ and reaction solvent *i*-PrOH) was consumed much more rapidly than any of the other identifiable Si-species (Scheme 9).



Scheme 9. *Silane species observed by GC during reaction of $PhSiH_3$ (**1.25**) with i-PrOH.*

Interestingly, this suggests that alcohols play an important role as silane ligands in HAT-initiated reactions, likely as a result of increased Si electrophilicity and more rapid ligand exchange with the catalyst. They do not simply just increase the hydridic character of the silane by the formation of a pentavalent Si-species, analogous to that observed in 2014,[51] when silicate **1.29** was observed by NMR at -70 °C during reaction of $PhSiH_3$ with *t*-BuOK (Figure 3).

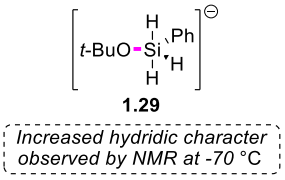
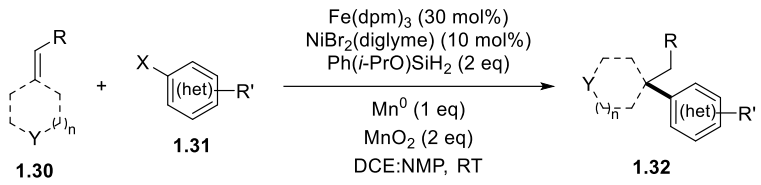


Figure 3. *Pentavalent silane species **1.29** observed by NMR during reaction of $PhSiH_3$ with t-BuOK.*

The superior reductant **1.26** can be synthesised on a large-scale[50]. In application of Ph(*i*-PrO)SiH_2 to some of the aforementioned alkene hydrofunctionalisation reactions, it was shown that they proceeded with lower metal-catalyst loadings (as

low as 0.05 mol%), in a range of aprotic solvents, all in superior yield to previously reported literature. Interestingly, *tert*-butyl hydroperoxide was employed in some reactions to suppress hydrosilylation reactions (see later Scheme 21, p.16), along with the proposed role of reoxidising the metal species (mechanism not suggested). Attempts by Shenvi's group to synthesise the ethoxy motif, $Ph(OEt)SiH_2$, proved unsuccessful due to instability of the Si-species to moisture.[50]

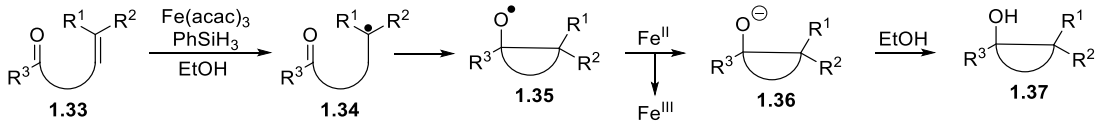
Recently (2019) the Shenvi group has applied MH-HAT in a new field of dual-catalysis, in which radicals generated via Fe-H HAT are captured by nickel to enter into a reductive cross-coupling cycle with (hetero)aryls (**1.31**) (Scheme 10).[52] This work is complementary to the rapidly emerging field of radical-based cross-coupling reactions utilising dual catalysis with nickel, such as sp^3 decarboxylative couplings.[53,54]



Scheme 10. *Iron-Nickel dual-catalysis for the formation of alkyl-(hetero)aryl quaternary centres.*

Bonjoch Group

In 2018, the Bonjoch group made an important contribution to the MH-HAT field and provoked some intriguing discussion points for the work outlined in this thesis. The unprecedented C-C coupling reaction of alkene tethered ketones (**1.33**) to tertiary alcohols (**1.37**) is depicted below (Scheme 11). The proposed pathway involves the formation of a unstable intermediate alkoxy radical (**1.35** from **1.34**) which can, crucially, be converted to the alkoxide anion (**1.36**).[55] The radical-anion turnover is the key feature to this methodology, as alkoxy radicals have been shown to undergo rapid ring-opening, with rates faster than for the corresponding ring-closure.[56]



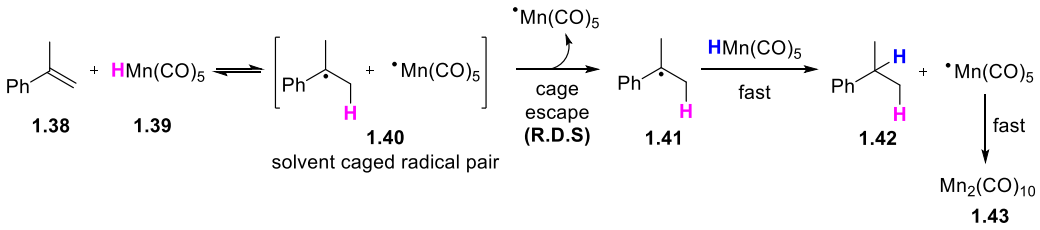
Scheme 11. *Overview of Bonjoch's HAT-mediated alkene-ketone cyclisation reaction.*

This work was later expanded to the use of hydrazones to access complex amines.[57]

1.1.3 – Metal-Hydride Hydrogen Atom Transfer Mechanism

Mechanistic Proposal

The MH-HAT mechanism was proposed during early research in the field of alkene hydrofunctionalisation, when Halpern *et al.* provided evidence that the hydrogenation of α-methylstyrene (**1.38**) by $HMn(CO)_5$ (**1.39**) proceeded via a free radical mechanism (Scheme 12).[58] He reported the first definitive demonstration of a CIDNP (chemically induced dynamic nuclear polarisation) effect to arise from a reaction in which one of the geminate radical pairs is an inorganic metal-centred complex (**1.40**). The technique detects enhanced absorption or emission of signals (^{1}H NMR), when unpaired electrons are generated under the reaction conditions. It was proposed that the Mn-H bond undergoes homolysis to form the radical cage pair (**1.40**), which escapes its cage (**1.41**), and is subsequently quenched with a second equivalent of Mn-H (**1.39**) to form the desired hydrogenated product **4.42** (Scheme 12).[58] It is to be noted that no species, other than the reactants and products (**1.42** and **1.43**), were fully characterised.



Scheme 12. *Proposed HAT mechanism for the hydrogenation of α-methyl styrene (**1.38**). R.D.S = rate determining step.*

However, the synthetic work that preceded Halpern only rarely gave mention to such a mechanism and it is not until recently that the hypothesis has been widely accepted in the literature.

Mechanistic Evidence

Early mechanistic studies on the addition of a Co-H species, $HCo(CN)_5^{3-}$, to a set of activated alkenes showed that the rate of formation of the organocobalt species (analogous to **1.40**, Scheme 12) increased with increasing electron density on the alkene.[59] This supports the theory that the alkene acts as a nucleophile, and the metal

hydride as an electrophile, in HAT reactions. This finding led to several hypotheses regarding how the metal hydride species interacts with an alkene (Figure 4).

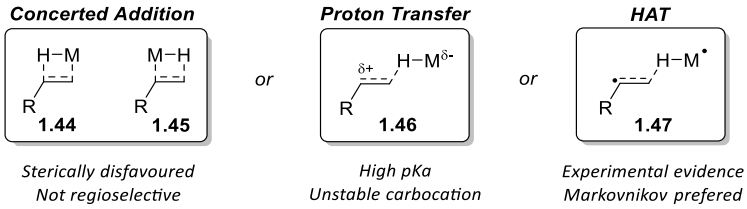


Figure 4. *Hypotheses for metal hydride interaction with an alkene.*

One such hypothesis was the concerted addition of the metal hydride across the double-bond, forming a four-centred transition state (**1.44** and **1.45**). This would not only be sterically demanding but also implies simultaneous M-C bond formation, which would not agree with Halpern's early findings of a free radical mechanism.[58] It is also to be questioned whether a concerted addition would be completely regioselective for Markovnikov products and proceed exclusively via **1.45**.

Another proposed mechanism was initial protonation of the alkene by the metal hydride (**1.46**). However, the relatively high p*K*a of metal hydrides,[60] although highly dependent on ligand effects, suggests protonation of the alkene would be disfavoured. In addition, protonation would result in the generation of an unfeasibly high energy secondary carbocation species, rendering this pathway energetically unfavourable.

HAT appears the most plausible mechanism (**1.47**). The same study, which found alkenes to behave as nucleophiles in reaction with $HCo(CN)_5^{3-}$, showed that the rate of reaction was not dependent on $[CN^-]$.[59] This observation rules out any formation of a metal-alkene coordinated species such as a four-centred complex, since a CN ligand would be expelled prior/upon coordination. Furthermore, the bond dissociation energy (BDE) of 1st row transition metal hydrides is 45-55 kcal/mol,[61] low enough that homolytic cleavage would readily proceed (cf. Br-Br 46 kcal/mol).[62]

Halpern provided further support for the HAT mechanism when he reacted $DMn(CO)_5$ with α-methylstyrene.[58] He found that hydrogenation proceeded with isotopic

exchange; deuterium was incorporated into both the final product and the substrate. The incorporation of deuterium into the substrate provided evidence for reversible formation of the radical pair (see **1.40**, Scheme 12, p.9). In addition, the overall rate constant for the hydrogenation with $DMn(CO)_5$ was found to be larger than that with $HMn(CO)_5$ (k_H/k_D = 0.4 at 65 °C).[58] This phenomenon, known as inverse kinetic isotope effect (KIE), is commonly observed amongst reversible hydrogen atom transfers from metal hydrides.[63–65]

The inverse KIE observed in MH-HAT reactions is reasoned to be due to the lower stretching frequencies of M-H/D bonds in the starting material compared to those of C-H/D bonds in the caged pair intermediate, i.e. the C-H/D bonds being formed are stronger than the M-H/D bonds being broken (Figure 5). The formation of the cage pair is favoured more for deuterium than hydrogen, thus the overall reaction rate is faster.

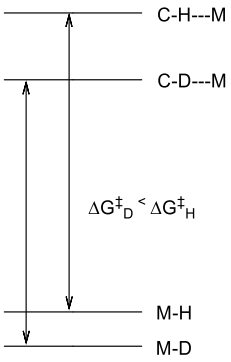
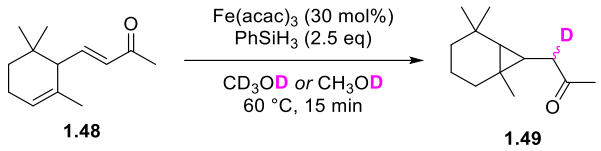


Figure 5. *Rationale for the observed inverse kinetic isotope effect.*

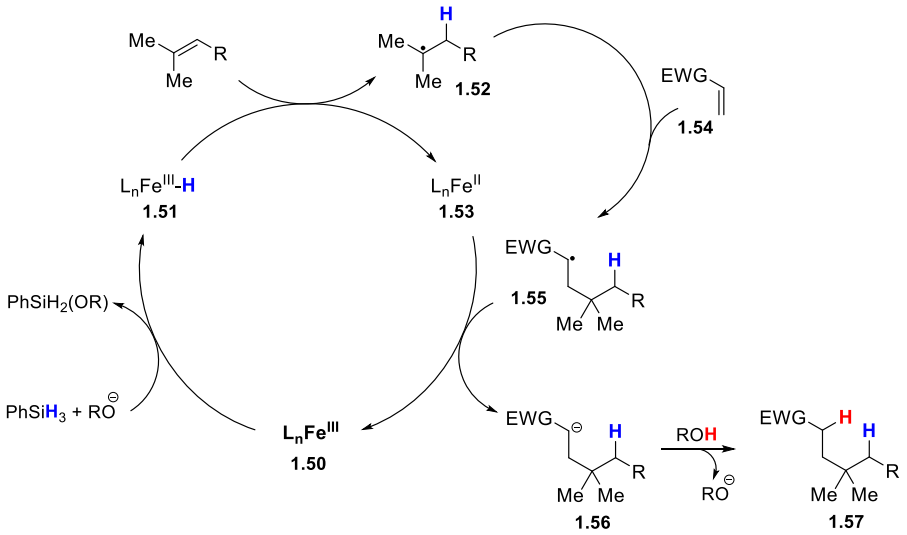
Recent Mechanistic Advances

During mechanistic studies of the alkene-alkene cross-coupling reaction (see Scheme 5, p. 5), Baran *et al*. found that $Fe(acac)_3$ was necessary for the reaction to proceed.[32,33] The outcome of the reaction was not altered in the absence of O_2 (air), evidence that O_2 is not responsible for re-oxidation of the Fe-catalyst (in this system). Conducting the HAT-mediated cyclisation of **1.48** in deuterated solvent, gave deuterated product **1.49** exclusively (Scheme 13).



Scheme 13. *Mechanistic study of the HAT-mediated reductive cyclisation reaction of **1.48**.*

No deuterium was incorporated on the cyclohexene ring, providing evidence that the hydrogen that adds across the alkene originates from $PhSiH_3$; this was confirmed by deuterium incorporation when $PhSiD_3$ was employed.[33] Importantly, submission of non-deuterated product to the deuterated reaction conditions showed no H-D exchange, proving deuterium incorporation is not an artefact of solvent exchange. This observation led to the proposed mechanism depicted below (Scheme 14), for the HAT-mediated olefin-olefin cross-coupling where a Michael acceptor is employed as the acceptor alkene.

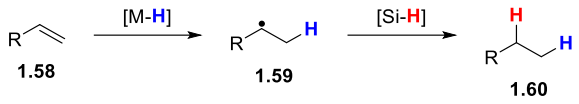


Scheme 14. *Baran's mechanistic hypothesis for alkene-alkene cross-coupling.*

Isolation of intermediates proved challenging, but the agreed initial step is metal hydride formation (**1.51**), followed by reaction with a carbon-carbon double-bond to form radical species **1.52**. This reactive species can then undergo cross-coupling with an acceptor alkene (**1.54**), to yield intermediate radical **1.55**. It is then believed that the iron species **1.53** is re-oxidised to the original configuration **1.50** in generation of the anionic intermediate **1.56**, which can be protonated (presumably by alcoholic solvent) to yield the desired cross-coupled product **1.57**. A more comprehensive and

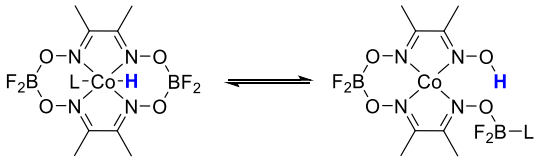
lengthy discussion of the MH-HAT reaction mechanism can be found in Baran's most recent alkene-alkene cross-coupling studies,[66] however, an alternative proposal has more recently (2019) been put forward (see later, Scheme 22, p.17).

In the absence of a sufficiently electron-withdrawing group (EWG), the source of hydrogen for the second reduction/termination reaction remained to be fully understood. Shenvi *et al.*, through careful deuteration studies, found that the main second reduction pathway for related alkene (**1.58**) hydrogenation methodology (Scheme 15) does not involve a M-H species. It is in fact the silane itself that quenches intermediate radical **1.59** to give hydrogenated product **1.60**.[50]



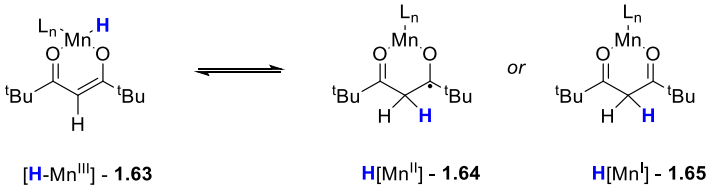
Scheme 15. *Shenvi's metal-catalysed HAT alkene hydrogenation methodology.*

Initially, Shenvi envisaged that hydrogen may be derived from a non-innocent ligand (acac-type ligands have since been shown to be redox active[67]). This hypothesis was inspired by Norton, who showed that Co-H complexes **1.61** and **1.62** (Scheme 16) may exist in equilibrium, as Co-H and O-H tautomers.[68] It was proposed that both species were capable of undergoing HAT.



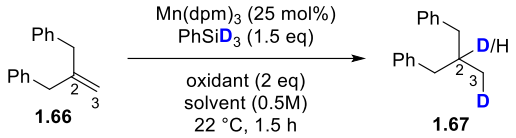
Scheme 16. *Tautomerisation of Co-H complex **1.61**.*

This hypothesis was tested with the analogous metal hydride complex, β-diketonate **1.63**, which would involve C-H tautomer **1.64** or **1.65** (Scheme 17).



Scheme 17. *Tautomerisation of Mn-H complex **1.63**.*

Since Ph(*i*-PrO)SiH_2 (**1.26**) allowed hydrogenation reactions to be performed in aprotic solvents (see Scheme 9, p.7), that cannot exchange with free or bound diketonate, the competing sources of hydrogen/deuterium could be investigated. Some of the key findings of the study are shown in Scheme 18, for the hydrogenation/deuteration of alkene **1.66**.

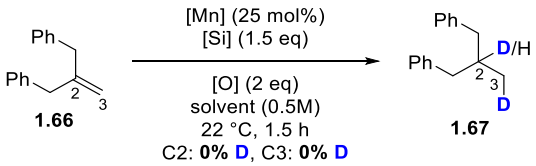


conditions A: iPrOH, TBHP = C2: **63% D**, C3: **100% D**
conditions B: **d_8**iPrO**D**, ^{t}BuOO**D** = C2: **67% D**, C3: **100% D**

Scheme 18. *Involvement of the ligand in the HAT reaction.*

Under both reaction conditions A and B, complete incorporation of deuterium at C3 was observed for the conversion of **1.66** to **1.67**. However, this alone does not rule out hydrogen-scrambling with the ligand, as Mn-D might be preferentially transferred to the alkene (even as a small population in equilibrium), adhering to the known inverse kinetic isotope effect associated with MH-HAT (see Figure 5, p.11). Furthermore, only 63% and 67% incorporation of deuterium at C2 was seen, which is suggestive of a competing non-silane derived source for the second hydrogen delivery.

When deuterated catalyst, Mn(d_1-dpm)$_3$ (25 mol%) in hexanes was employed (conditions A), no deuterium incorporation was observed at either position of **1.67** (Scheme 19).



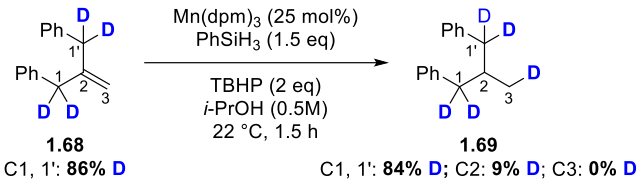
conditions A: Mn(**d_1**-dpm)$_3$, Ph(i-PrO)SiH_2, TBHP, hexanes
conditions B: Mn(**d_1**-dpm)$_3$, $PhSiH_3$, TBHP, hexanes
conditions C: Mn(dpm)$_3$, $PhSiH_3$, TBHP, **d_8**-iPrO**D**
conditions D: Mn(dpm)$_3$, $PhSiH_3$, tBuOO**D**, cyclohexane

Scheme 19. *Involvement of the ligand in the HAT reaction.*

The same absence of deuterium incorporation was observed with: $PhSiH_3$ and Mn(d_1-dpm)$_3$, $PhSiH_3$ and d_8-iPrOD and Mn(dpm)$_3$ and $PhSiH_3$ and *t*-BuOOD (conditions B, C

and D, respectively). Taking the results of these experiments into account and those shown previously, it can be stated with confidence that HAT does not result from 'non-innocent' β-diketonate ligand. However, reduction of **1.66** with $Mn(dpm)_3$ under fully deuterated reaction conditions (Scheme 18, conditions B) still gave only partial deuteration at C2, so where is the internal hydrogen coming from?

Deuteration of substrate **1.66** in the benzylic positions to give **1.68** provided insight into the origins of the internal deuterium. Reduction of **1.68** with $PhSiH_3$ delivered 9% deuterium incorporation at C2, during the hydrogenation reaction, to give **1.69** (Scheme 20).

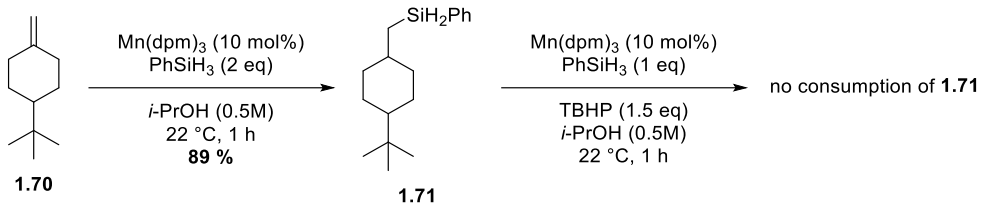


Scheme 20. *Isotope scrambling of **1.68**.*

This level of deuterium incorporation is lower than the reverse isotope labelling experiment (37% H, Scheme 18, conditions A), indicating a normal KIE of H-transfer. This scrambling could proceed either via a $Mn^{(II)}$ reverse HAT or through inter-substrate transfer. Unless there is a very high inverse KIE from the metal hydride, this scrambling must occur between the intermediate substrate radical and **1.66**, since 100% deuterium incorporation at C3 is seen (M-H formed by reverse HAT would label C3 with H, Scheme 18).

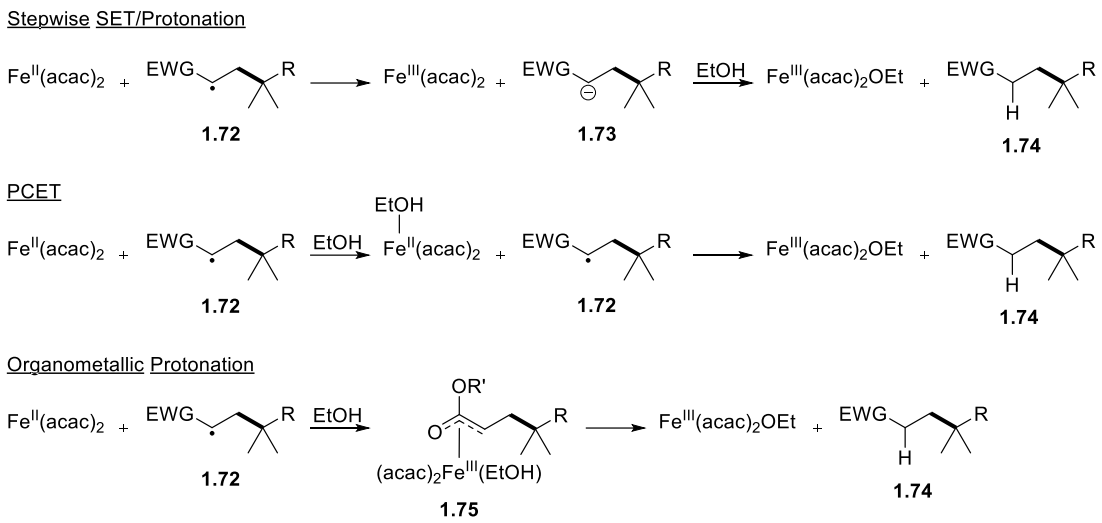
Finally, it was observed that the hydrogenation of **1.66** in the absence of TBHP gave a 70% yield of the desired hydrogenated product **1.67** (with 1 equivalent of Mn complex). This result suggests that the reduction of the radical intermediate does not occur exclusively from the metal hydride, since the Mn(II) product cannot reform a Mn(III)−H (the reaction was shown not to be catalytic in the absence of TBHP). Thus it was concluded, based on the evidence from the isotope labelling and stoichiometric reactions, that the main second reductant appears to be the silane itself. Minor reductant pathways via M-H species or inter-substrate reactions are also viable.

Interestingly, the resulting silyl radical formed from the reduction pathway has been reported to add to alkenes in the absence of TBHP. This is showcased below in Scheme 21, where **1.70** undergoes hydrosilylation in good yield to afford **1.71**, which remained inactive to further HAT reaction. Thus, TBHP has two suggested roles in Shenvi's HAT methodology; re-oxidation of the metal complex and suppression of competing side-reactions.



Scheme 21. *Hydrosilylation reaction of **1.70** to **1.71** observed in the absence of TBHP.*

A computational and mechanistic study of the roles of iron complexes in MH-HAT alkene cross-coupling reactions has recently been conducted by Holland *et al.* (2019).[69] The results explain several observations that had, to-date, proved challenging to rationalise; and may prove very important for the discovery and optimisation of new MH-HAT reactions moving forward. Four key observations were made by the Holland group: 1) The rate-limiting step in the catalytic cycle was the formation of the Fe-H complex, highlighting the importance of the choice of reductant; 2) the very weak Fe-H bond (17 kcal/mol) performs irreversible HAT to alkenes, in contrast to previous studies on isolable metal-hydride complexes where addition was reversible; 3) the organic radical intermediates can reversibly form organometallic species, which help protect the free radicals from side reactions; 4) the previously proposed mechanism for quenching of product radicals (**1.72** to **1.74**) (SET from Fe^{II} complexes to generate stabilised carbanions such as **1.73**) is less favourable than alternative pathways such as concerted proton-coupled electron transfer (PCET) or protonation of enolate-iron(III) complexes (**1.75**) (Scheme 22).



Scheme 22. *Mechanisms for quenching radical **1.72**, where EWG = CO_2R'.*

In summary, there is strong evidence that alkenes undergo MH-HAT to form carbon-centred radicals, which may subsequently undergo cross-coupling, cyclisation, reduction or dimerisation reactions. The resulting newly formed radical species can then undergo termination with a Si-H species (major pathway) or a M-H species (minor pathway), as proposed by Shenvi for hydrogenation of unfunctionalised alkenes.[50] When the product radical is adjacent to an electron-withdrawing group, as in alkene cross-coupling reactions, there is new found evidence to suggest that PCET/organometallic protonation pathways are more favourable[69] rather than a SET pathway (as proposed by Baran[66]).

2 – Introduction to Radical Cyclisations of Nitriles

There are limited reports in the literature of the addition of carbon-centred radicals to nitriles, some examples of which are outlined in Figure 6.

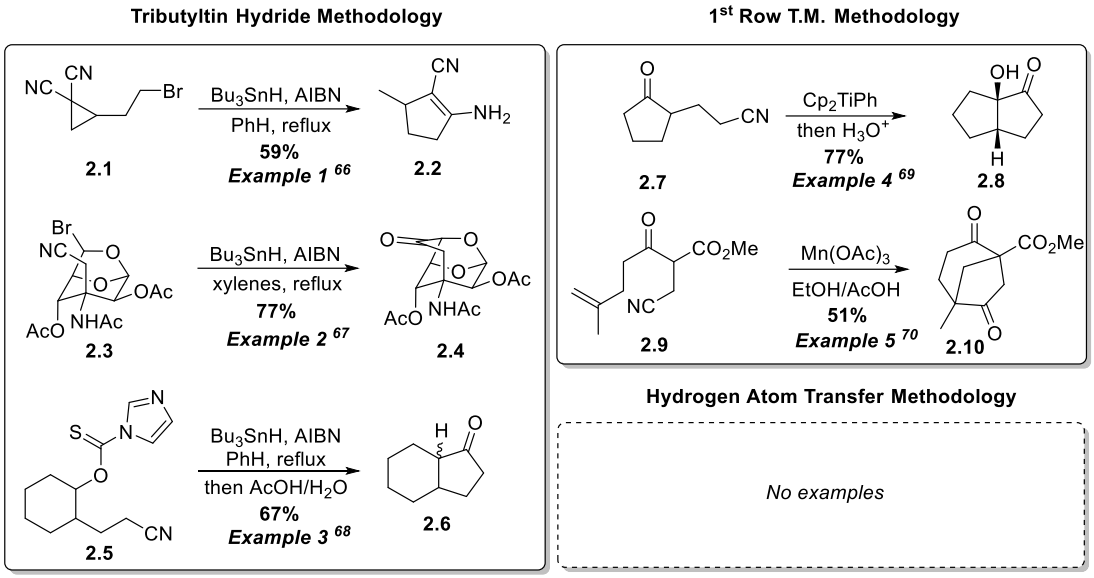


Figure 6. *Radical cyclisations – addition of carbon-centred radicals to nitriles.*

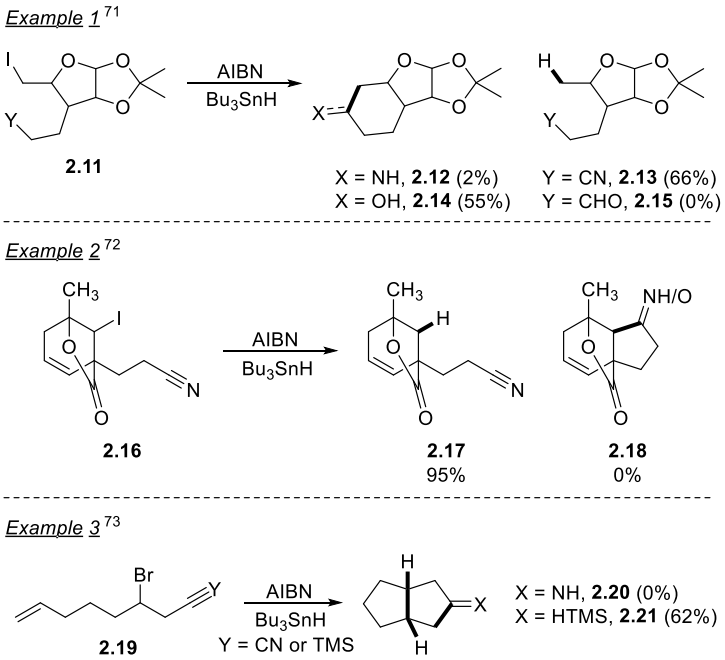
Examples 1-3 utilise classical tributyltin hydride radical chemistry to perform: unexpected cyclisations of dicyanocyclopropanes (**2.1**) to form enaminonitriles (**2.2**)[70]; the synthesis of the carbocyclic core of Tetrodotoxin (**2.4** from **2.3**)[71]; and de-oxygenation-mediated cyclisations (**2.6** from **2.5**).[72] The scope of the tributyltin hydride methodology is broad but its usage has been limited in recent years due to the toxic nature of tin, as alluded to earlier.[8]

Example 4 utilises titanium to coordinate to the cyano group of **2.7**, which lowers the LUMO, to encourage cyclisation with the generated ketyl radical, to form the fused cyclic system **2.8**.[73] Interestingly, example 5 reports a Mn(III)-based oxidative free-radical tandem cyclisation of **2.9**, which is terminated by addition to the nitrile group to yield **2.10**.[74] Whilst both are intriguing transformations, the scope of such transition metal-mediated cyclisations of nitriles is limited.

Surprisingly, prior to this work, there were no examples of MH-HAT-mediated reactions in which the radical trap is a nitrile. There are multiple examples in the

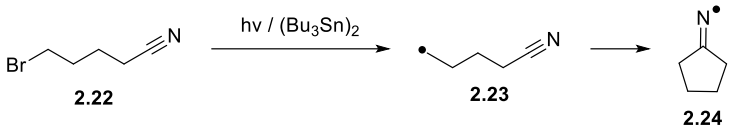
literature in which a nitrile is conserved in the presence of a HAT-mediated alkene hydrofunctionalisation or cross-coupling reaction (e.g. with acrylonitrile), where the addition of a carbon-centred radical favours addition to the alkene (not the nitrile).[33,50]

The limited number of reported radical cyclisations onto nitriles (in comparison to other radical traps) is likely due to the slow rate of addition of radicals to nitriles. Indeed, there are multiple reports describing unsuccessful radical cyclisations onto a nitrile group due to the competing rates of free-radical quenching by Sn-H or other hydrogen donor sources. In contrast, their carbonyl or alkyne variants undergo ring closure successfully as is shown in Scheme 23 for substrates **2.11**, **2.16** and **2.19**.[75–77]



Scheme 23. *Examples of unsuccessful radical cyclisations of nitriles.*

The rate of addition of carbon-centred radicals to nitrile groups has been previously studied. 5-Bromovaleronitrile (**2.22**) was used to establish the rate constant of cyclisation of the 4-cyanobutyl radical (**2.23**) to the corresponding cyclopentiminyl radical (**2.24**) (Scheme 24).[78]



Scheme 24. *Cyclisation of 4-cyanobuyl radical (**2.23**) to form the corresponding cyclopentiminyl radical (**2.24**).*

Kinetic measurements using electron paramagnetic resonance (EPR) spectroscopy, found $k_C^{C\equiv N} = 4 \times 10^3\ s^{-1}$. This is more than an order of magnitude slower than the analogous 5-hexynyl radical ($k_C^{C\equiv C} = 1 \times 10^5\ s^{-1}$), 5-hexenyl radical ($k_C^{C=C} = 2.5 \times 10^5\ s^{-1}$) and 5-oxa-5-hexenyl radical ($k_C^{C=O} = 8.7 \times 10^5\ s^{-1}$) at 25 °C.[73] The comparison is depicted graphically below in Figure 7.

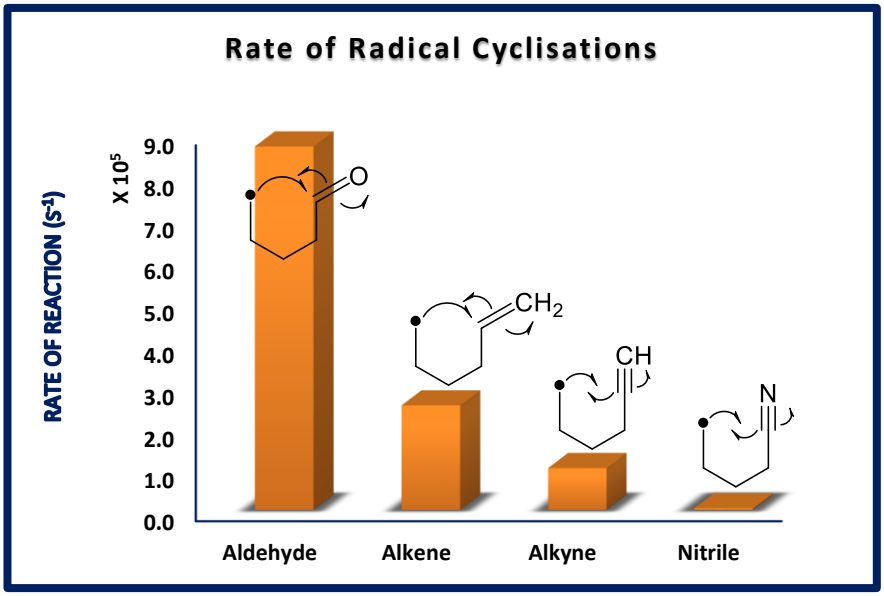


Figure 7. *Graphical representation of the rates of radical cyclisation of common functional groups.*

This could explain why the nitrile groups were conserved in the aforementioned alkene hydrofunctionalisation reactions and the attempted radical cyclisations shown earlier in Scheme 23. An explanation for this kinetic trend shown above in Figure 7 cannot be made using thermodynamic data, as parameters such as bond strength do not directly correlate with the observed rates. Computational methods may be best suited to understanding the relatively slow nature of radical-mediated ring closure onto nitriles and might offer an opportunity for future insight.

2.1 – Iminyl Radicals

2.1.1 – Structure and Properties

Iminyl radicals are planar nitrogen-centred radicals, as depicted in Figure 8. The single unpaired electron (radical) occupies a 2p orbital, lying orthogonal to the π-orbitals of the C=N bond.

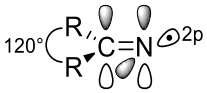
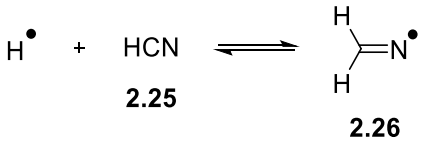


Figure 8. *Structure of iminyl radicals ($R_2C{=}N^{\bullet}$).*

The study of iminyl radicals began in 1962 when Cochran *et al*. generated the methyleneiminyl radical (**2.26**) during vacuum uv photolysis of HCN (**2.25**) in argon (Scheme 25).[79] The reversible addition of hydrogen atoms to hydrogen cyanide was characterised by electron spin resonance (ESR) spectroscopy and detection could be increased in the presence of HI ($H^{\bullet}$ source).[79] Further studies showed that hyperconjugation, from σ-orbitals of C-H bonds to the formally non-bonding 2p orbital of the unpaired electron on nitrogen, increases the stability of iminyl radicals.[80,81]



Scheme 25. *Formation of methyleneiminyl radical **2.26**.*

The electronic characteristics of iminyl radicals can be inferred from the relative rate of hydrogen abstraction from a hydrogen donor such as tributyltin hydride. The greater the electrophilicity of an iminyl radical, the faster the rate of hydrogen abstraction, yielding a nucleophilic stannyl radical. Results from a study by Zard and Newcomb in 1997[82], on the absolute rate constants for iminyl radical reactions, are shown in Figure 9.

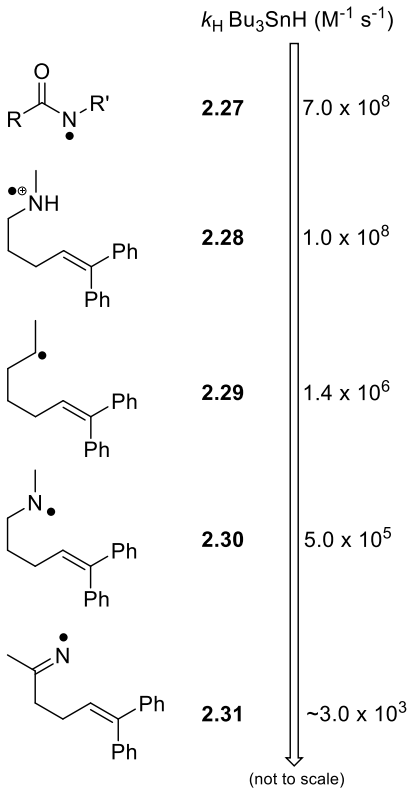
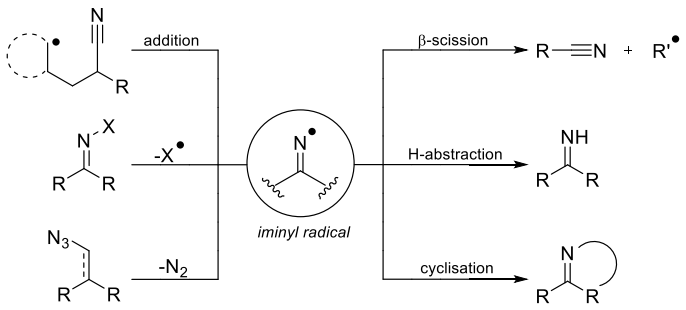


Figure 9. *A comparison of rate constants for radical ring-closure at 25 °C.*

Alkyl radicals (such as **2.29**) are classified as nucleophilic and quench at a reasonable rate (k = 1.4 x 10^6 M^{-1} s^{-1}) with tributyltin hydride, whereas amidyl (**2.27**) and aminium cation (**2.28**) radicals are classified as electrophilic, and thus react with tributyltin hydride at considerably faster rates (k = 7.0 and 1.0 x 10^8 M^{-1} s^{-1}, respectively). In contrast, aminyl (**2.30**) and iminyl (**2.31**) radicals are orders of magnitude slower to quench with Bu_3SnH reagents (5.0 x 10^5 and ~3.0 x 10^3 M^{-1} s^{-1}, respectively) and can be classed as nucleophilic radicals. It is to be noted that these trends also held true when the rates were measured with a different HAT reagent (thiophenol).[82]

2.1.2 – Synthetic Application

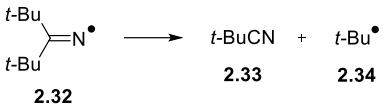
Iminyl radicals are commonly generated via radical additions to nitriles, homolysis of weak N-X bonds (e.g. X = Cl) or extrusion of N_2 from organic azides (Scheme 26).[83] The fate of the resulting iminyl radical determines the outcome of the reaction. Common reactions involve abstraction of hydrogen to afford imines (usually hydrolysed to the corresponding ketones, see examples earlier in Figure 6, p.18), β-scission and addition reactions (which will be discussed herein).



Scheme 26. *Generation and transformation of iminyl radicals.*

β-Scission

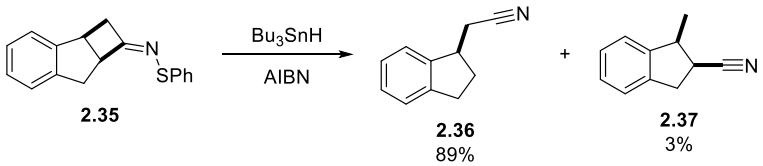
Iminyl radicals may undergo β-scission reaction to form a nitrile whilst expelling a radical (usually stabilised). An early example of this was shown by Ingold, who reported that di-*tert*-butyliminyl radical (**2.32**) decays to give pivalonitrile (**2.33**) and *tert*-butyl radical (**2.34**) with first order kinetics (above -25 °C) (Scheme 27).[84]



2.32 **2.33** **2.34**

Scheme 27. *β-scission of di-tert-butyliminyl radical **2.32**.*

Kinetic studies on β-scission of the cyclobutyliminyl radical were performed by Roberts and Winter, who observed a rate constant of 10^3 s^{-1} at -73 °C for opening of the cyclic iminyl radical.[85] Zard reported a useful application of this rapid process; showing that a range of sulfenylimines (such as **2.35**), derived from their corresponding cyclobutanones, could be ring-opened following reaction with stannyl radicals to give products **2.36** and **2.37** (Scheme 28).[86]



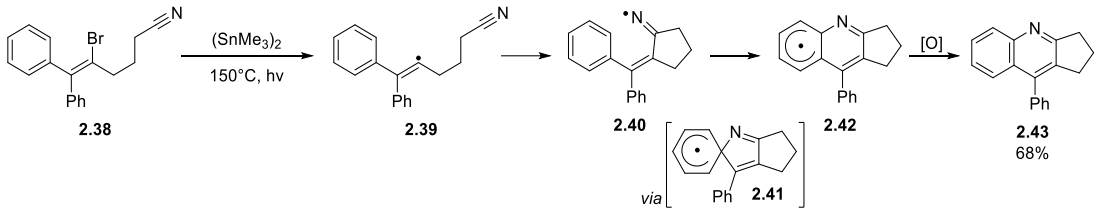
2.35 **2.36** 89% **2.37** 3%

Scheme 28. *Ring-opening induced by iminyl radicals derived from cyclobutanones.*

Tandem Radical Cyclisations of Nitriles

Iminyl radicals, generated by radical-addition to nitriles, have been shown to perform tandem radical cyclisations. Curran demonstrated that vinyl radical precursor **2.38**

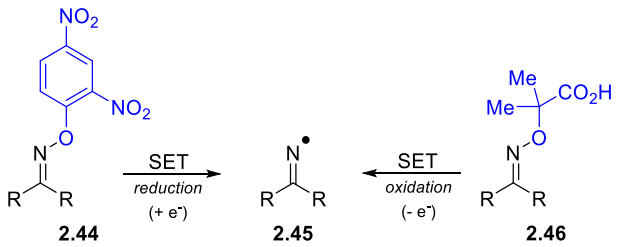
was able to undergo tandem radical cyclisation when irradiated in the presence of hexamethylditin (Scheme 29).[87] The formal 6-*endo-dig* cyclisation (**2.40** to **2.42**) was reported as proceeding via by initial 5-*exo-dig* cyclisation to give **2.41** followed by a neophyl rearrangement. Re-aromatisation of radical **2.42** to give quinoline **2.43** was proposed to be oxidative, although the exact mechanism and oxidant source is unclear.



Scheme 29. *Synthesis of quinoline **2.43** by radical tandem cyclisation.*

Leonori Group (Recent Literature)

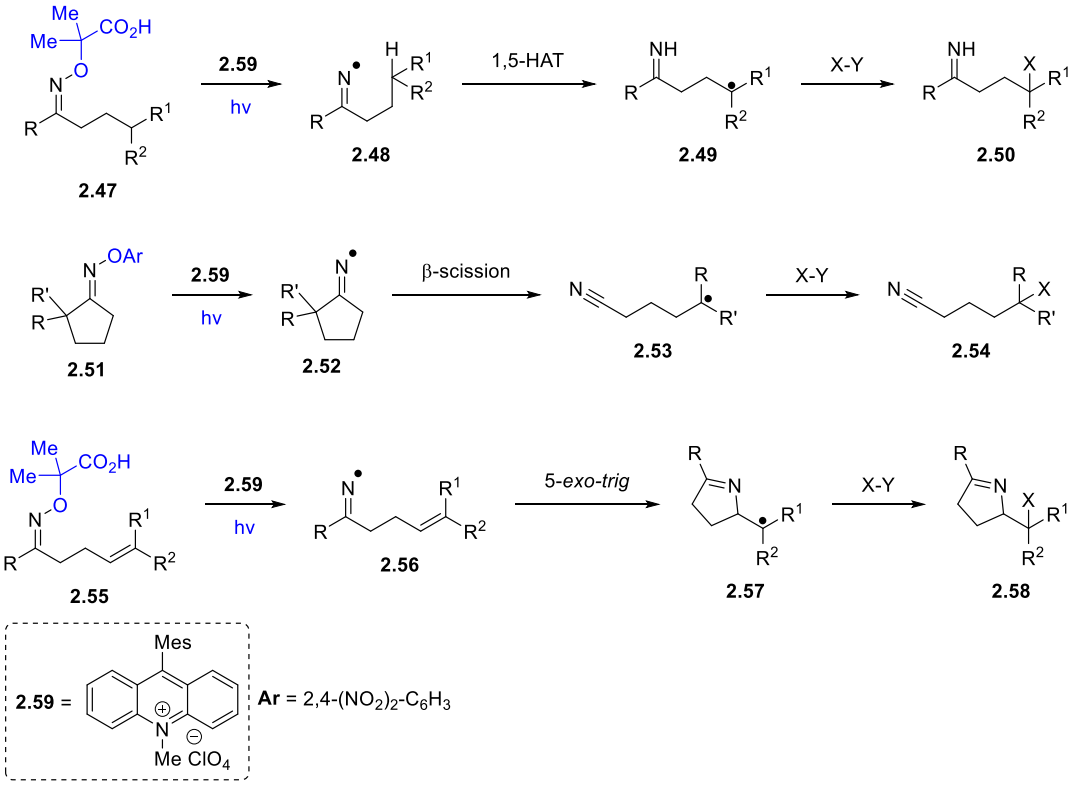
Recently, the Leonori group has developed two classes of oximes that provide access to iminyl radicals by both reductive and oxidative visible-light mediated single electron transfer (SET) (Scheme 30).[88,89] The electron-poor O-aryl oximes (**2.44**) are able to accept an electron from an excited photocatalyst; the resulting radical anion then undergoes cleavage to give the desired nitrogen-centred iminyl radical (**2.45**) and a stabilised phenol anion leaving group. On the other hand, electrophore **2.46** may be deprotonated and then lose an electron to a photo-excited catalyst, the resulting radical would then expel carbon dioxide and acetone to give desired iminyl radical **2.45**.[88,89] Both processes utilise homolysis of the weak N-O bond.



Scheme 30. *Visible-light mediated generation of iminyl radicals via oxidative or reductive SET.*

The characteristics of iminyl radicals (β-scission, HAT and nucleophilicity) were harnessed in 3 different reactions using this methodology (with photocatalyst **2.59**) and are shown below in Scheme 31. Following N-O bond cleavage, alkyl substituted

oximes (**2.47**) are set up to undergo a 1,5-HAT process that yields a carbon-centred radical (**2.49** from **2.48**). Trapping of the radical (e.g. fluorination with selectfluor) yields functionalised imine **2.50** which may be hydrolysed to the corresponding ketone.[89] Cyclic oxime ethers (**2.51**), when cleaved to **2.52**, can undergo β-scission and the resulting stabilised radical (**2.53**) may be trapped (e.g. chlorination with NCS) to yield the functionalised nitrile product (**2.54**).[89] Finally, upon N-O homolysis, oxime ether **2.55** is arranged to undergo a 5-*exo-trig* cyclisation event between the nucleophilic iminyl radical (**2.56**) and proximal alkene. The resulting radical (**2.57**) may be trapped (e.g. with a Michael acceptor) to afford the functionalised heterocycle product **2.58**.

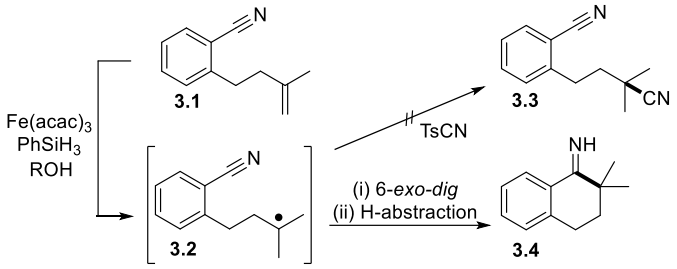


Scheme 31. *Overview of Leonori's iminyl radical methodologies.*

3 – HAT Mediated Cyclisation Reactions of Nitriles

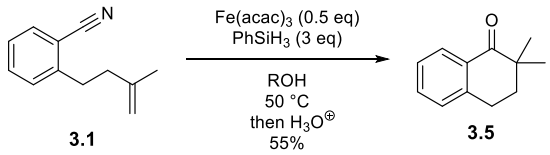
3.1 – Project Outline and Aims

When attempting to apply HAT-mediated hydrofunctionalisation methodology to substrate **3.1**, an interesting observation was made (Scheme 32).[90] The product gave consistent ionisation corresponding to cyclic imine **3.4** (by LCMS), rather than expected hydrofunctionalised product **3.3**, however isolation was not attempted by the GSK chemist.



Scheme 32. *Potential HAT-mediated radical cyclisation onto a nitrile group.*

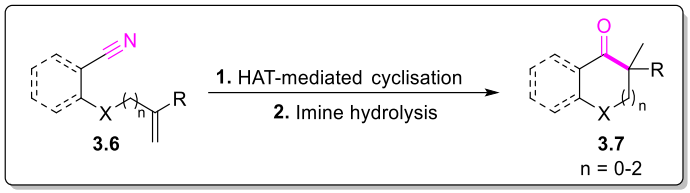
The experiment was repeated (in the absence of TsCN) in order to confirm it was indeed the proposed HAT-mediated cyclisation product previously observed by LCMS, and not simply reduction of the alkene (which has the same mass). Pleasingly, the 6-*exo-dig* cyclisation of **3.1** proceeded as desired and dimethyl ketone **3.5** was isolated in moderate yield (55%, unoptimised) following imine hydrolysis (Scheme 33).



Scheme 33. *Confirmation of the radical cyclisation – promoted by HAT.*

The conventional method for preparing such hindered ketones employs forceful reaction conditions (MeI, NaH, PhH, reflux, 96 h)[91] to alkylate the α-position of the ketone, whereas this newly discovered radical cyclisation was complete in 1 hour at 50 ^{o}C in alcoholic solvent.

As discussed previously (Figure 7, p.20), radical additions to nitriles are challenging; and the trapping of a radical formed from HAT, with a nitrile group, has not previously been reported. The aim of this project was to develop the aforementioned HAT-methodology, to provide access to new (hetero)cyclic compounds (**3.7**) via radical cyclisation with templates bearing nitrile groups (**3.6**) (Scheme 34).



X = C, O, NH, NR
R = Me, F, BR_2, O, NR_2

Scheme 34. *Outline of the methodology proposed for this project.*

It is hoped this work will add to the ever-expanding synthetic toolbox available to medicinal chemists.[92] Initial work was focussed on aromatic systems for ease of reaction monitoring, but efforts to extend this methodology towards aliphatic templates were also made. Reactions were carried out to explore tolerance of ring size, heteroatoms at the X position and functionality of the R group (see Scheme 34 above). Extensive optimisation of the reaction conditions, along with efforts to elucidate the reaction mechanism, were also made.

3.2 – Results and Discussion

This section will discuss the following for the HAT mediated alkene-nitrile cyclisation study:

- Synthesis of substrates
- Reaction optimisation
- Substrate scope
- Mechanistic discussion
- Interesting observations
- Challenging substrates

3.2.1 – Synthesis of Substrates

With the exception of 2-allylbenzonitrile (**3.8**), 2-(2-methylallyl)benzonitrile (**3.3**) and 2-(3-methylbut-3-en-1-yl)benzonitrile (**3.1**) shown in Figure 10, the starting materials for the desired HAT reactions were not commercially available. In order to demonstrate the scope of this methodology, a range of HAT substrates required synthesis. Herein the methods used to access the desired nitrile substrates are described in detail.

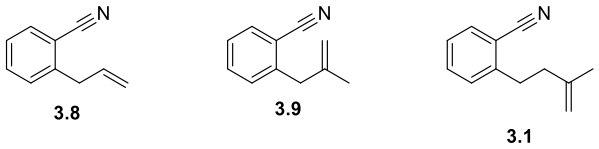
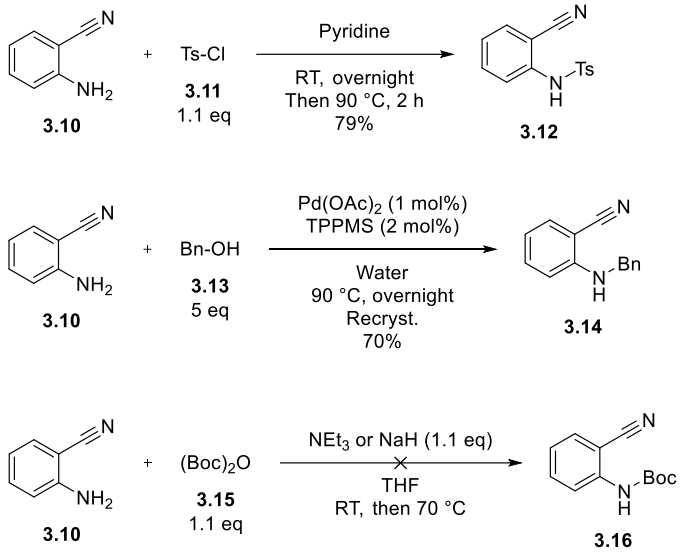


Figure 10. *Commercial nitrile substrates.*

Protection of 2-aminobenzonitrile (**3.10**) (shown below in Scheme 35) was sought to simplify subsequent alkylation reactions and also to investigate any potential interesting protecting group effects in the HAT methodology. Protection of **3.10** by reaction with tosyl chloride (Ts-Cl) (**3.11**) under basic conditions proceeded well to give **3.12** in good yield, with loss of yield attributed to bis-tosylation. Pleasingly, 2-(benzylamino)benzonitrile (**3.14**) was synthesised in good yield on a large scale through hydrogen borrowing reaction with benzyl alcohol (Bn-OH) (**3.13**),[93] without

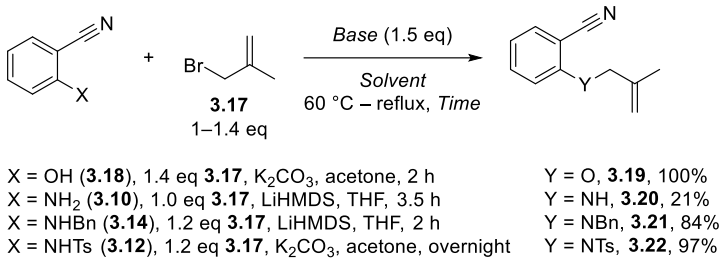
the need for column chromatography. This avoided the potentially troublesome alkylation with benzyl bromide or reductive amination with benzaldehyde which might prove difficult due to the poor nucleophilicity of 2-aminobenzonitrile. The poor nucleophilicity of 2-aminobenzonitrile was exposed when attempts to synthesise Boc-protected aniline (**3.16**) by reaction with Boc-anhydride [$(Boc)_2O$] (**3.15**) failed, with no consumption of starting material observed.



Scheme 35. *Protection of 2-aminobenzonitrile (**3.10**).*

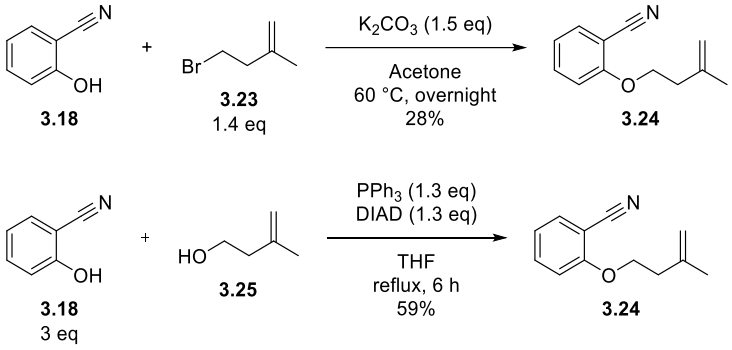
A number of substrates were synthesised by alkylation reaction with 3-bromo-2-methylprop-1-ene (**3.17**) as shown below in Scheme 36. Alkylation of 2-hydroxybenzonitrile (**3.18**), 2-(benzylamino)benzonitrile (**3.14**) and *N*-(2-cyanophenyl)-4-methylbenzene-sulfonamide (**3.12**) all proceeded smoothly in high yield to give **3.19**, **3.21** and **3.22** respectively. Conversely, alkylation of 2-aminobenzonitrile (**3.10**) proved troublesome due to poor reactivity (starting material was not consumed) and competing bis-alkylation side-reaction (only 21% yield of **3.20** obtained). Investigation into different bases (K_2CO_3 vs. NaH vs. LiHMDS) and solvents (DMF vs. THF vs. MeCN vs. Acetone) was carried out, but no significant improvement in reaction profile was obtained (results not shown). Pleasingly however, access to **3.20** proved facile through Buchwald-Hartwig chemistry (see later,

Table 2, p.33).



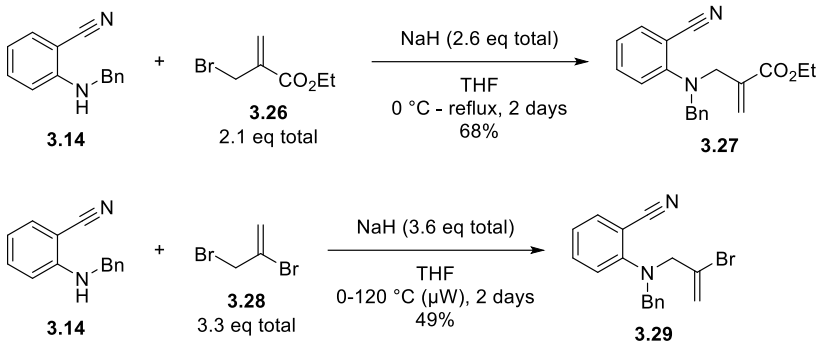
Scheme 36. *Nitrile motifs obtained by alkylation with 3* -bromo-2-methylprop-1-ene (**3.17**).

Alkylation of 2-hydroxybenzonitrile (**3.18**) with 4-bromo-2-methylbut-1-ene (**3.23**) proceeded poorly to give the desired product **3.24** in low yield (28%) (Scheme 37) along with recovery of unreacted starting material. Pleasingly, **3.24** was synthesised in improved yield (59%) by Mitsunobu reaction with alcohol **3.25**, although some difficulty in removing the troublesome triphenylphosphine oxide by-product was encountered.



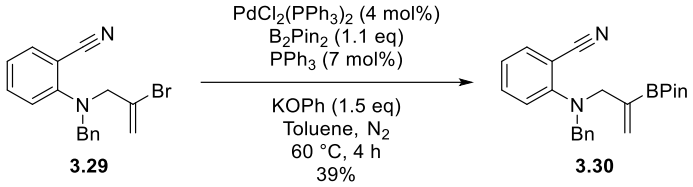
Scheme 37. *Synthesis of 2-((3-methylbut-3-en-1-yl)oxy)benzonitrile (**3.24**).*

Synthesis of functionalised alkene analogues, alkenyl-ester **3.27** and alkenyl bromide **3.29** was achieved through alkylation reactions (Scheme 38). Reaction of 2-(benzylamino)benzonitrile (**3.14**) with ethyl 2-(bromomethyl)acrylate (**3.26**) yielded **3.27** in reasonable yield (68%), though full conversion of starting material could not be achieved even with further additions of base and electrophile. Reaction of **3.14** with 2,3-dibromoprop-1-ene (**3.28**) proceeded slowly, with the reaction stalling overnight. Attempts to increase conversion with further additions of base and electrophile only modestly improved the reaction profile. However, **3.29** was nevertheless isolated in moderate yield (49%).



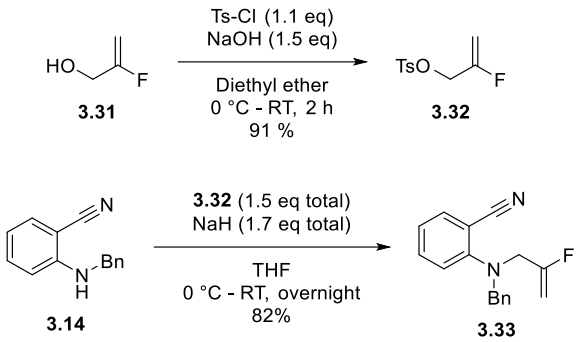
Scheme 38. *Synthesis of functionalised nitrile motifs **3.27** and **3.29**.*

With **3.29** in hand, further functionalisation was carried out in the form of a Miyaura borylation (Scheme 39).[94] The desired alkenylboronic acid pinacol ester (**3.30**) was isolated in modest yield (39%), along with unconsumed starting material (**3.29**) (9%), de-brominated starting material (6%) and de-allylated starting material (7%) (not shown). It is thought that the remaining material was lost due to instability of the boronic acid side-product on silica gel.



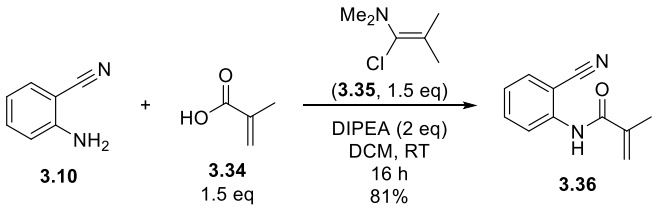
Scheme 39. *Miyaura borylation of alkenyl bromide **3.29**.*

Fluorinated analogue **3.33** was also synthesised. Firstly, electrophile **3.32** was prepared through tosylation of commercially available fluorinated alcohol **3.31**,[95] which proceeded well (91% yield) (Scheme 40). Alkylation of 2-(benzylamino)benzonitrile (**3.14**) with the prepared electrophile **3.32** proceeded smoothly to give vinyl fluoride **3.33** in good yield (82%).



Scheme 40. *Synthesis of fluorinated alkene-nitrile motif **3.33**.*

Amide coupling, using Ghosez's reagent (**3.35**) (T3P and HATU were trialled without success), between 2-aminobenzonitrile (**3.10**) and methacrylic acid (**3.34**) yielded desired amide-substrate **3.36** in good yield (Scheme 41). It is to be noted that excess acid and coupling reagent were used to ensure complete consumption of aniline **3.10**, which was found to be inseparable with the desired amide **3.36** on silica.

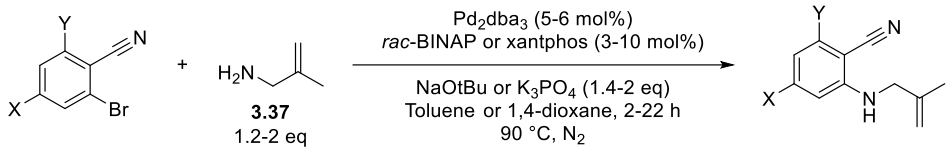


Scheme 41. *Synthesis of **3.36** via amide coupling.*

To investigate electronic effects on the nitrile group, a range of substrates (**3.20** and **3.44**–**3.48**) was synthesised by Buchwald-Hartwig amination with amine **3.37**,[96] as shown below in

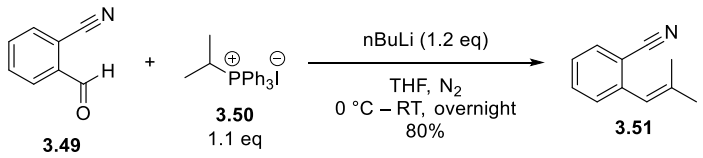
Table 2. Pleasingly **3.20** was synthesised in superior yield under Buchwald-Hartwig conditions than by alkylation (entry 1) (*cf.* earlier Scheme 36, p.30). Superior yields were achieved for electron donating-substituents (entries 2, 3 and 6) than for electron-deficient substrates (entries 4 and 5), with reduced yield mainly attributed to proto-debromination. Efforts to optimise conditions were not made.

Table 2. *Synthesis of nitrile motifs (**3.20** and **3.44–3.48**) by Buchwald-Hartwig reaction.*



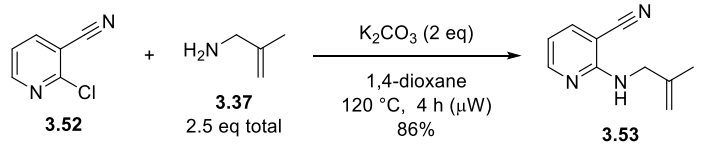
Entry	X	Y	S.M No.	Product No.	Yield (%)
1	H	H	**3.38**	**3.20**	83
2	Me	H	**3.39**	**3.44**	72
3	OMe	H	**3.40**	**3.45**	81
4	CO_2Me	H	**3.41**	**3.46**	64
5	CF_3	H	**3.42**	**3.47**	34
6	H	Me	**3.43**	**3.48**	84

To investigate the effect of benzyl versus tertiary radical, styrene-type substrate **3.51** was synthesised in good yield by Wittig reaction of the corresponding aldehyde **3.49** and phosphonium salt **3.50** (Scheme 42).[97]



Scheme 42. *Wittig reaction to access styrene analogue **3.51**.*

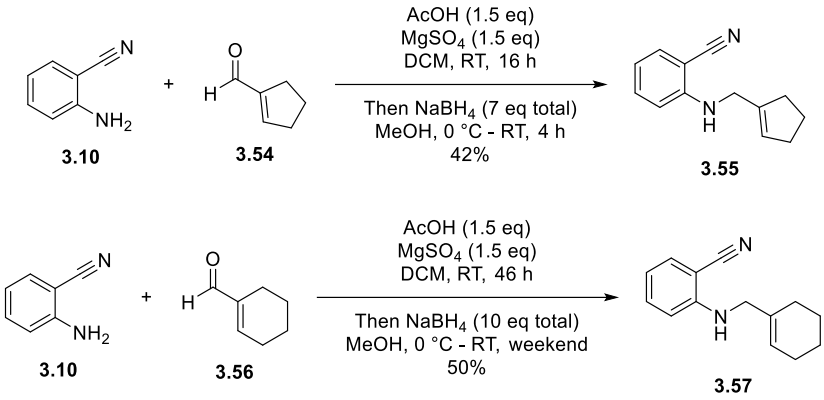
Synthesis of pyridine-substrate **3.53** was achieved by S_NAr reaction of chloropyridine **3.52** with amine **3.37** under microwave conditions (Scheme 43); the desired substrate was isolated in good yield (86%).



Scheme 43. *Synthesis of desired pyridine-substrate **3.53** via S_NAr of chloropyridine **3.52**.*

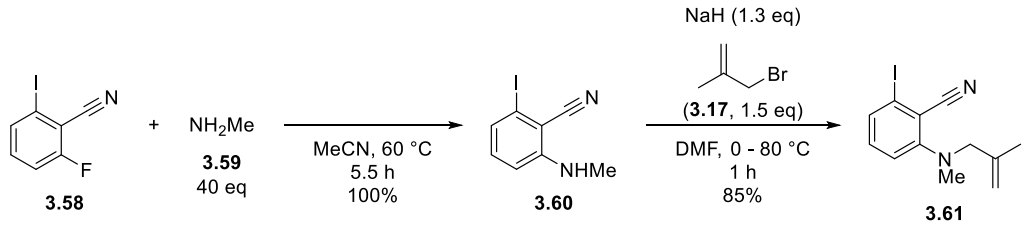
To investigate the formation of spirocycles, cyclic alkene substrates **3.55** and **3.57** where synthesised via reductive amination (Scheme 44) of aniline **3.10** with commercially available aldehydes **3.54** and **3.56.** The reactions required large

excesses of reducing agent ($NaBH_4$) as the imines formed were stabilised by conjugation.



Scheme 44. *Synthesis of **3.55** and **3.57** via reductive amination.*

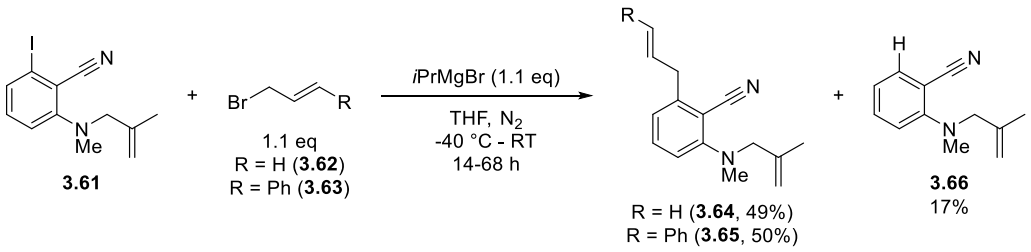
To facilitate mechanistic studies, the synthesis of substrates that are able to undergo tandem cyclisations was required. Firstly, key intermediate **3.61** was prepared as shown in Scheme 45. S_NAr reaction of commercially available aryl-fluoride **3.58** with excess methylamine (**3.59**) proceeded quantitatively to afford **3.60**, which was subsequently deprotonated and alkylated with 3-bromo-2-methylprop-1-ene (**3.17**) to yield intermediate **3.61** in good yield (85%). This route provided a 'two-for-one' opportunity, as **3.61** is a substrate for the alkene-nitrile cyclisation methodology in its own right.



Scheme 45. *Synthesis of desired intermediate **3.61** via S_NAr followed by alkylation.*

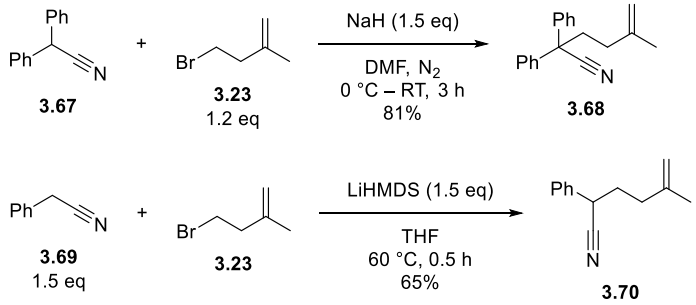
From **3.61**, desired tandem cyclisation substrates (**3.64** and **3.65**) could be accessed via iodide-magnesium exchange[98] with isopropylmagnesium bromide followed by reaction with the corresponding alkenyl bromides (**3.62** and **3.63**) as shown in Scheme 46. Both reactions gave reasonable yields of the desired substrates **3.64** and **3.65** (49% and 50%), with loss of yield attributed to de-iodination via quenching of

the organo-magnesium species to give side-product **3.66**, which was isolated for confirmation.



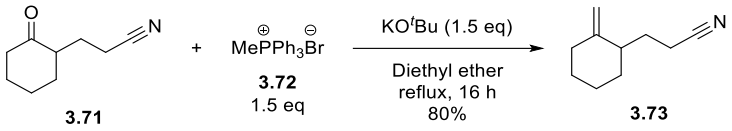
Scheme 46. *Synthesis of tandem cyclisation substrates **3.64** and **3.65**.*

Investigation into 'aliphatic' substrates, in which the alkene-nitrile chain is not tethered by an aromatic group, was initially made possible by synthesis of **3.68** and **3.70** (Scheme 47). Pleasingly, alkylation of 2,2-diphenylacetonitrile (**3.67**) with 4-bromo-2-methylbut-1-ene (**3.23**) proceeded well (under N_2) and yielded the desired product **3.68** in good yield (81%). It is to be noted that the same reaction in THF, under air, only yielded 49% of **3.68** (result not shown). The alkylation of 2-phenylacetonitrile (**3.69**) proved more challenging. It was established that LiHMDS gave a cleaner reaction profile than NaH, but issues with bis-alkylation remained. The desired mono-alkylated product (**3.70**) and undesired bis-alkylated product were inseparable by normal and reverse phase chromatography. However pleasingly, after purification by multiple MDAPs, pure **3.70** was isolated in reasonable yield (65%).



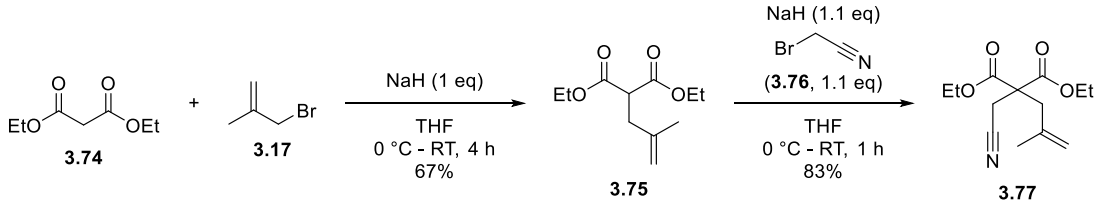
Scheme 47. *Synthesis of 'aliphatic' substrates **3.68** and **3.70**.*

Following literature procedure,[99] aliphatic substrate **3.73** was synthesised in good yield (80%) by Wittig reaction of commercially available ketone **3.71** with methyltriphenylphosphonium bromide (**3.72**) (Scheme 48).



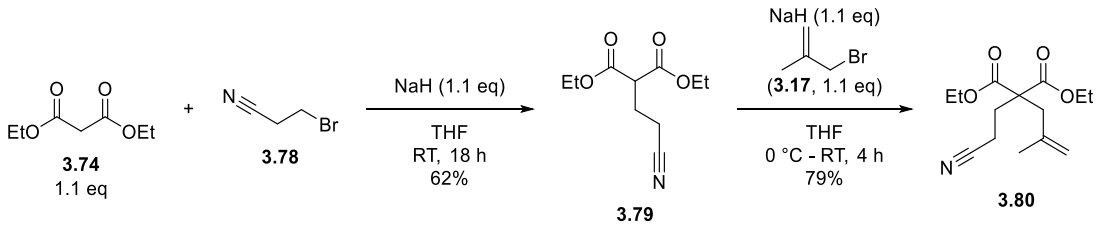
Scheme 48. *Synthesis of substrate **3.73** via Wittig reaction.*

Following literature procedure,[100] alkylation of diethyl malonate (**3.74**) with 3-bromo-2-methylprop-1-ene (**3.17**) yielded desired intermediate **3.75**. Further deprotonation and reaction with 2-bromoacetonitrile (**3.76**) afforded the desired bis-alkylated substrate **3.77** in good yield (83%) (Scheme 49).



Scheme 49. *Synthesis of **3.77** via bis-alkylation of diethyl malonate (**3.74**).*

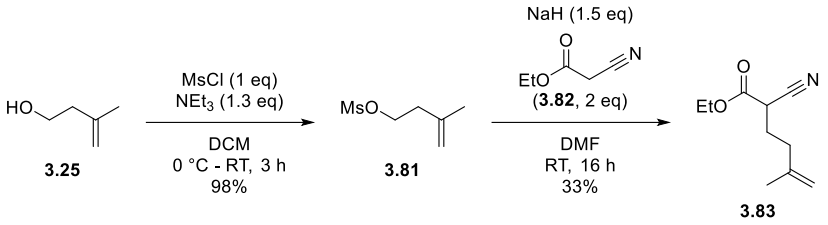
Synthesis of analogue **3.80** was achieved in a similar manner, though the alkylation steps in reverse order. Following literature procedure,[101] alkylation of diethyl malonate (**3.74**) with 3-bromopropane nitrile (**3.78**) afforded intermediate **3.79**. Further deprotonation and reaction with 3-bromo-2-methylprop-1-ene (**3.17**) yielded the desired bis-alkylated substrate **3.80** in good yield (79%) (Scheme 50).



Scheme 50. *Synthesis of **3.80** via bis-alkylation of diethyl malonate (**3.74**).*

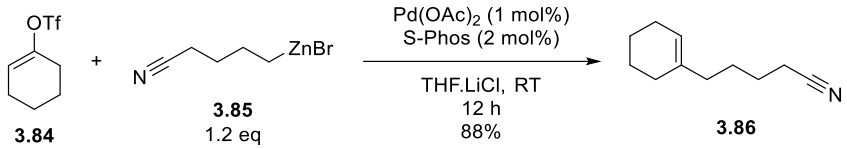
Mesylation of commercially available alcohol **3.25** proceeded smoothly to yield desired electrophile **3.81**.[102] Reaction of **3.81** with deprotonated ethyl 2-

cyanoacetate (**3.82**) yielded the desired substrate **3.83** in modest yield (33%) (Scheme 51).[103]



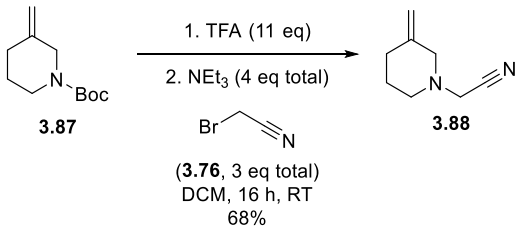
Scheme 51. *Alkylation of ethyl 2-cyanoacetate (**3.82**) to afford desired substrate **3.83**.*

Below will be described the synthesis of aliphatic alkene-nitrile substrates, with the aim of accessing more complex ring systems following the HAT cyclisation methodology. Extending the scope of literature conditions,[104] the Negishi coupling of commercially available triflate **3.84** and organozinc **3.85** yielded desired aliphatic alkene-nitrile substrate **3.86** in high yield (88%) (Scheme 52).



Scheme 52. *Negishi coupling to yield desired aliphatic substrate **3.86**.*

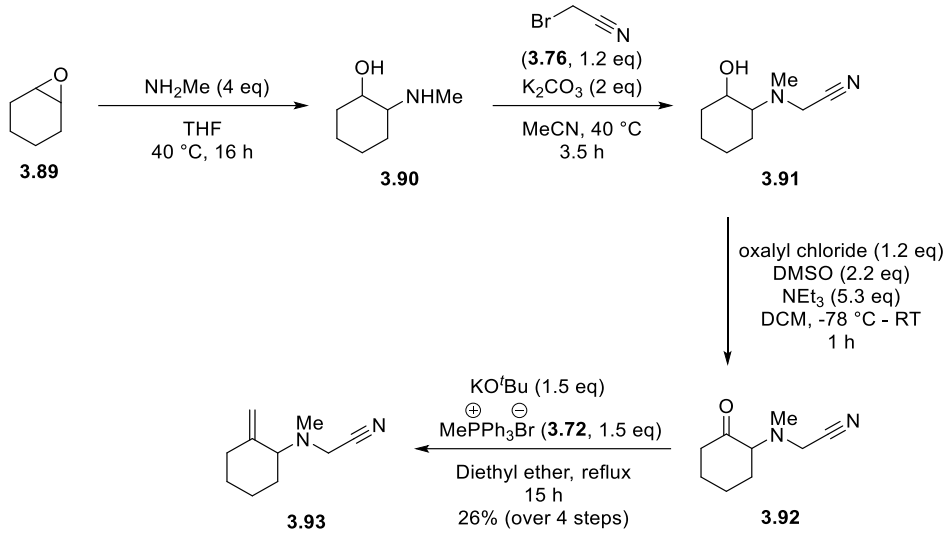
Removal of the Boc-group from commercial **3.87**, under acidic conditions, followed by removal of excess acid *in vacuo* and alkylation with 2-bromoacetonitrile (**3.76**), afforded desired alkene-nitrile substrate **3.88** in reasonable yield (68%) (Scheme 53).



Scheme 53. *Deprotection and alkylation of **3.87** to yield alkene-nitrile substrate **3.88**.*

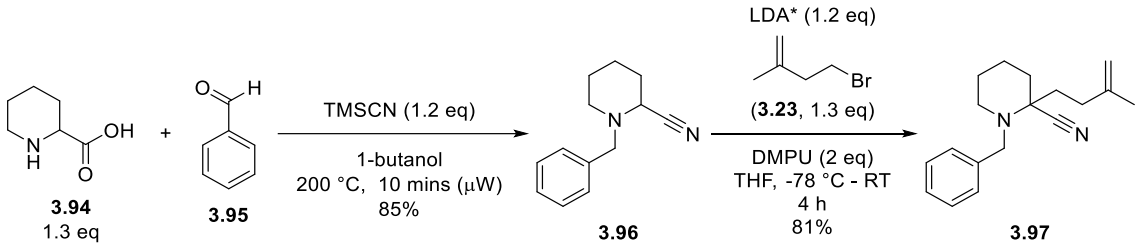
The telescoped synthesis of desired substrate **3.93**, in which all intermediates were used as crude, is outlined below in Scheme 54. Ring-opening of commercial epoxide **3.89** with methylamine gave amino-alcohol **3.90**, subsequent *N*-alkylation (with **3.76** to give **3.91**) and followed by Swern oxidation[105] afforded intermediate crude ketone **3.92**. Finally, Wittig reaction of **3.92** yielded the desired alkene-nitrile **3.93** in

respectable yield (26% over 4 steps), given that no purification was performed at intermediate stages.



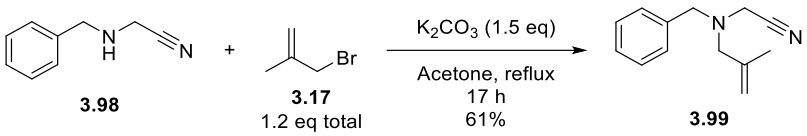
Scheme 54. *Telescoped synthesis of desired alkene-nitrile substrate **3.93**.*

Following literature procedure, the decarboxylative Strecker reaction[106] of commercial α-amino acid **3.94** with benzaldehyde (**3.95**) and trimethylsilyl cyanide (TMSCN) afforded α-amino nitrile **3.96** in good yield (85%) (Scheme 55). Lithiation/deprotonation of **3.96** and alkylation with 4-bromo-2-methylbut-1-ene (**3.23**) yielded the desired alkene-nitrile substrate **3.97** in 81% yield.



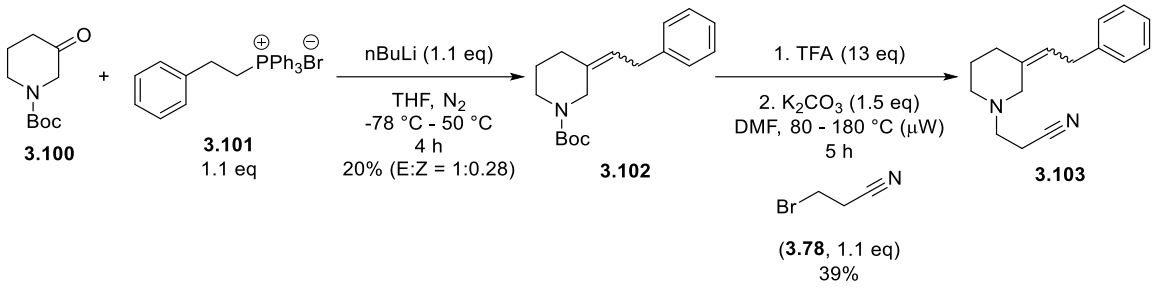
Scheme 55. *Synthesis of alkene-nitrile substrate **3.97**, *freshly prepared.*

Alkylation of commercial 2-(benzylamino)acetonitrile (**3.95**) with 3-bromo-2-methylprop-1-ene (**3.17**) is shown in Scheme 56. A reasonable yield (61%) of desired substrate **3.99** was obtained, considering the commercial starting material **3.98** was impure (~80% purity by LCMS).



Scheme 56. *Synthesis of alkene-nitrile substrate **3.99** via alkylation.*

The multi-step synthesis of alkene-nitrile **3.103** is outlined in Scheme 57. Wittig reaction of commercial ketone **3.100** gave a poor yield (20%) of desired intermediate **3.102**, which was subsequently deprotected and alkylated to give the desired alkene-nitrile **3.103** in modest yield (39%).



Scheme 57. *Synthesis of desired alkene-nitrile **3.100** via Wittig and alkylation reactions.*

3.2.2 – Reaction Optimisation

The optimisation for this methodology proved challenging, and the key was a detailed understanding of varying reaction outcome under differing atmospheres. Initial scoping of reaction conditions (LCMS data) was carried out to identify optimal reaction concentration, time and temperature (0.25M, 50 ^{o}C, 1 h) (full results can be found in the experimental, Table 12-16, p.161). This information was then used to carry out the extensive reaction optimisation (HPLC, using internal standard) which will be discussed in detail below.

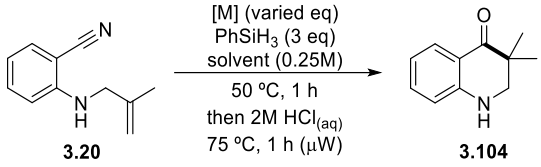
Conditions were screened for conversion of test substrate **3.20** to ketone **3.104** and the key are results shown below in Table 3 (for extensive data see Table 15 in experimental, p.166). Since oxygen might be required for the regeneration of the catalyst, but could also detrimentally intercept crucial organic radicals on our pathway, experiments were performed in sealed vials with a limited headspace of air, open to air, or occasionally under inert gas (N_2); in all cases using solvents that were not degassed. To access the ketone, it was found that hydrolysis of the imine intermediate was most effective under microwave conditions.

Examining firstly the catalyst, the reaction provided higher yields when using $Fe(acac)_3$ rather than $Mn(dpm)_3$ (entry 1 *vs.* entry 2). Switching from EtOH as solvent to *i*PrOH resulted in no change in yields for reactions performed under similar conditions (see Table 15, p.166); however, *i*PrOH was preferred for reactions conducted open to the air because of its higher boiling point. Comparison of entries 3 and 4 showed that for small scale reactions, loading at 50 mol% of $Fe(acac)_3$ worked better than 20% when open to air. However, both results were inferior to entry 1 which was performed in a sealed vial.

The key breakthrough came when comparing entry 4 and 5, which were conducted on a larger, more relevant, scale (0.5 mmol). The reaction performed open to air (entry 6) with 20 mol% catalyst gave the best isolated yield of desired ketone **3.104** (94%) after just 1 hour at 50 ^{o}C, compared to entry 5 (with limited air) which suffered from incomplete consumption of starting material.

These results suggest that the volume of air (concentration of oxygen in solution) is important to the outcome of the reaction. When the reaction was scaled up, the vial size remained constant, thus the headspace of air was no longer sufficient (as it was on a small scale). In contrast, when open to air on a small scale, the reaction appeared to be more sensitive to air as the relative concentration of oxygen to free radical species was higher.

Table 3. *Screening of reaction conditions for conversion of **3.20** to **3.104**.*



3.20 3.104

Entry[a]	[M] (mol%)	Solvent	Atmosphere[b]	Yield (%)	
				3.20	3.104
1	$Fe(acac)_3$ (50)	EtOH	Headspace of air	3	81
2	$Mn(dpm)_3$ (50)	EtOH	Headspace of air	14	66
3	$Fe(acac)_3$ (50)	*i*PrOH	Open to air	<1	70
4	$Fe(acac)_3$ (20)	*i*PrOH	Open to air	<1	57
5[b]	$Fe(acac)_3$ (20)	*i*PrOH	Headspace of air	19	71
6[b]	**$Fe(acac)_3$ (20)**	***i*PrOH**	**Open to air**	**-**	**94**

[a] HAT: 0.1 mmol; solution yield quoted, quantified by HPLC using an internal standard. [b] 0.5 mmol scale, isolated yields quoted.

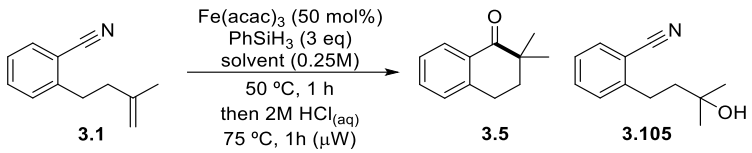
For completeness, optimisation for conversion of substrate **3.1** (bearing an all-carbon side-chain) to ketone **3.5** was also carried out, and subtle differences compared to the N-linked substrate **3.20** were discovered. The key results are shown below in Table 4 (for extensive data see Table 16 in experimental, p. 167).

Substrate **3.1** performed moderately well (59% yield) on a small scale under the sealed conditions (entry 1), with the competitive formation of oxidised side-product **3.105** observed, reflecting slower radical cyclisation kinetics than for substrate **3.20**. To enhance the kinetics, hexafluoroisopropanol (HFIP) was selected as a co-solvent.

HFIP is a known Lewis acid[107] and might facilitate cyclisation onto the nitrile group. Addition of HFIP as a co-solvent with EtOH (1:1) increased the yield of desired product **3.5** to 77% (entry 2). This was increased yet further to 86% under inert atmosphere (entry 3). Aerobic conditions on a 0.1 mmol scale (entry 4), were not beneficial, with the undesired tertiary alcohol **3.105** predominating at lower temperature (entry 5).

However, on larger scale (0.5 mmol), aerobic conditions with 20 mol% catalyst (optimum for substrate **3.20**) gave a good yield of **3.5** (entry 6), although a superior yield was observed with EtOH:HFIP (N_2, entry 7). Conducting the reaction under N_2 in pure EtOH depleted the conversion (entry 8), highlighting the importance of HFIP for substrate **3.1** when the concentration of oxygen is limited.

Table 4. *Screening of reaction conditions for conversion of **3.1** to **3.5**.*



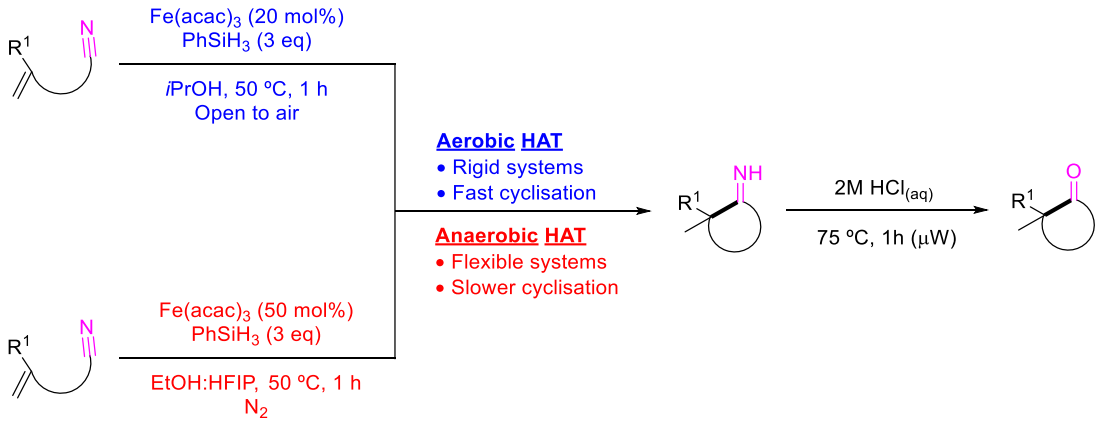
Entry[a]	Solvent	Atmosphere	Yield (%)		
			3.1	**3.5**	**3.105**
1	EtOH	Headspace of air	3	59	8
2	EtOH:HFIP	Headspace of air	<1	77	5
3	EtOH:HFIP	N_2	4	86	3
4	*i*PrOH	Open to air	<1	52	18
5[b]	*i*PrOH	Open to air	21	11	51
6[c*]	*i*PrOH	Open to air	-	74	-
7[c]	**EtOH:HFIP**	**N_2**	**-**	**83**	**-**
8[d*]	EtOH	N_2	-	33	-

[a] HAT: 0.1 mmol; solution yield quoted, quantified by HPLC using an internal standard. [b] HAT conducted at RT. [c] 0.5 mmol scale, isolated yields quoted. *20 mol% $Fe(acac)_3$. [d] 0.5 mmol scale, NMR yield quoted as **3.1** and **3.5** co-elute during chromatography.

The beneficial effect of HFIP may be due to its Lewis acid character, although its benefits may extend beyond this - oxygen has a high solubility in fluorinated solvents,[108] which may facilitate catalyst turnover under sealed conditions (see Figure 11, homogeneous solution Table 4 entry 7 *vs.* heterogeneous for Table 4 entry 8). The use of HFIP in other radical-based (HAT) methodologies is reported, though its effects are unknown.[109,110]

Figure 11. *Reaction images. EtOH (Table 4, Entry 8) on the left (heterogeneous) and EtOH:HFIP (Table 4, Entry 7) on the right (homogeneous).*

In summary, two optimised sets of reaction conditions were established for HAT-mediated cyclisations of alkene-nitriles (Scheme 58). When the kinetics of alkene-nitrile cyclisation are fast, 'aerobic' conditions may be employed. Whereas when the cyclisation is slower or competing oxidative side-reactions are prevailing, 'anaerobic' conditions are preferred. For example, the amino-tethered substrate **3.20** outperforms its all-carbon variant **3.10**, likely due to the planar N atom, positioning the two reacting groups in closer proximity, resulting in faster cyclisation.

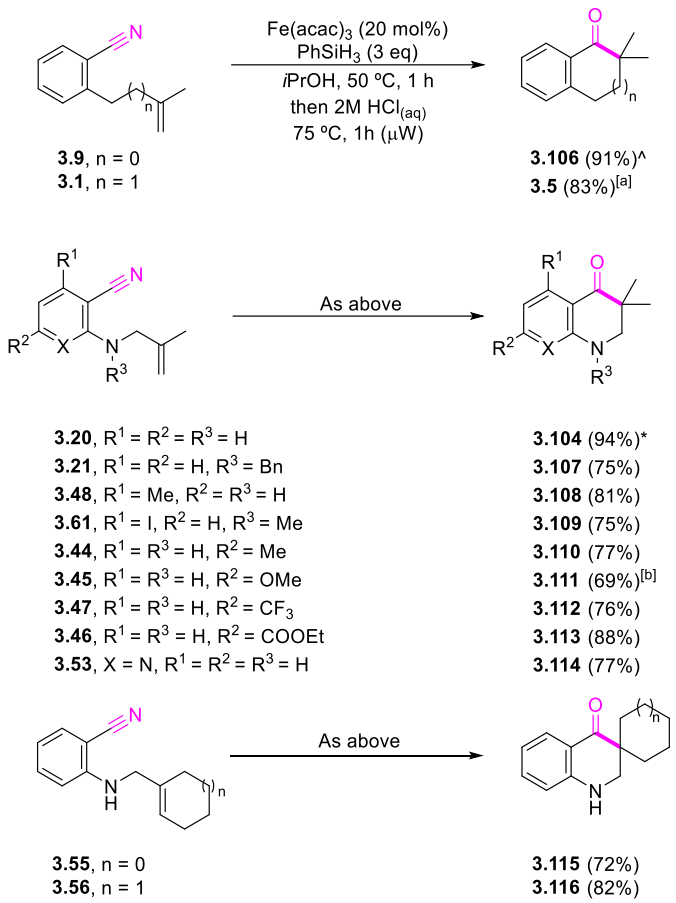


Scheme 58. *Outline of the two HAT conditions established for alkene-nitrile cyclisation.*

3.2.3 – Substrate Scope

The optimised aerobic conditions (Table 3, entry 6, p.33) were applied to a range of aromatic substrates (Scheme 59). The 5-*exo*-*dig* cyclisation of alkene-nitrile **3.9** proceeded excellently (91%), with catalyst loading as low as 5 mol% also giving good yield (78% on 5 mmol scale). A slight drop in yield (83%) for the 6-*exo*-*dig* variant for substrate **3.1** was observed. Benzyl protection of the tethering-nitrogen was well tolerated (**3.107**, 75%) (although not required, *cf.* **3.104**, 94%) as was the inclusion of steric hindrance *ortho* to the nitrile (**3.108**, 81%). The presence of an *ortho* iodide was also well tolerated (**3.109**, 75%).

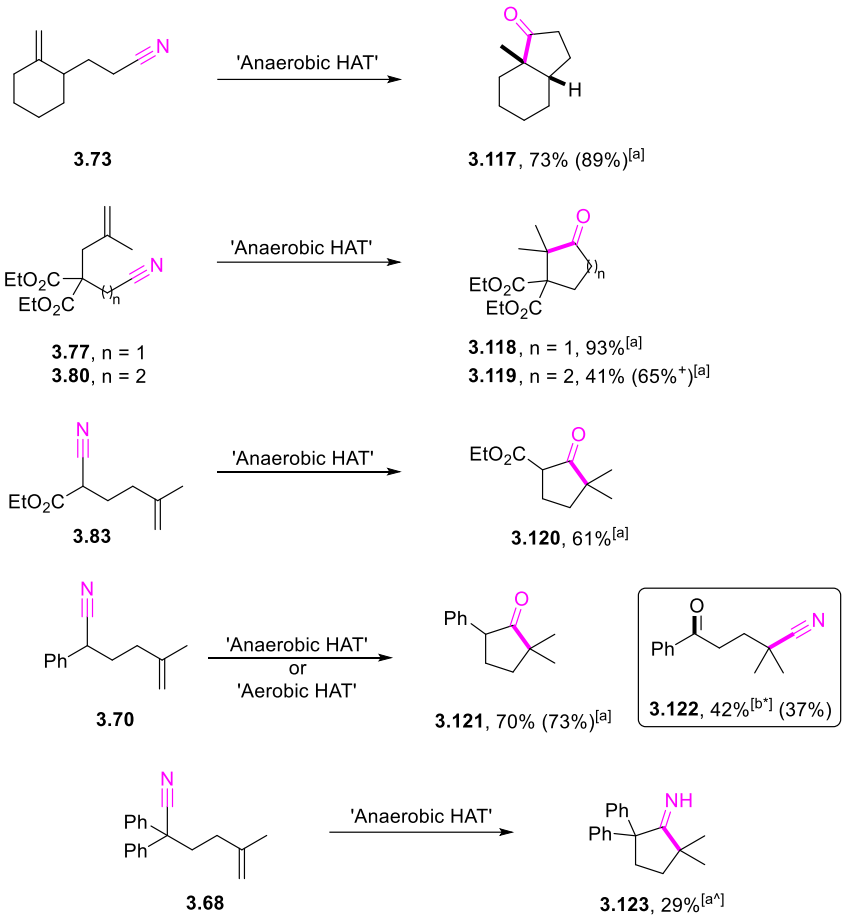
Pleasingly, the HAT reaction of **3.20** to **3.104** was performed on a 1 g scale without decrease in yield (94% on 0.5 and 5.8 mmol scale). Cyclisation proceeded smoothly with electron-donating aryl substituents *para* to the nitrile, operating either by inductive effect (**3.44** gave **3.110**, 78%) or mesomeric effect (**3.45** gave **3.111**, 69% with extended imine hydrolysis time). Similarly, electron-withdrawing groups (CF_3, **3.112**) (CO_2Et, **3.113**) was not detrimental to cyclisation (76% and 88% yield, respectively), as did pyridine **3.114** (77%). Facile access to spirocycles **3.115** and **3.116** was also achieved in good yields (72% and 82% respectively), providing a new entry to structurally complex scaffolds.



Scheme 59. *Aromatic substrate scope for HAT-mediated cyclisation of alkene-nitriles. Isolated yields quoted. All reactions were performed on a 0.5 mmol scale using conditions from* Table 3 *entry 6, unless otherwise stated. If 'X' is undefined, assume it is CH. ^ 78% yield with 5 mol% Fe on 5 mmol scale. [a] Conditions were taken from entry 7,* Table 4. **94% yield on 1g (5.8 mmol) scale. [b] Hydrolysis for 5 h.*

Attention turned to alkene-nitrile cyclisations in which the alkene and nitrile are not rigidly held by an aromatic ring (Scheme 60). Utilising 'anaerobic' conditions (Table 4, entry 7, p.42), *cis*-fused aliphatic ring system **3.117** was formed in good yield (73% isolated) from **3.73**. Substrate **3.77** derived from diethyl malonate cyclised in excellent yield (93%) to form 5-membered saturated ring **3.118** and the analogous 6-membered product **3.119** was obtained from **3.80** (65% NMR yield). Ethyl cyanoacetate-derived **3.83** cyclised in good yield (61%) to form **3.120**. Interestingly, substrate **3.70** underwent 5-*exo*-*dig*-cyclisation followed by reversible nitrile translocation. Under aerobic conditions, the resulting benzyl radical is trapped by oxygen leading to the formation of benzoyl derivative **3.122** (see discussion later, Scheme 61, p.47).[111] However, under anaerobic conditions, the iminyl radical was preferentially trapped and the resulting imine was hydrolysed on work-up to the

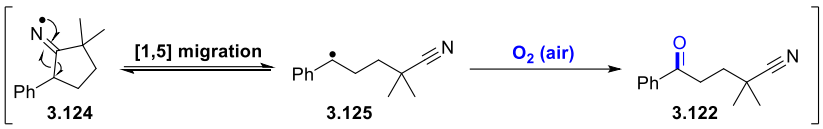
expected ketone **3.121** (70%). The diphenyl variant **3.68** underwent cyclisation to yield the highly sterically hindered, and consequently hydrolytically stable, imine **3.123**.



Scheme 60. *Construction of aliphatic ring systems by HAT-mediated cyclisation of alkene-nitriles. Isolated yield quoted, NMR yield determined with an internal standard given in parenthesis were applicable. [a] Inert conditions were taken from Table 3, entry 7. [b] Aerobic conditions were taken from Table 2, entry 6. * 30 mins reaction time and hydrolysis omitted, isolated product was impure. ^ 75 mol% Fe(acac)$_3$ and 4.5 eq PhSiH$_3$. + NMR yield as some fractions of **3.119** co-eluted on silica with the hydrogenated starting material.*

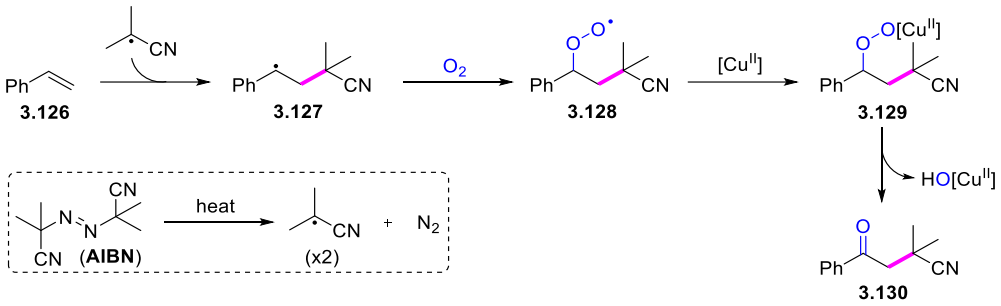
The mechanism for the formation of ketone **3.122** is thought to proceed as is shown below in Scheme 61. Firstly, the desired HAT-mediated 5-*exo*-*dig* cyclisation proceeds to give cyclised iminyl radical **3.124**, which may then undergo a reversible [1,5] migration reaction to give the stabilised benzyl radical intermediate **3.125**. In the presence of O_2, **3.125** can be trapped out as ketone **3.122**. The excellent selectivity shown likely reflects the strength of the Si-H bond, impeding abstraction by stabilised benzylic radical **3.125**; meanwhile, the electrophilic iminyl radical **3.124** may more

rapidly abstract an H atom from the hydridic Si-H bond, due to polarity matching. Whereas trapping of molecular oxygen occurs rapidly for benzylic radical **3.125**, while electrophilic iminyl radical **3.124** should be slow to form a weak N-O bond through coupling to O_2.



Scheme 61. *Proposed reaction pathway to ketone **3.122**.*

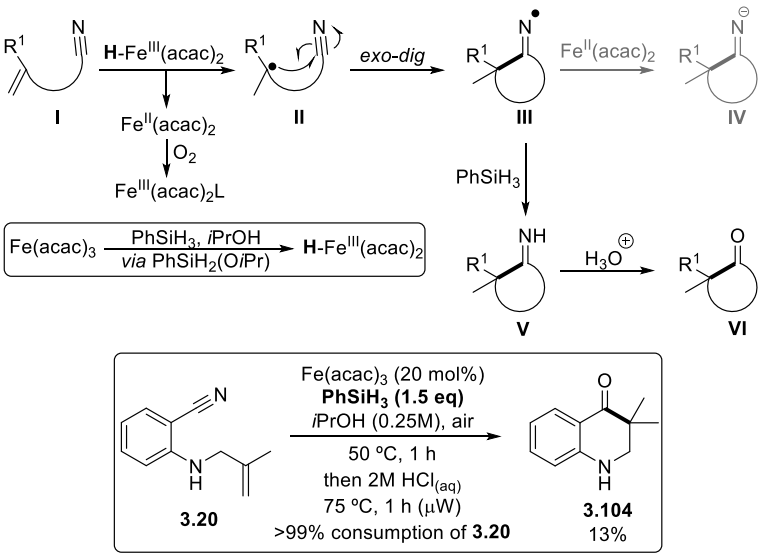
This reaction pathway is supported by a report on the oxidative coupling of styrene (**3.126**) with AIBN in the presence of a copper catalyst (Scheme 62).[111] It is proposed that an intermediate [Cu^{II}] species (**3.129**) is formed following reaction of **3.127** with dioxygen (**3.128**) which, upon elimination of [Cu^{II}]OH, gives desired ketone **3.130**. The proposed mechanism was supported by DFT studies and one can imagine a similar process for the reaction observed above in Scheme 61 using iron in the place of copper.



Scheme 62. *Plausible reaction mechanism for the oxidative coupling of styrene (**3.126**) and AIBN in the presence of a copper catalyst and oxygen.*

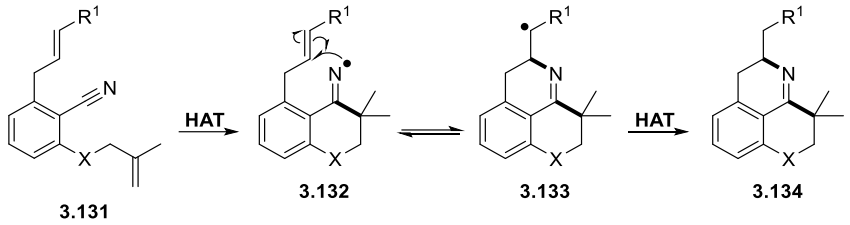
3.2.4 – Mechanistic Discussion

A simplified mechanism[66] for coupling of alkenes to nitriles is shown below in Scheme 63. HAT from *in situ*-generated $HFe(acac)_2$ to the alkene (**I**) sets up the *exo-dig* cyclisation (**II**). Then the fate of the resulting iminyl radical (**III**) is to be considered. In the examples by Bonjoch[55] (alkoxyl radicals) and Baran[32,33,66] (radicals α- to an electron-withdrawing group), single electron transfer (SET) is proposed to convert the radical to the corresponding anion, with Fe^{II} being simultaneously oxidised to Fe^{III}. The iminyl radical present in this methodology may not be so easily reduced by electron transfer (**III** to **IV**), and instead may abstract H from $PhSiH_3$ (**III** to **V**) (supported by large drop-off in yield for **3.104** when only 1.5 eq of $PhSiH_3$ is used, shown in the box below). The resulting imine (**V**) is then hydrolysed *in situ* with aqueous acid to the corresponding ketone (**VI**). Finally, the Fe^{II} species can be oxidised to Fe^{III} in the presence of oxygen to complete the catalytic cycle.



Scheme 63. *Proposed mechanism for HAT-mediated alkene-nitrile cyclisation.*

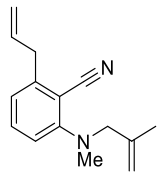
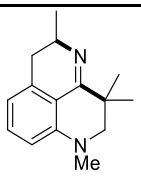
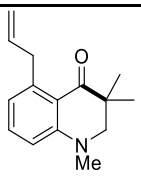
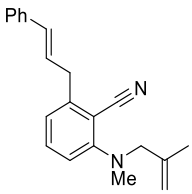
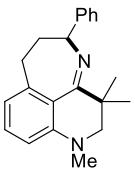
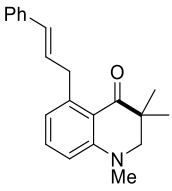
If the iminyl radical intermediate is not converted rapidly to the anion, then it should be possible to intercept it in a tandem cyclisation reaction (concept shown below in Scheme 64).



Scheme 64. *Outline of the HAT-mediated tandem cyclisation methodology.*

To test this hypothesis, substrates **3.64** and **3.65**, capable of undergoing a second cyclisation, were subjected to the aerobic HAT reaction conditions (results shown below in Table 5). Encouragingly, tricycle **3.135** was isolated and characterised from the tandem cyclisation of substrate **3.64**, albeit only in trace amounts. The poor conversion to **3.135** is unsurprising, since 6-*exo*-*trig* from the iminyl radical yields an unstabilised primary alkyl radical, likely in equilibrium with the corresponding open iminyl radical (e.g. **3.133** *vs*. **3.132** in Scheme 64 above).

Table 5. *HAT-mediated tandem radical cyclisation reactions of **3.64** and **3.65**.*

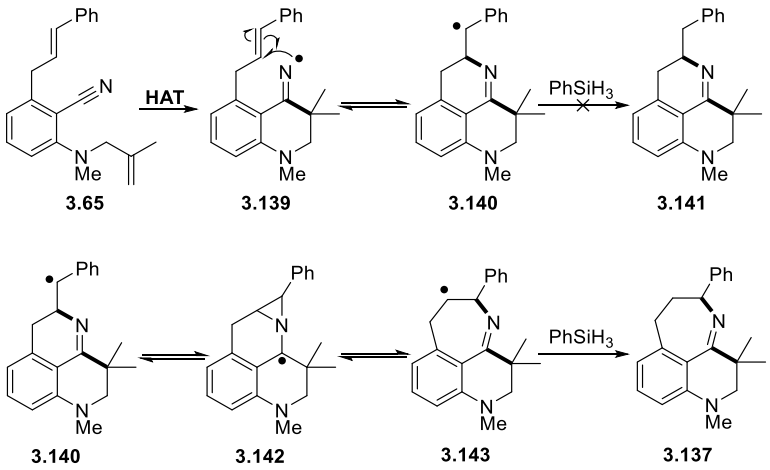
Substrate	Products	
 **3.64**	 **3.135** Trace	 **3.136** 18%
 **3.65**	 **3.137** 14%	 **3.138** 10%

Yields determined by ^{1}H NMR with an internal standard (products isolated by MDAP for characterisation). Reactions performed under the aerobic conditions taken from Table 3, entry 6.

Attention next turned to the benzyl variant **3.65**. Pleasingly, tandem product **3.137** was obtained as the major quantified product in a much-improved conversion compared to the reaction of **3.64**. It is to be noted that in both cases the reaction

mixtures obtained were complex. The mono-cyclised ketones **3.136** and **3.138** were quantified and reduction of the allyl group was also detected, along with unreacted starting material. The remaining components detected in the LCMS appeared to be masses of dimers. Pleasingly, this observation of tandem radical cyclisations supports the proposal that the lifetime of the iminyl radical is not negligible, and provided inspiration for further HAT methodologies (discussed later in Chapter 2).

Unexpectedly, the structure of the tandem cyclised product obtained from HAT reaction of **3.65** was the seven-membered ring **3.137**. A potential pathway could involve 6-*exo*-*dig* cyclisation from the iminyl radical **3.139**, followed by formation of an aziridinylcarbinyl radical **3.142**[112] which can ring-open to the 7-membered ring to form **3.143** upon quenching of the radical (Scheme 65). Once again, a benzylic radical (**3.140**) is incapable of abstracting a hydrogen from the silane (to **3.141**), allowing product to arise from the less stabilised secondary radical **3.143** (see comparison with **3.125** in Scheme 61, p. 47).

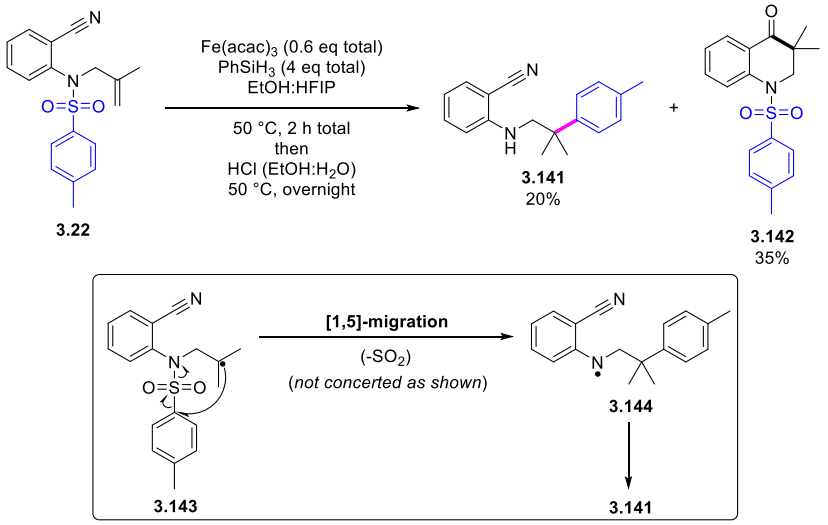


Scheme 65. *Suggested pathway for the formation of 7-membered heterocycle **3.137**.*

3.2.5 – Intriguing Observations

During this research a number of interesting side-reactions were observed; several brought about further exploration (see Chapter 3 later). It is to be noted that much of the chemistry discussed in this section was performed prior to extensive optimisation of conditions, before the role of HFIP and oxygen in the reaction was fully understood.

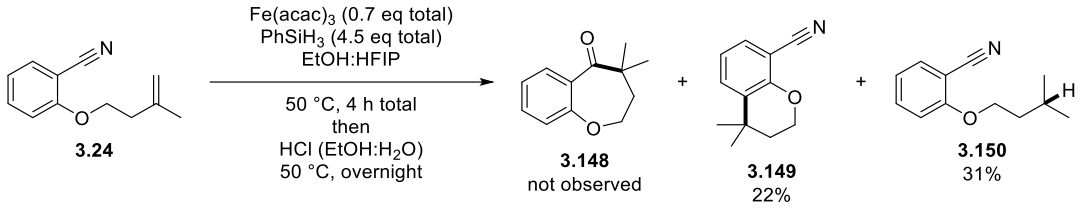
When tosylated analogue **3.22** was subjected to HAT conditions, only a modest 35% yield of the desired dimethyl ketone **3.145** was isolated (Scheme 66). Alongside the expected 6-*exo*-dig cyclisation reaction, a major side-reaction occurred. Interestingly, the radical formed through the HAT reaction attacked at the *ipso*-position of the tosyl group to give the major side-product **3.144** by loss of sulfur dioxide (proposed via radical intermediates **3.146** and **3.147**). It is to be noted that de-allylation was also observed (<20% by LCMS, result not shown). This is an example of a radical Smiles rearrangement, which have been reviewed recently.[113]



Scheme 66. *[1,5] Tolyl group migration reaction, upon release of sulfur dioxide, to give* ***3.144****.*

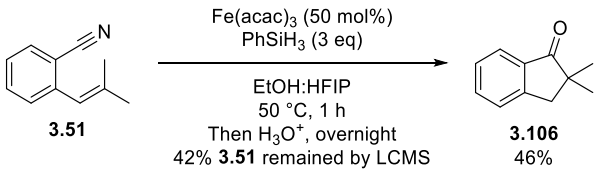
Whilst attempting to expand to a 7-*exo-dig* cyclisation of substrate **3.24**, it was found that the kinetics were too slow for the desired cyclisation towards **3.148**, and the major product isolated from the reaction featured the premature reduction of the starting material **3.150** (Scheme 67). However, the major side-product (**3.149)** arising from radical addition to the electron-poor aromatic ring, was isolated in modest yield

(22%). This reaction could be considered as somewhat complementary to the Friedel-Crafts alkylation, which generally only works for electron-rich systems.



Scheme 67. *HAT-mediated addition into electron-poor aromatic ring to form **3.149**.*

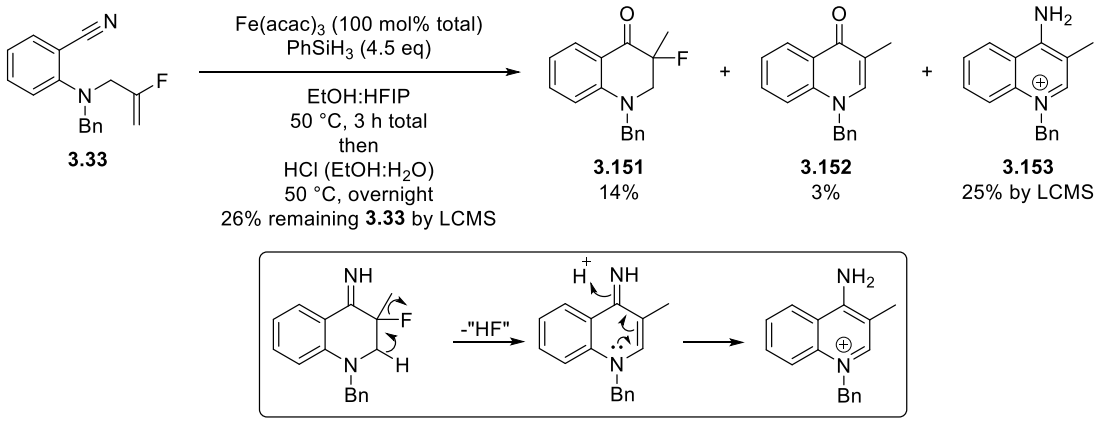
To investigate whether styrene-type substrates were tolerated in this methodology, **3.51** was subjected to HAT conditions (Scheme 68). It was expected that the presumably more stable benzyl radical might be formed in preference to the tertiary radical. The benzyl radical would then most likely be quenched rather than undergo a 4-*exo-dig* or 5-*endo-dig* cyclisation. In fact, clean conversion of **3.51** to product **3.106**, arising from cyclisation of the intermediate tertiary-centred radical followed by imine hydrolysis was observed. However, full consumption of starting material could not be achieved, even with further additions of catalyst.



Scheme 68. *Investigation of benzyl vs. tertiary radical via HAT reaction of substrate **3.51**.*

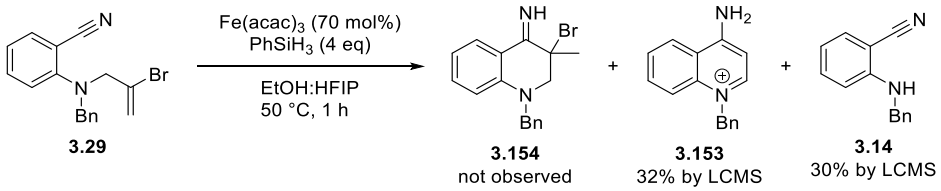
Use of an electrophilic radical example, generated via the HAT reaction with fluorinated substrate **3.33**, was investigated (Scheme 69). The desired 6-*exo-dig* cyclisation proceeded, although the reaction was sluggish (with 26% S.M., **3.33**, remaining by LCMS) even with further additions of catalyst. The desired α-fluoro ketone **3.151** was isolated in poor yield (14%) after purification by MDAP, with 3% enone **3.152** present by ^{1}H NMR. During aqueous workup of the reaction mixture, it was observed that a side-product remained in the aqueous phase. Purification of a sample of the aqueous layer was carried out by MDAP and the side-product was confirmed to be the aminoquinolinium species **3.153**, presumed to be formed as shown below (Scheme 69). Whilst this side-reaction proved problematic in this

instance, it may be exploited in the future as a methodology to access functionalised aminoquinolines.



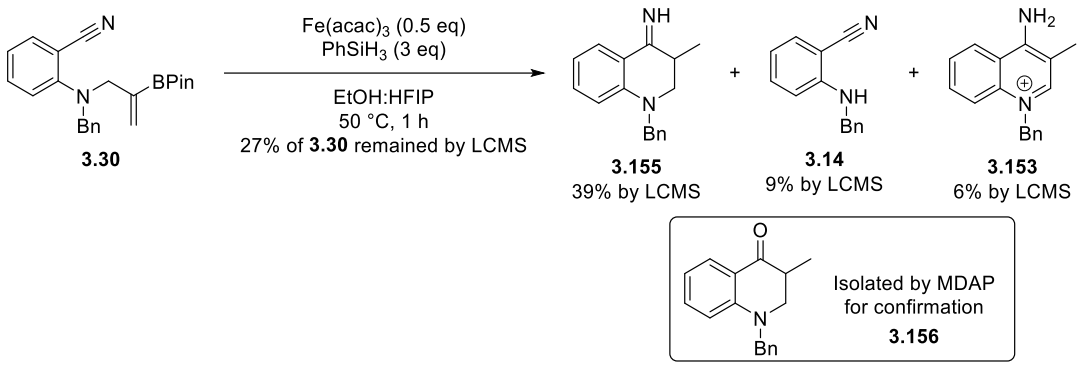
Scheme 69. *HAT-mediated cyclisation of fluorinated substrate **3.33** to give desired α-fluoro ketone **3.151**, and undesired enone **3.152** and aminoquinolinium **3.153**.*

Under HAT conditions, brominated alkene **3.29** also produced aminoquinolinium **3.153** as the major component in the reaction mixture (Scheme 70), as well as deallylated material (**3.14**), however no desired *exo-dig* cyclised product (**3.154**) was observed.



Scheme 70. *HAT-mediated cyclisation of fluorinated substrate **3.29**.*

Further investigation of the functional group tolerance of the α-substituent to the generated radical was undertaken. Alkenylboronic acid pinacol ester (**3.30**) was subjected to HAT conditions as shown below in Scheme 71, unfortunately none of the desired cyclised imine intermediate with an α-boron species was detected by LCMS. The major product observed was cyclic imine **3.155**, resulting from elimination of the boronic acid pinacol ester. Other minor side-products were de-allylated starting material (**3.14**) and aminoquinolinium (**3.153**). It is to be noted that the starting material was not fully consumed. Confirmation of the formation of intermediate cyclic imine **3.155** was achieved by isolation of the corresponding ketone **3.156** by MDAP.



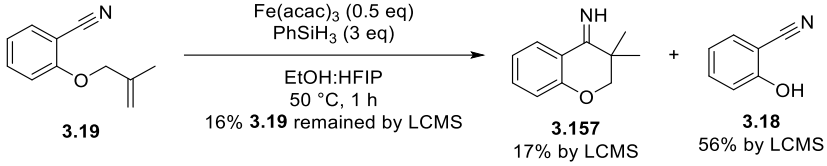
Scheme 71. *HAT-mediated cyclisation of alkenylboronic acid pinacol ester **3.30**.*

The instability of α-carbonyl organoboranes has been previously reported,[114] but this issue may be overcome by the use of amine-borane adducts such as BMIDA.[115] Switching to BMIDA should also increase the nucleophilicity of the generated radical, as there is no longer possibility for donation of the radical species into the vacant boron p-orbital due to occupation by the amine lone pair.[116] Further investigation of BMIDA in this situation could be explored in the future.

3.2.6 – Challenging Substrates

Some of the substrates investigated during this research failed to yield the desired products in satisfactory amounts or not at all.

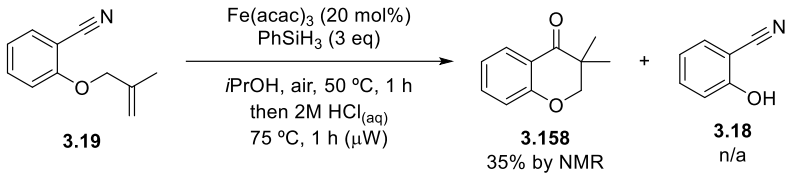
When oxygen-linked substrate **3.19** was subjected to HAT conditions, the major product (by LCMS) was found to be de-allylated starting material (i.e. undesired phenol **3.18**) (Scheme 72). Only a small amount (17%) of the desired cyclised imine intermediate **3.157** was observed by LCMS, along with unconsumed S.M. (16%). Although problematic in this instance, one could envisage developing HAT as a method for deprotection of aromatic allyl ethers.



Scheme 72. *De-allylation reaction observed as the major pathway for oxygen-linked substrate **3.19**.*

This reaction was later revisited using the optimised aerobic HAT conditions (Scheme 73). The desired cyclised product (**3.158**) was quantified from the crude reaction

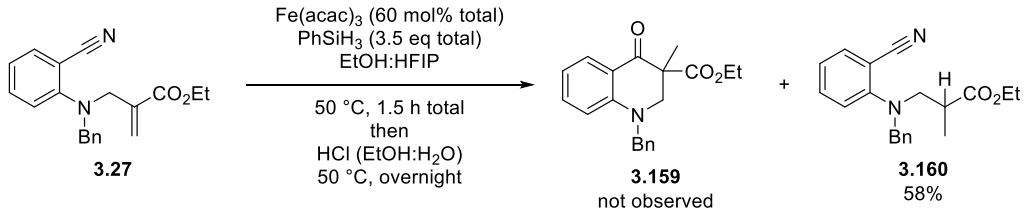
mixture (35% yield), using ^{1}H NMR with an internal standard. The phenol side-product (**3.18**) could not be quantified due to overlapping peaks in the NMR spectrum, though it still appeared as a major component.



Scheme 73. *Quantification of **3.158** by NMR.*

It is interesting that de-allylation occurred so readily for the oxygen-linked substrate **3.19** but it was only observed as a minor side-reaction for the nitrogen-linked analogues. This stark difference in reactivity is surprising since the BDE of a C-N bond is lower than that of C-O. Oxygen is also more electronegative than nitrogen, thus an oxyl radical would be expected to be less stable. However, phenoxyl radicals are considerably more stable,[117] on account of the delocalisation of the radical into the aromatic ring to form a C=O double bond which is stronger than C=N.[62] This may lead to an overall more stabilised transition state for the breaking of the C-O bond in the deallyation reaction.

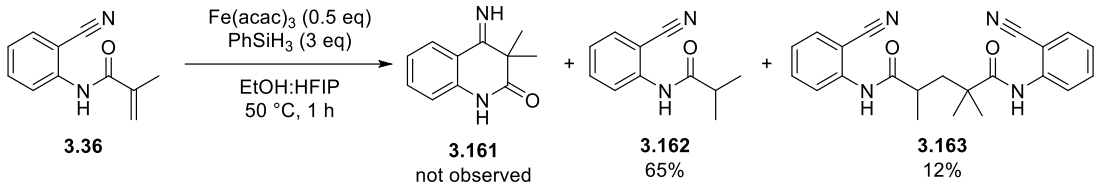
When alkenyl-ester **3.27** was subjected to HAT reaction conditions, the initial radical formed (α to the ethyl ester) appeared to be too stabilised (not nucleophilic enough) to undergo cyclisation (towards **3.159**), with the major product isolated being reduced S.M. **3.160** (Scheme 74). It is possible that the desired 6-*exo-dig* cyclisation reaction does proceed, but the cyclised product is in equilibrium with the open chain, and the latter is quenched to give reduced S.M. **3.160**.



Scheme 74. *Reduction observed for substrate **3.27** to give the major product (**3.160**).*

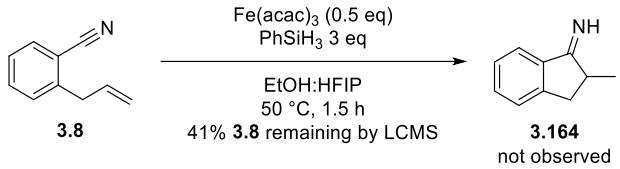
A similar outcome was obtained when amide **3.36** was subjected to HAT conditions (Scheme 75). The desired cyclised product **3.161** was not observed and the major

isolated product was reduced S.M. **3.162**, along with alkene-alkene cross-coupled dimer **3.163**.



Scheme 75. *Reduction observed for substrate **3.36** to give the major product (**3.162**).*

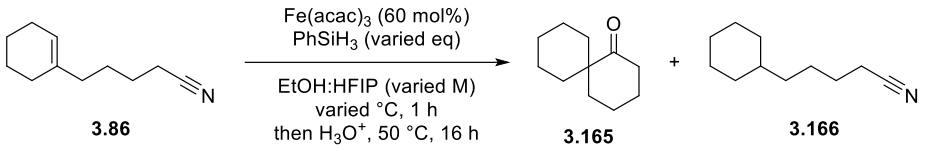
Allyl-substrate **3.8**, which would produce a secondary carbon-centred radical upon HAT, was investigated for radical-cyclisation (Scheme 76). Disappointingly, there was no evidence of the cyclised imine **3.164** by LCMS. The only identifiable component in the reaction mixture was remaining starting material (41%).



Scheme 76. *Unsuccessful HAT reaction of allyl-substrate **3.8**.*

Aliphatic substrate **3.86**, which may undergo 6-*exo*-*dig* cyclisation to yield spirocyclic ketone **3.165** (following imine hydrolysis) was investigated (by analysis of the crude reaction ^{1}H NMR spectra) and the results are shown in Table 6. Unfortunately, the kinetics of radical-cyclisation versus reduction of S.M. (**3.165** *vs.* **3.166**) was difficult to overcome, and in all cases the major reaction pathway was reduction. Differing reaction temperatures had little influence on the outcome (*cf.* entries 1-3). Gradual silane addition yielded a complex mixture (entry 4) and removal of HFIP resulted in poorer conversion to the cyclised product **3.165** (entry 5). Lowering the reaction concentration from 0.25M to 0.06M had a positive effect (entry 6), however further dilution to 0.01 M (entries 7 and 8) resulted in complex mixtures. Finally, lowering the number of $PhSiH_3$ equivalents from 3.5 to 1 did not affect the reaction outcome greatly (entries 9 and 10).

Table 6. *Investigation of the conversion of **3.86** to **3.165**, along with undesired **3.166**.*

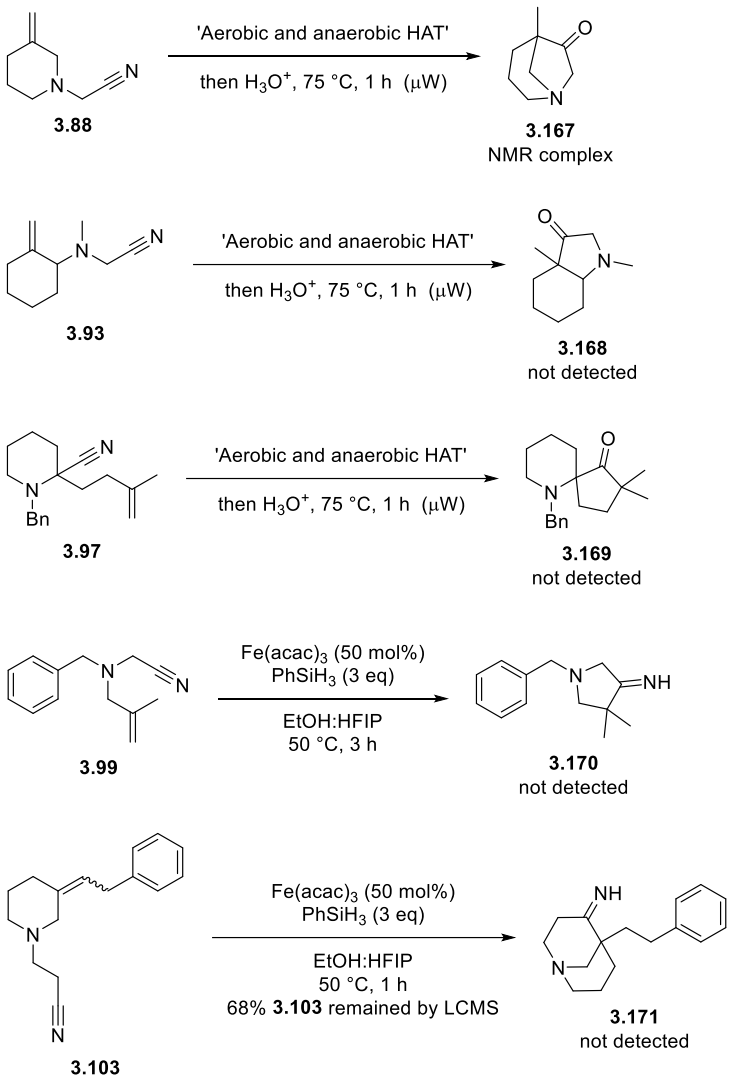


3.86 3.165 3.166

Entry	EtOH:HFIP (M)	$PhSiH_3$ (eq)	Temp (°C)	Ratio (3.165:3.166)
1	0.25	3.5	50	0.29:1
2	0.25	3.5	RT	0.27:1
3	0.25	3.5	75	0.34:1
4	0.25	3.5^	50	NMR complex
5	0.25*	3.5	50	0.14:1
6	0.06	3.5	50	0.42:1
7	0.01	3.5	50	NMR complex
8	0.01	3.5	75	NMR complex
9	0.25	1.0	50	0.39:1
10	0.06	1.0	50	0.43:1

All reactions performed on a 0.25 mmol scale, in sealed vials (with a headspace of air). Ratio of **3.165**:**3.166** determined by ^{1}H NMR. *Reaction ran in absence of HFIP (pure EtOH). ^ 0.5 eq of $PhSiH_3$ added every 5 mins until 3.5 eq achieved.

The substrates shown in Scheme 77 all failed to yield desired cyclised products. The NMR spectra obtained of the crude reaction mixture was often too complex to interpret and purification (on silica gel) did not lead to isolation of any desired material. The reactions containing substrates with chromophores (**3.99** and **3.103**) where analysed directly by LCMS, those without (**3.88**, **3.93** and **3.97**) were analysed by ^{1}H NMR (following hydrolysis). No further substrates were explored for this methodology.



Scheme 77. *Failed HAT-mediated alkene-nitrile cyclisation reactions.*

3.3 – Summary

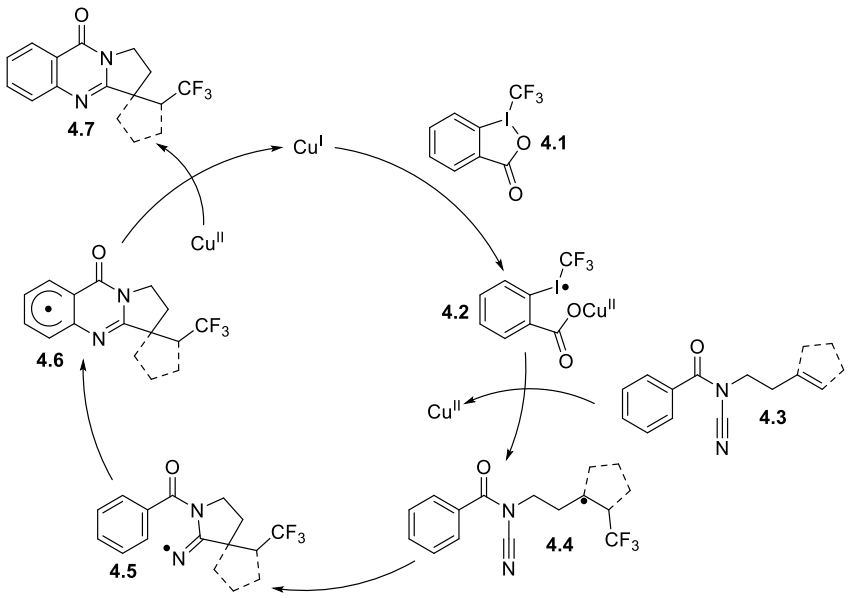
In summary, an iron-mediated HAT reaction between alkenes and nitriles has been developed. This work adds to the expanding scope of HAT methodology, and allows for the formation of hindered ketones, spirocycles and fused bicyclic systems. The reaction has been optimised to proceed catalytically under air and has been shown to scale-up without loss of yield. A second set of anaerobic reaction conditions was established, for more flexible substrates and the generation of cyclic aliphatic scaffolds. Highlights of the work discussed in Chapter 1 were published in Chemistry – A European Journal (2018).[1]

4 – HAT-Mediated Domino Reaction

4.1 – Introduction

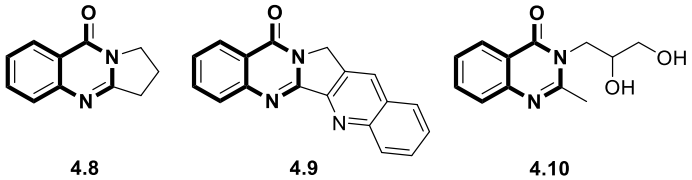
Encouraged by previous experiments, which utilised iminyl radicals to perform tandem radical cyclisation reactions (see earlier, Table 5, p. 49), it was envisaged that this approach could be applied to more elaborate systems. Ideally, the new methodology would be higher yielding, utilise more tractable starting materials, be operationally simple and generate products more directly relevant to medicinal chemistry.

The initial inspiration for this chapter of work came from the publication by Cui *et al*.,[118] in which Togni's reagent (**4.1**) was employed with a copper catalyst (Cu_2O) to effect domino-radical cyclisations of *N*-cyanamide alkenes (**4.3**) (Scheme 78). It is proposed that the Cu^{I} precatalsyt is transformed to a highly reactive Cu^{II} radical complex (**4.2**) when treated with Togni's reagent **4.1**. Subsequently, a CF_3 radical is transferred from complex **4.2** to alkene **4.3** to form the CF_3-C(sp^3) bond and α-alkyl radical **4.4**, releasing a Cu^{II} complex in the process. 5-*Exo-dig* cyclisation affords amidinyl radical **4.5** and further cyclisation generates cyclohexadienyl radical **4.6** which is oxidised by Cu^{II} to furnish quinazolinone **4.7**.



Scheme 78. *Proposed pathway for copper-catalysed trifluoromethylation/cyclisation of unactivated alkenes.*[118]

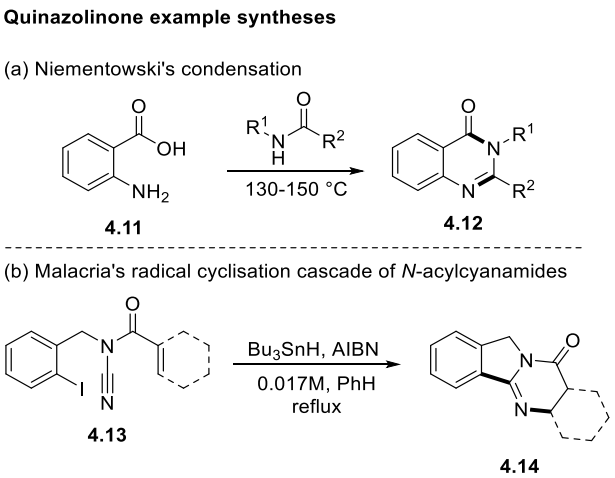
Quinazolinones are an important class of nitrogen-containing heterocycles and the scaffold has been labelled as a 'privileged structure' within medicinal chemistry.[119] Approximately 200 naturally occurring quinazolinone alkaloids (such as **4.8** and **4.9**, Figure 12) have been isolated,[120] and they show a wide range of biological properties such as analgesic, anti-bacterial, anti-fungal, anti-convulsant, anti-inflammatory, anti-HIV and anti-cancer activities.[121] For example, diproqualone (**4.10**) (Figure 12) is in widespread clinical use for its anti-inflammatory, analgesic and sedative effects.



4.8 Deoxyvasicinone **4.9** Luotonin A **4.10** Diproqualone

Figure 12. *A selection of quinazolinone alkaloids (deoxyvasicinone and luotonin A) and GABAergic drug (diproqualone).*

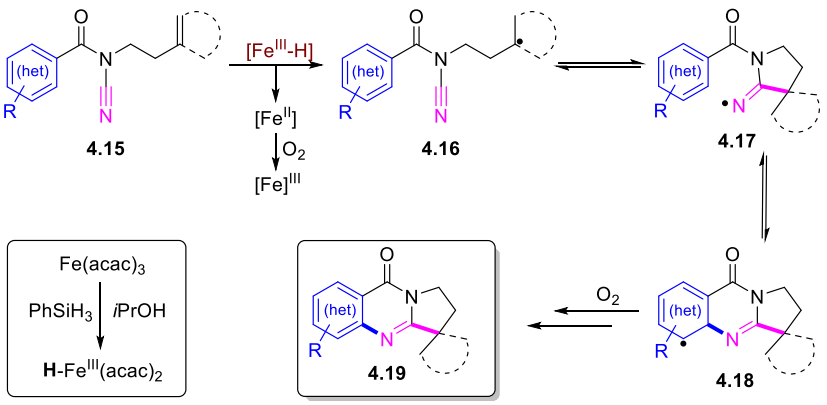
Commonly, methods to synthesise these important cores start from *o*-aminobenzamides or *o*-aminobenzoic acids (**4.11**), an example being the classical Niementowski quinazolinone synthesis (Scheme 79a).[122,123] Since its inception by Malacria in 2007,[124] interest has emerged in using *N*-cyanamides (**4.13**) as the building block for radical cascade (domino) reactions (Scheme 79b). Subsequently, *N*-cyanamide alkenes have been developed as radicophiles for 1,3-dicarbonyl,[125] trifluoromethyl (as seen previously in Scheme 78),[118] phosphoryl,[126] and sulfonyl radicals.[127]



Scheme 79. *Quinazolinone synthesis; (a) classical approach, (b) radical domino approach.*

N-cyanamide alkenes were identified as potential HAT-substrates based on the previous work outlined and the attraction of facile access to complex (spiro)quinazolinone scaffolds. The outlined methodology (Scheme 80) met the requirements of having tractable starting materials, via disconnection of the the amide bond, and generating medicinally relevant privileged compounds. Furthermore, it has been shown that the introduction of sp^3 centres, such as a spirocentre, can greatly enhance a molecule's potential to be a drug candidate.[128]

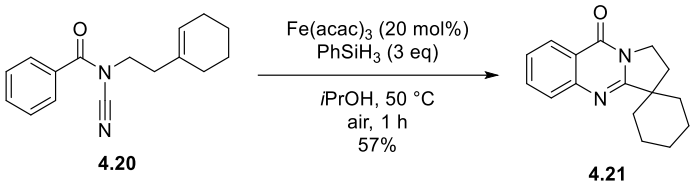
As shown below in Scheme 80, MH-HAT reaction of **4.15** to alkyl-radical **4.16** would set up 5-*exo*-*dig* cyclisation, the amidinyl radical **4.17** may then undergo sequential cyclisation onto the (hetero)aryl ring to afford radical **4.18**, which undergoes re-aromatisation to yield desired (spiro)quinazolinone **4.19**. The pathway would require 2 oxidative events, to turnover Fe^{II} to Fe^{III} and to re-aromatise radical **4.18**.



Scheme 80. *Proposed outline of the HAT-mediated domino radical cyclisation of N-cyanamide alkenes (**4.15**) to (spiro)quinazolinones (**4.19**).*

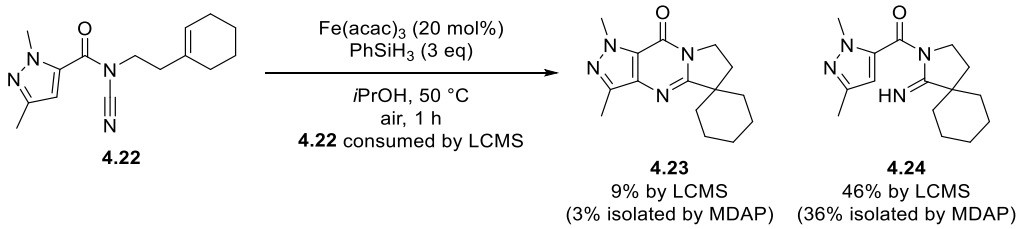
4.1.1 – Preliminary Investigations

Prior to extensive optimisation and substrate scoping, initial probing of the methodology was carried out. Subjecting model phenyl-substrate **4.20** to the previously optimised aerobic alkene-nitrile conditions (entry 6, Table 3, p.41) pleasingly gave desired quinazolinone **4.21** in moderate yield (57%) (Scheme 81).



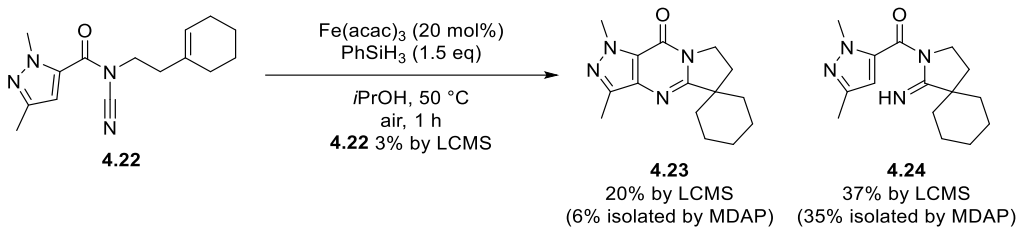
Scheme 81. *Unoptimised HAT-mediated domino reaction of **4.20** to spiroquinazolinone **4.21**.*

This result was a promising starting point, but the extension to heteroaromatic substrates was desired. The same aerobic HAT conditions were applied to pyrazole-substrate **4.22**. Unfortunately, they did not translate well (Scheme 82). The major species in the reaction mixture (as analysed by LCMS) corresponded to the mono-cyclised amidine **4.24** (46% by LCMS, 36% isolated), whilst the desired product **4.23** was only formed in minor amounts (9% by LCMS, 3% isolated).



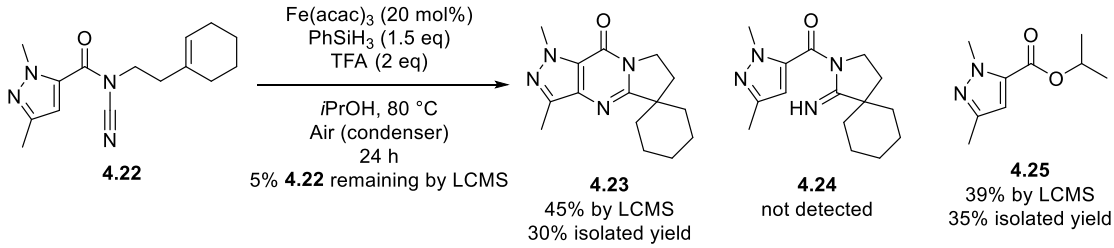
Scheme 82. *HAT-mediated domino reaction of pyrazole substrate **4.22**.*

Halving the equivalents of $PhSiH_3$ (from 3 to 1.5 eq) had little impact on the reaction outcome (Scheme 83), although the LCMS detection and isolated yield of the desired product **4.23** doubled (20% by LCMS, 6% isolated), the major species remained the mono-cyclised amidine **4.24** (37% by LCMS, 35% isolated).



Scheme 83. *HAT-mediated domino reaction of pyrazole substrate **4.22**.*

By elevation of the reaction temperature and the addition of TFA, the formation of the undesired amidine **4.24** could be suppressed, leading to higher isolated yield (30%) of the desired heterocycle **4.23** (Scheme 84). However, this was at the expense of longer reaction times (24 h) and a competing esterification side-reaction, which led to significant conversion to isopropyl ester **4.25** (35%). The addition of TFA was inspired by Starr's hydropyridylation methodology, where protonation of the pyridine motif was key for carbon-centered radical addition and subsequent oxidative re-aromatisation.[129] Here, it is envisaged that protonation of the pyrazole motif may result in similar effects, but also that protonation of the intermediate amidinyl radical to the radical cation may occur, altering the electrophilicity of the reactive species.



Scheme 84. *HAT-mediated domino reaction of pyrazole-substrate **4.22**.*

Encouraged by the initial results, the HAT-mediated domino methodology was further optimised, and the substrate scope explored.

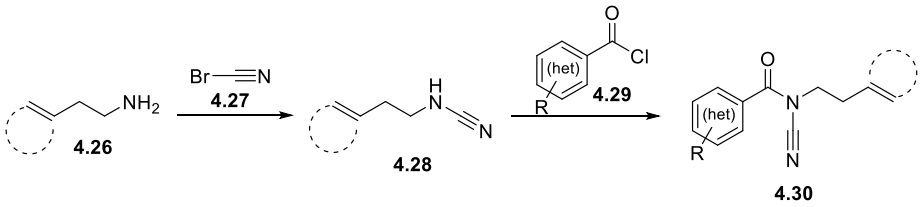
4.2 – Results and Discussion

This section will discuss the following for the HAT mediated domino cyclisation of N-cyanamide alkenes study:

- Synthesis of substrates
- Reaction optimisation
- Substrate scope
- Mechanistic discussion
- Challenging substrates
- Removing amide moiety

4.2.1 – Synthesis of Substrates

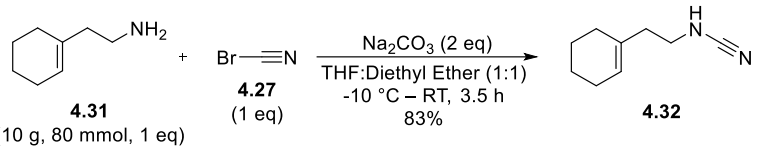
The general strategy for preparing the desired *N*-cyanamide alkene starting materials is outlined below in Scheme 85. Cyanamide intermediates were obtained from the reaction of the corresponding amines (**4.26**) with cyanogen bromide (**4.27**). The cyanamides (**4.28**) were then used directly without further purification in an acylation reaction with the corresponding (hetero)aryl acid chlorides (**4.29**) to obtain the desired starting building blocks (**4.30**) after purification on silica gel. The simple two-step and generally high-yielding process was applicable to a large proportion of the substrates prepared for this project.



Scheme 85. *General synthetic strategy for the preparation of N-cyanamide alkenes (**4.30**).*

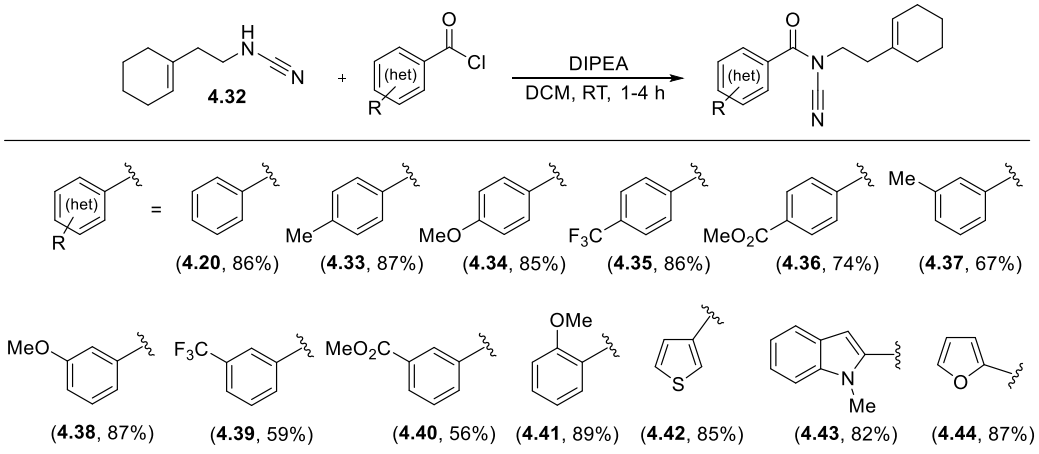
2-(Cyclohex-1-en-1-yl)ethan-1-amine (**4.31**) was chosen as the model alkene-amine fragment as it is commercially available and inexpensive (£3.44/g Sigma Aldrich). The reaction with cyanogen bromide to form *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (4.**32**) is known in the literature[130] and was reproducible in good yield (83%) on large

scale (Scheme 86). This procedure is referred to as general method 1 (G.M. 1) for this section.



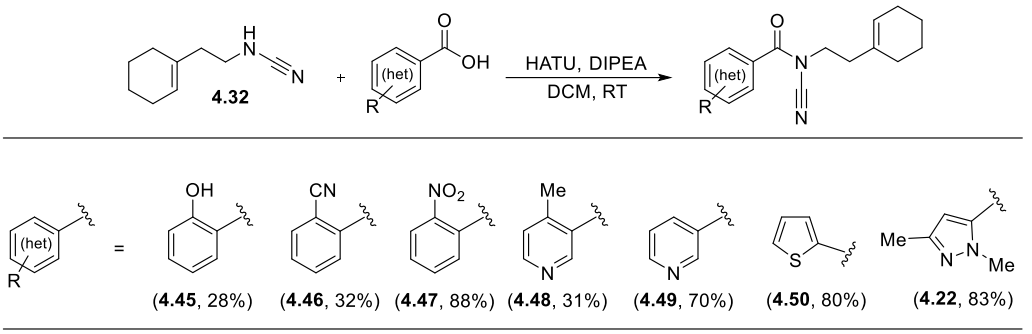
Scheme 86. *Synthesis of N-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**).*

Facile acylation of *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**) with a range of commercially available substituted (hetero)aryl chloride derivatives afforded the desired *N*-cyanamide alkenes (**4.20** and **4.33**–**44**) in good-excellent yields, as shown below in Scheme 87. This procedure is referred to as general method 2 (G.M. 2).



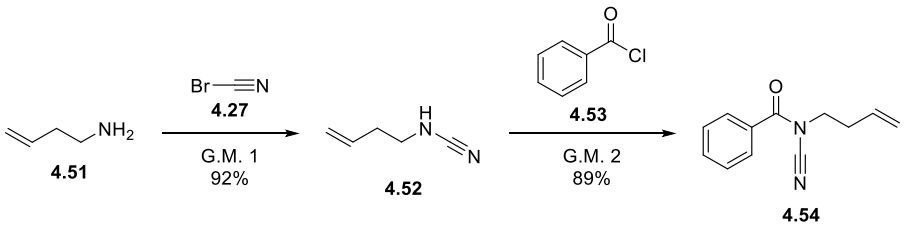
Scheme 87. *Synthesis of N-cyanamide alkenes via acylation reaction.*

Where the acyl chloride was not available, a HATU-mediated amide coupling of the corresponding commercially available carboxylic acid was carried out (Scheme 88) to obtain the desired *N*-cyanamide alkenes (**4.22** and **4.45**–**50**).



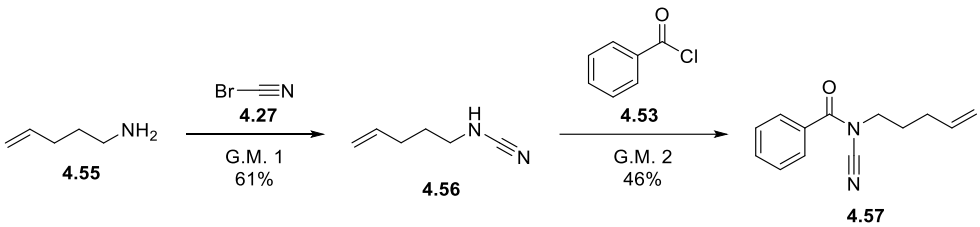
Scheme 88. *Synthesis of N-cyanamide alkenes via HATU coupling.*

Alternative alkene-amines were also applied this methodology. Using standard procedures, commercially available but-3-en-1-amine (**4.51**) was converted to *N*-(but-3-en-1-yl)cyanamide (**4.52**) followed by acylation with benzoyl chloride (**4.53**) to yield *N*-(but-3-en-1-yl)-*N*-cyanobenzamide (**4.54**) in excellent yield (89%) (Scheme 89).



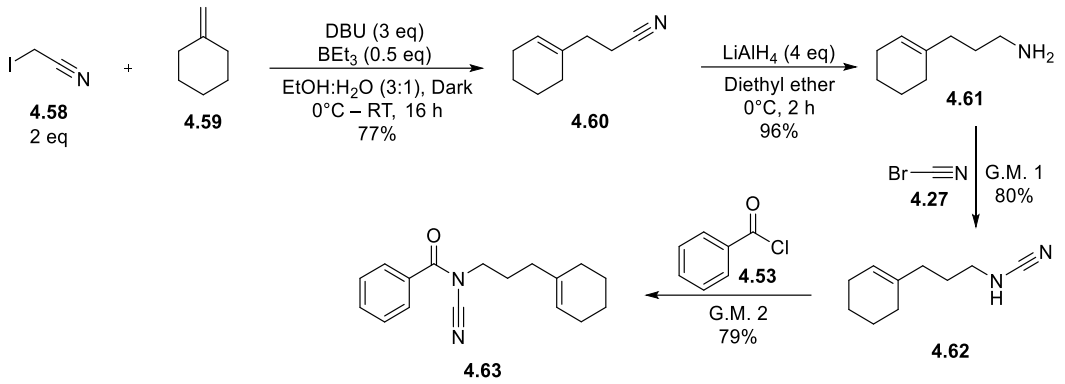
Scheme 89. *Preparation of N-(but-3-en-1-yl)-N-cyanobenzamide (**4.54**).*

The same method was used to prepare *N*-cyano-*N*-(pent-4-en-1-yl)benzamide (**4.57**) from commercially available pent-4-en-1-amine (**4.55**), as shown in Scheme 90.



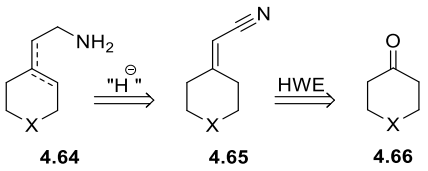
Scheme 90. *Preparation of N-(but-3-en-1-yl)-N-cyanobenzamide (**4.57**).*

Following literature procedure, nitrile (**4.60**) was prepared via an atom transfer radical addition-elimination (ATRA) process (from **4.58** and **4.59**),[131] reduction of nitrile **4.60** to the corresponding amine **4.61** proceeded smoothly.[132] Conversion to the cyanamide intermediate **4.62**, followed by acylation with benzoyl chloride under standard conditions afforded desired starting material *N*-cyano-*N*-(3-(cyclohex-1-en-1-yl)propyl)benzamide (**4.63**) in good yield (79%).



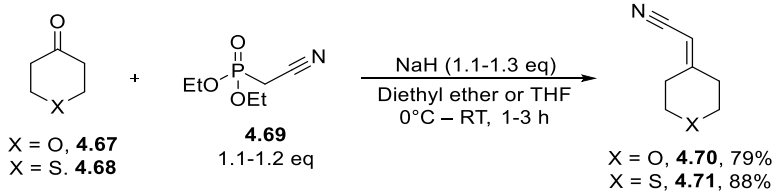
Scheme 91. *Synthesis of N-cyano-N-(3-(cyclohex-1-en-1-yl)propyl)benzamide (**4.63**).*

To explore the incorporation of heteroatoms (in the resulting spirocycle ring, following HAT reaction), the synthesis of intermediate amines **4.64** (where X = O, S and NBoc) was desired (Scheme 92). The position of the C=C bond could be either internal or external to the ring, as the HAT reaction of each is expected to give the same tertiary carbon-centred radical. Retrosynthetic analysis identified α,β-unsaturated nitrile **4.65** as a suitable intermediate that could be prepared from the corresponding commercially available ketone (**4.66**) via Horner-Wadsworth-Emmons (HWE) reaction. Reduction of α,β-unsaturated nitrile **4.65** with a hydride source would furnish the desired amine **4.64**, where 1,2-reduction could be favoured over 1,4 by addition of a Lewis acid ($AlCl_3$).[133,134]



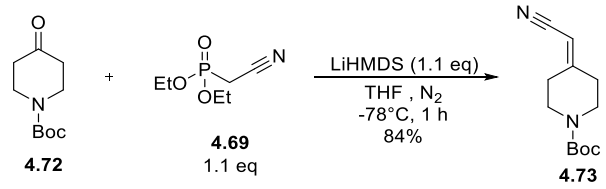
Scheme 92. *Retrosynthetic analysis of desired amine **4.64** where X = O, S and NBoc.*

Following literature procedures, HWE reaction of ketones **4.67** and **4.68** with diethyl cyanomethylphosphonate (**4.69**) gave the desired intermediate α,β-unsaturated nitriles **4.70**[132] and **4.71**[135] in good yields (Scheme 93).



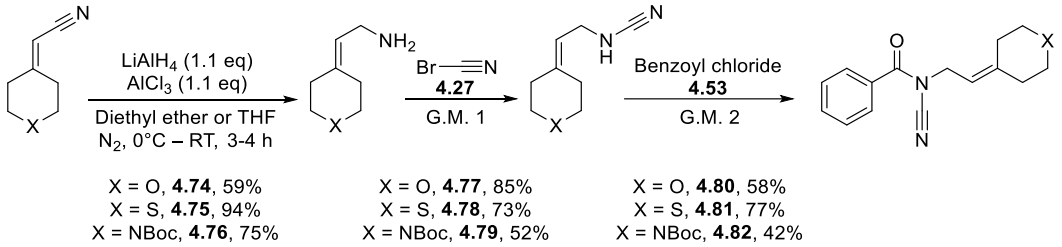
Scheme 93. *Horner-Wadsworth-Emmons reaction towards **4.70** and **4.71**.*

HWE reaction to afford Boc-protected piperidine α,β-unsaturated nitrile **4.73** also proceeded smoothly following literature procedure.[136]



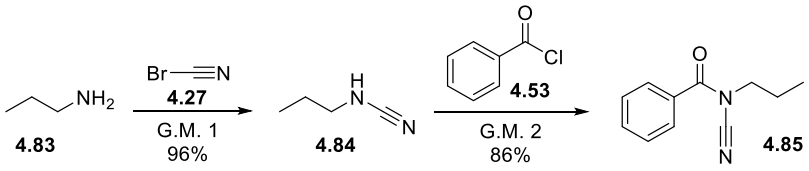
Scheme 94. *Horner-Wadsworth-Emmons reaction to afford **4.73**.*

1,- Reduction of intermediates **4.70**, **4.71** and **4.73** with $LiAlH_4/AlCl_3$ reducing system gave desired amines **4.74**–**76**, which were converted directly to cyanamides **4.77**–**79** by reaction with cyanogen bromide (**4.27**) using G.M. 1 (Scheme 95). Finally, acylation of the crude cyanamides with benzoyl chloride (**4.53**) under G.M. 2 afforded the desired starting materials **4.80**–**82** in moderate-good yields.



Scheme 95. *Synthesis of desired N-cyanamide alkenes **4.80–82**.*

To investigate the possibility of an intermolecular reaction, propylamine (**4.83**) was chosen as the model amine since it is a relatively unhindered primary amine and is a liquid (not a gas) unlike its methyl and ethyl variants. Conversion of propyl amine (**4.83**) to cyanamide **4.84** under G.M. 1 proceeded excellently and was followed by acylation with benzoyl chloride (**4.53**) (G.M. 2) to afford *N*-cyano-*N*-propylbenzamide (**4.85**) as the desired model substrate in high yield (86%).



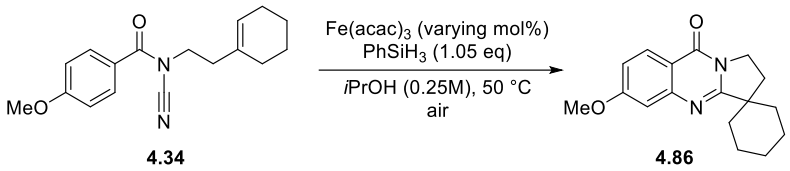
Scheme 96. *Synthesis of N-cyano-N-propylbenzamide (**4.85**).*

4.2.2 – Reaction Optimisation

Phenyl Substrates

With optimised aerobic conditions for alkene-nitrile cyclisation established (entry 6, Table 3, p.41), investigation to see how well these translated to model-substrate *N*-cyanamide alkene **4.34** was carried out (Table 7).

Table 7. *Optimisation of catalyst loading for the HAT-mediated domino reaction of **4.34** to **4.86** (reactions performed on a 0.5 mmol scale).*

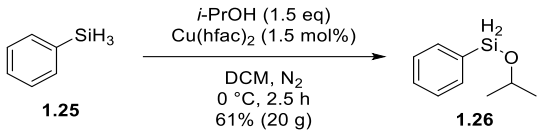


Entry	$Fe(acac)_3$ (mol %)	Time (h)	LCMS (% UV)		Isolated yield **4.86** (%)
			4.34	**4.86**	
1	20	1	0	82	73
2	10	1	3	86	74
3	5	2	10	85	74

Using a lower number of equivalents of $PhSiH_3$ (compared to previous alkene-nitrile methodology[1]), to avoid quenching of the intermediate amidinyl radical by excess [Si]-H, the conditions translated well to give desired quinazolinone **4.86** in good yield (entry 1). Lowering the catalyst loading to 10 mol% was tolerated and not detrimental to the isolated yield or reaction conversion (entry 2). However, decreasing catalyst loading further to 5 mol% (entry 3) resulted in an extended reaction time and incomplete consumption of starting material **4.34** (10% remained by UV LCMS detection after 2 h); nonetheless, the isolated yield remained unchanged, suggesting a cleaner reaction profile (see alternative theory later, p.80). As such, 10 mol% catalyst loading was chosen since $Fe(acac)_3$ is a relatively inexpensive and non-toxic complex, and less activated systems might prove more challenging at loadings of 5 mol%.

Heterocyclic Substrates

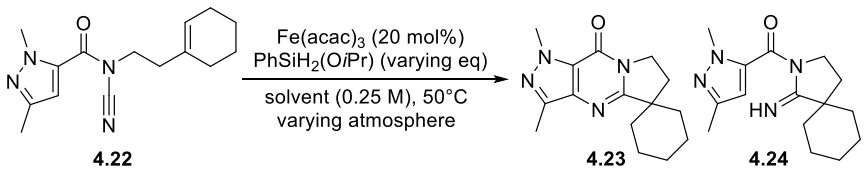
In order to replace isopropanol as the reaction solvent (see earlier esterification problem, Scheme 84, p.63), isopropoxy*(*phenyl*)*silane (**1.26**) (since commercialised as RubenSilane) was prepared and distilled on a large scale following literature procedure (shown below in Scheme 97).[50] As discussed earlier (Scheme 9, p.7), this active reductant allows MH-HAT reactions to be performed in a variety of solvents (without the need for alcoholic solvent).



Scheme 97. *Synthesis of isopropoxy(phenyl)silane (**1.26**).*

The conversion of **4.22** to desired heterocycle **4.23** was studied further (by LCMS) and the key results are highlighted below in Table 8, however, it proved difficult to achieve efficient conversion of starting material whilst maintaining good selectivity between **4.23** and **4.24**.

Table 8. *Optimisation for the HAT-mediated domino reaction of **4.22** to **4.24**, reactions on a 0.5 mmol scale.*



Entry	$PhSiH_2(OiPr)$ (eq)	Solvent	Atmosphere	Time (h)	LCMS (%UV)		
					4.22	**4.23**	**4.24**
1	1.5	THF	Open (air)	1	16	14	37
2	1.5	EtOAc	Open (air)	1	31	29	12
3	1.0	EtOAc	Open (air)	2	44	31	12
4[a]	1.5	EtOAc	O_2	2	36	37	2
"	"	"	"	68	30	52	2
5	3.0	EtOAc	O_2	2	18	36	12
"	"	"	"	19	16	33	15
6[b]	3.0*	EtOAc	O_2	18	9	43	18

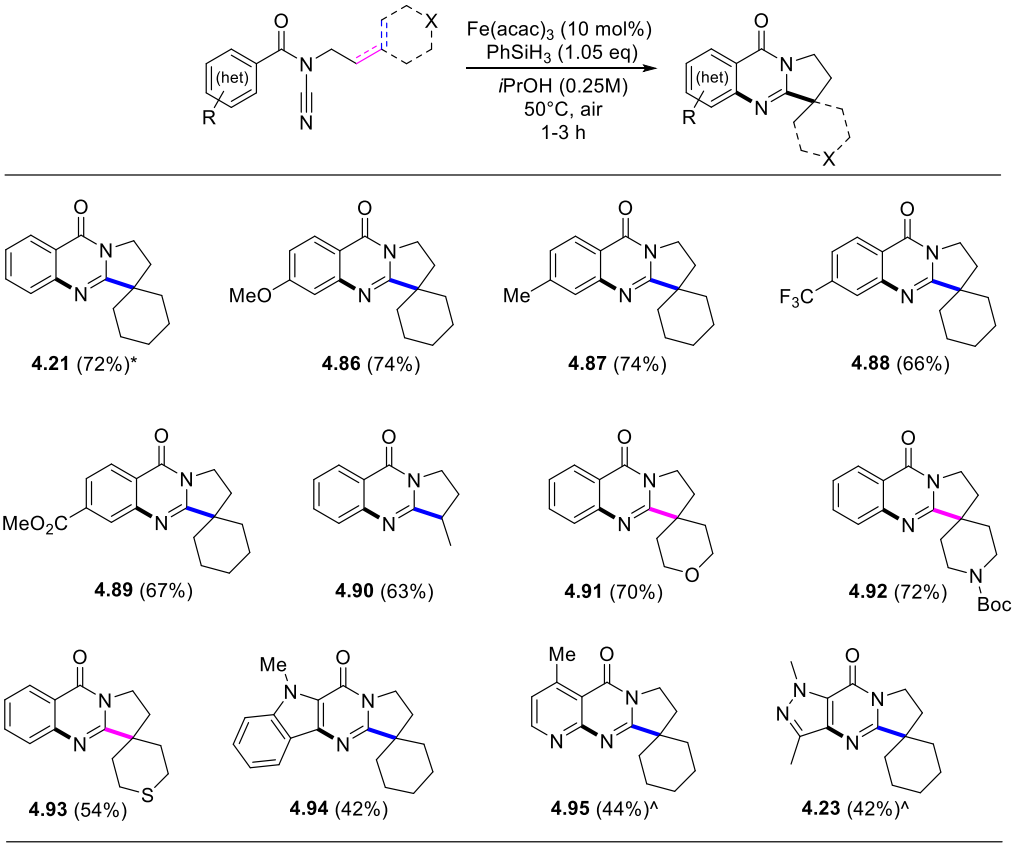
[a]37% isolated yield of **4.23**. [b]42% isolated yield of **4.23**. *2 x 1.5 eq, 2nd addition made after 1 h.

The new conditions, using $PhSiH_2(OiPr)$ (**1.26**), were trialled in THF (inhibitor free) and the result can be seen above in Table 8 (entry 1). Moderate conversion of **4.22** was observed; however, the major product was the mono-cyclised amidine **4.24**. A change of solvent to ethyl acetate (entry 2) resulted in a switch in selectivity, with preference now for the domino product **4.23**, however the conversion of S.M. was poorer. Lowering the loading of $PhSiH_2(OiPr)$ to 1 equivalent (entry 3) gave no significant difference in selectivity between **4.23** and **4.24**. Application of a balloon of oxygen to the reaction vial (entry 4) saw a notable improvement in the selectivity, suggesting that a higher concentration of oxygen accelerates the re-aromatisation event towards **4.23**, however only a modest conversion of starting material was obtained even with prolonged reaction time (68 h). To increase conversion, 3 equivalents of $PhSiH_2(OiPr)$ were used (entry 5). Although conversion improved, it was to the detriment of selectivity; presumably because increasing the concentration of [Si]-H leads to greater trapping of the amidinyl radical to give **4.24**. It is to be noted that increasing $Fe(acac)_3$ loading did not result in increased conversion (see extensive results in experimental, Table 17, p.226). In an attempt to increase conversion and retain good selectivity, two additions of 1.5 equivalents of $PhSiH_2(OiPr)$ (3 eq total) were made (entry 6). An isolated yield of 42% was obtained (entry 6), which was pleasing considering the challenging nature of the reaction and the complexity of product formed in a single procedure from simple starting material **4.22**. Finally, in general the reactions highlighted Table 8 had a clean reaction profile (by LCMS) and often the only other products observed (by LCMS) were as a result of oxidation of the alkene starting material (M+16 or M+32).

In summary, a change of silane source from $PhSiH_3$ to $PhSiH_2(OiPr)$[50] allowed the reaction to be conducted in EtOAc rather than *i*PrOH (avoiding unwanted esterification); and applying a neat O_2 atmosphere rather than air, gave a reasonable conversion to the desired heterocycle **4.23** over the mono-cyclised intermediate **4.24**. Full details of the extensive list (>30) of conditions screened are shown in the experimental section (Table 17, p.226), yields could not be increased beyond *ca.* 40% as it remained a balancing act between conversion and selectivity.

4.2.3 – Substrate Scope

The optimised conditions were applied to a range of aromatic *N*-cyanamide alkenes and the results are shown below for those substrates that were successful in yielding the desired (spiro)quinazolinones in moderate-good yields (Scheme 98).



Scheme 98. *Substrate scope for the HAT-mediated domino cyclisation reaction of N-cyanamide alkenes. Isolated yields are quoted. All reactions were performed on a 0.5 mmol scale using conditions from Table 1 entry 2, unless otherwise stated. *5 mmol scale yielded 65%. ^20 mol% $Fe(acac)_3$, 1.5-3.0 eq $PhSiH_2(OiPr)$, O_2 balloon, EtOAc, 50 °C.*

Satisfyingly, the reaction yielding spiroquinazolinone **4.21** could be scaled 10-fold (5 mmol) whilst maintaining a good isolated yield (65%), comparable to its 0.5 mmol variant (72%). Electron-donating substituents were well tolerated to give isolated yields of 74% for both **4.86** and **4.87**. Electron-withdrawing substituents (**4.88** and **4.89**) still gave good isolated yields (66% and 67%). Secondary-carbon radical-derived quinazolinone **4.90** was formed in good yield (63%), which is perhaps surprising given the previous nitrile methodology was not compatible with such substrates.

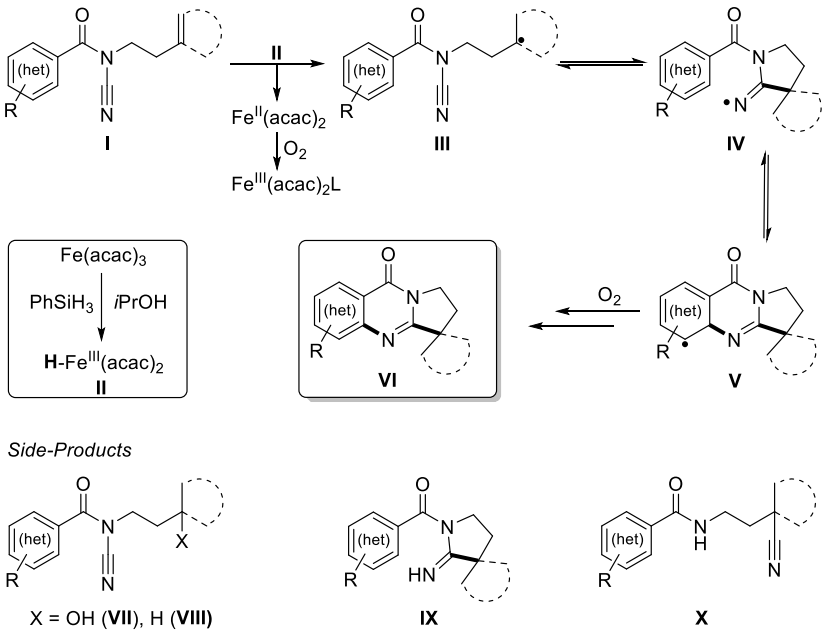
Incorporation of heteroatoms to form spiro-pyran (**4.91**), Boc-piperidine (**4.92**) and thiopyran (**4.93**) analogues all proved successful, which is pleasing as these types of spirocycles are heavily sought after in medicinal chemistry. Furthermore, it showed that the starting-alkene can be either internal (highlighted in blue) or external (highlighted in pink) to the ring (Scheme 98).

Attention next turned to heteroaromatic substrates, which were anticipated to prove challenging since the electronic nature of the aromatic ring influences the reaction outcome. Pleasingly, indole **4.94** was formed in moderate yield without modification of the standard reaction conditions; such an elaborate scaffold would be difficult to synthesise by other methods. Electron-deficient pyridine and pyrazole substrates required further optimisation (as seen earlier in Table 8, p.70) to achieve synthetically useful yields of desired quinazolinones **4.95** and **4.23**.

4.2.4 – Mechanistic Discussion

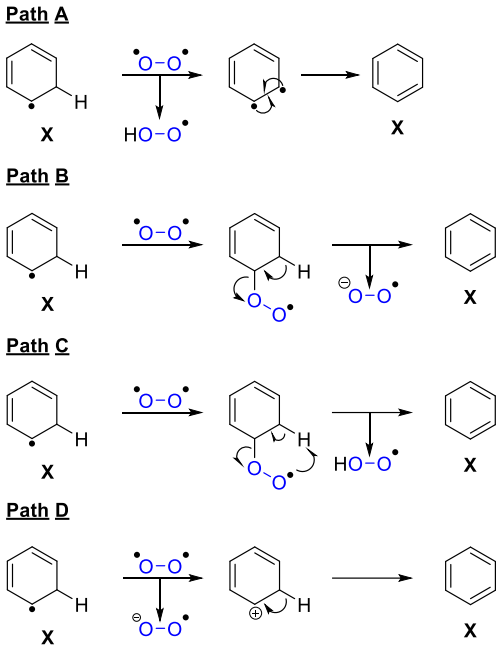
Based on the findings that oxygen is crucial for conversion to the desired quinazolinone over the mono-cyclised intermediate, an oxidative step was envisaged to be the key element in the reaction mechanism (Scheme 99). Firstly, HAT from *in situ* generated iron complex **II**[66] to *N*-cyanamide alkene **I** gives intermediate carbon-centred radical **III** (which has recently been shown to be closely associated with the metal centre[69]). Cyclisation of **III** gives nitrogen-centred amidinyl radical **IV**, which can undergo further cyclisation to give (hetero)aryl radical **V**. From this intermediate, the desired quinazolinone product **VI** may be obtained after re-aromatisation (see later, Scheme 100, p.75).

In general, it was observed that electron-rich aryls out-perform their electron-poor variants and stronger oxidative conditions (neat oxygen vs. air) were required for the conversion of heterocyclic pyridine and pyrazole substrates to the desired quinazolinones **4.95** and **4.23** (to avoid trapping of **IV** with [Si]-H to give **IX**). Other common minor side-reactions observed included, trapping of radical **III** with O_2 (**VII**) or [Si]-H (**VIII**), and collapse of iminyl-radical **IV** (β-scission/nitrile translocation) to the corresponding nitrile-amide (**X**).



Scheme 99. *Proposed mechanism of the HAT-mediated radical domino reaction to give quinazolinones **VI** and structures of side-products **VII–X**.*

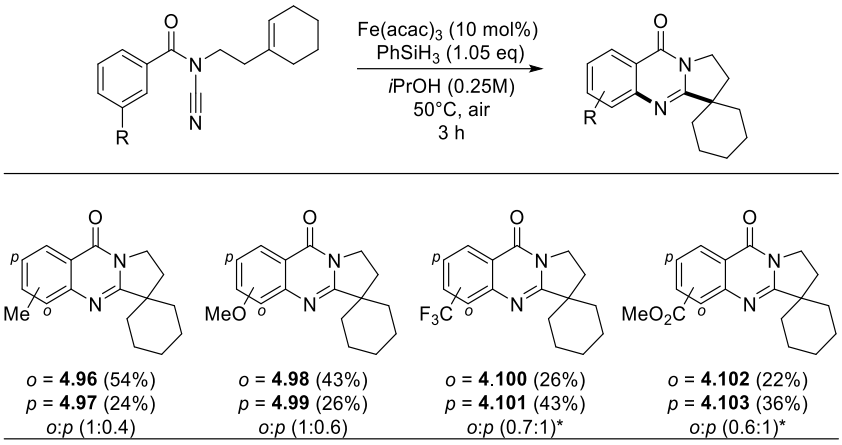
The pathway for oxidation of radical **V** (Scheme 99) is unclear, though probable scenarios are illustrated in Scheme 100 for simplified cyclohexadienyl radical **X** to benzene (**X**). Similar pathways for aromatisation (such as autoxidation of 1,4-cyclohexadienyl radicals), have been proposed to proceed via abstraction of a hydrogen atom by O_2 (path A),[137] perhaps rather than combination with O_2[138,139] and subsequent loss of a superoxide anion (path B) or hydroperoxyl radical (path C). The final proposed oxidation pathway arises from SET, though it is more tentatively put forward (path D).



Scheme 100. *Potential oxidation pathways of cylohexadienyl radical **X** to benzene (**X**).*

To further probe the mechanism and to expand the substrate scope, *meta*-substituted phenyl substituents were investigated with varying electronic properties (Scheme 101). Intriguingly, when electron-donating groups were placed *meta* to the *N*-cyanamide alkene, preferential cyclisation occurred *ortho* to the donating group rather than *para* (preference for **4.96** vs. **4.97** and **4.98** vs. **4.99**). Switching to electron-withdrawing groups at the *meta* position resulted in reversed selectivity, and cyclisation now occurred preferentially *para* to the directing group (preference for **4.100** vs. **4.101** and **4.102** vs. **4.103**). Both thermodynamic and kinetic rationalisations can be considered here. This phenomenon may arise from greater

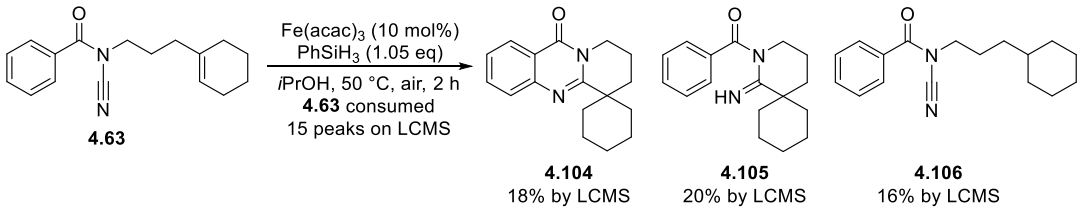
stabilisation/destabilisation of the resulting radical intermediate (**V**, Scheme 99) which is placed directly *ipso* to the directing group when cyclisation occurs *ortho*. Alternatively, the preference in *ortho* vs *para* selectivity may result in polarity pairing between the iminyl radical and the aryl ring (i.e. under kinetic control). This has been found to be the case for the addition of aryl radicals to substituted benzenes, where the radical addition is believed to be the rate determining step.[140]



Scheme 101. *Effect on ortho:para (o:p) selectivity with varying electronic groups on the phenyl ring. Isolated yields are quoted. All reactions were performed on a 0.5 mmol scale using conditions from Table 7 entry 2. *Products were inseparable on silica.*

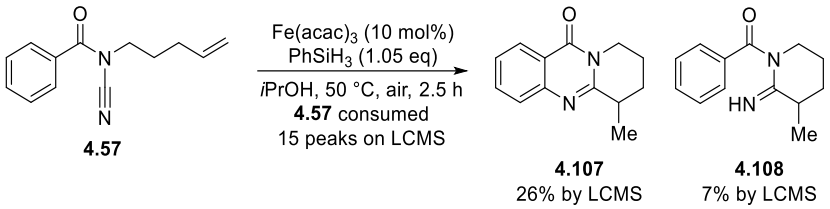
4.2.4 – Challenging Substrates

Substrate **4.63** was subjected to the optimised HAT conditions to compare 6-*exo-dig* cyclisation with 5-*exo-dig*, which thus far, had been the only ring size attempted. Unfortunately, the reaction to form quinazolinone **4.104** (involving 6-*exo-dig* cyclisation following initial HAT) was poor (18% UV by LCMS with correct MH^+), with a complex profile obtained (15 peaks on LCMS) (Scheme 102). Two major undesired side-products were observed, mono-cyclised amidine **4.105** (20% UV by LCMS with correct MH^+) and reduced starting material **4.106** (16% UV by LCMS with correct MH^+). Other notable masses observed were dimers ($2MH^+$) and oxidised starting material (MH^++16), the remaining minor peaks had unidentifiable mass spectra. It is to be noted that starting material **4.63** appeared to be fully consumed in the reaction (by LCMS). This result suggests that the faster rate of cyclisation for 5-*exo-dig*, compared to 6-*exo-dig*, allows the desired reaction pathway to proceed in the absence of the majority of side-reactions.



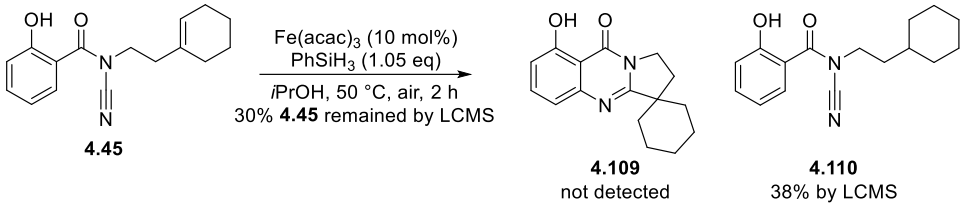
Scheme 102. *HAT-mediated domino reaction of **4.63** towards desired quinazolinone **4.104**.*

In order to increase the rate of 6-*exo-dig* cyclisation, substrate **4.57** was tested. The rationale was that the secondary carbon-centred radical generated from HAT would be less stabilised (and therefore more reactive) compared to substrate **4.63** which produces a tertiary carbon-centred radical. Unfortunately, a complex reaction profile was also obtained (15 peaks on LCMS) (Scheme 103). Desired quinazolinone **4.107** was observed (26% UV by LCMS with correct MH^+), along with lesser amounts of amidine **4.108** (7% UV by LCMS with correct MH^+). Other notable masses observed were dimers ($2MH^+$), the remaining minor peaks had unidentifiable mass spectra. Following these two results, efforts to exploit substrates involving 6-*exo-dig* cyclisation ceased.



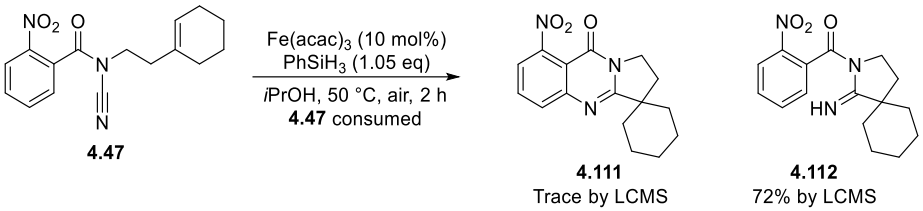
Scheme 103. *HAT-mediated domino reaction of **4.57** towards desired quinazolinone **4.107**.*

A set of challenging substrates was selected to probe how tolerant the reaction was towards more-challenging functional groups (OH, CN, NO_2), and substitution pattern (*ortho*). *Ortho p*henol-substituted substrate **4.45** was unsuccessful in forming any of the desired quinazolinone product **4.109** (Scheme 104) and S.M. **4.45** remained at 30% UV by LCMS. The major peak in the reaction mixture was reduced S.M. **4.110** (38% UV by LCMS with correct MH^+), which is perhaps unsurprising given that phenols can behave as HAT[141] (or PCET[142]) reagents themselves and therefore could quench the radical formed following initial HAT-reaction from Fe-H. Other notable masses observed were due to oxidised starting material (MH^++16 and +34).



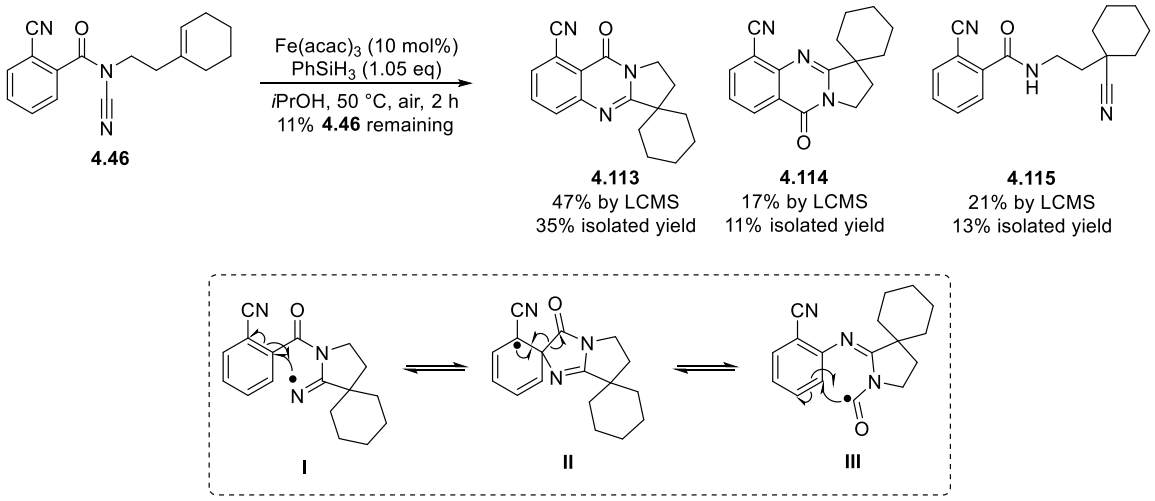
Scheme 104. *Unsuccessful HAT-mediated domino reaction of **4.45** towards desired quinazolinone **4.109**.*

Ortho nitro-substituted substrate **4.47** also proved to be challenging, with only trace amounts (<1% UV by LCMS with correct MH^+) of desired quinazolinone **4.111** observed in the reaction mixture (Scheme 105). The major species observed was the mono-cyclised amidine product **4.112** (72% UV by LCMS with correct MH^+), suggesting that the second cyclisation event/re-aromatisation was unfavourable. It is possible that more strongly oxidising conditions are required due to the strong electron-withdrawing nature of the nitro group (i.e. the HAT conditions developed for challenging heterocyclic substrates). However, this was not investigated.



Scheme 105. *Unsuccessful HAT-mediated domino reaction of **4.46** towards desired quinazolinone **4.111**.*

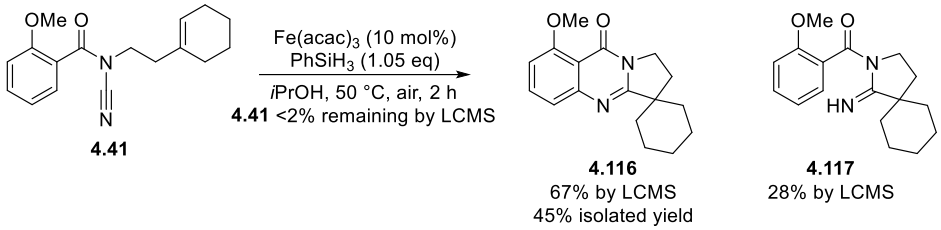
When a nitrile group was placed in the *ortho* position (**4.46**) the outcome of the reaction was particularly interesting (Scheme 106). The desired quinazolinone **4.113** was obtained in moderate yield (35%), along with β-scission side-product **4.115** (13%) and curiously quinazolinone regioisomer **4.114** was isolated in 11% yield. The suspected route to formation of **4.114** is outlined in the boxed area in Scheme 106. Involving *ipso* attack by the amidinyl radical (**I**), followed by fragmentation to the acyl radical (**II**) and then attack of the acyl radical (**III**) leading to the formation of **4.115** following re-aromatisation. This phenomenon has been studied previously on similar systems, the authors provided computational data that supported the pathway shown below.[143]



Scheme 106. *HAT-mediated domino reaction of **4.46**.*

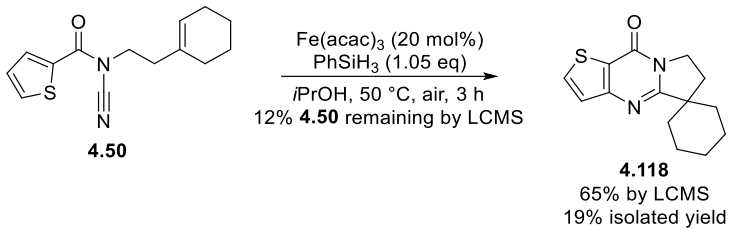
To investigate the effect of *ortho* substitution further, the methoxy group was chosen (**4.41**), as its *para* substituted analogue was one of the optimum substrates (74% yield see earlier, Scheme 98, p.72). Promisingly, the desired quinazolinone **4.116** was the major species in the reaction mixture (67% UV by LCMS of the crude reaction, 45% isolated yield) (Scheme 107). However, significantly more undesired mono-cyclised

amidine **4.117** (28% UV by LCMS of crude reaction with correct MH^+) was formed in comparison to the *para*-substituted analogue (trace amounts). This result suggests that *ortho* substitution hinders the second cyclisation event, perhaps by forcing the amide to adopt a conformation less-favourable for cyclisation. It is to be noted that none of the regio isomer of **4.116** was observed (*cf*. earlier, Scheme 106).



Scheme 107. *HAT-mediated domino reaction of **4.41** to afford desired quinazolinone **4.116**.*

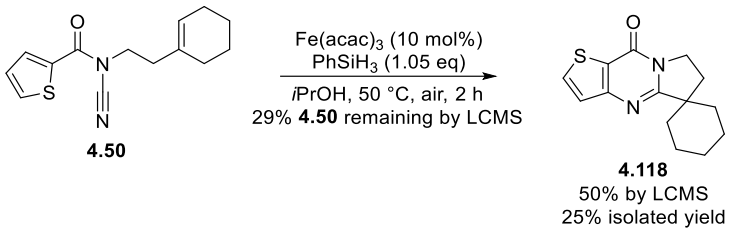
Heterocycles, other than the nitrogen-containing heterocycles previously discussed, were also investigated using this methodology. 2-Substituted thiophene substrate **4.50** was tested at 20 mol% Fe (before optimised conditions were established), and the result is shown below in Scheme 108. The reaction profile (after 3 hours) looked promising, with the desired product **4.118** as the major peak (65% UV by LCMS) and some S.M. **4.50** remaining (12% UV by LCMS). However, the desired heterocycle **4.118** was only isolated in a disappointingly low yield (19%) after purification.



Scheme 108. *HAT-mediated domino reaction of **4.50** towards desired heterocycle **4.118**.*

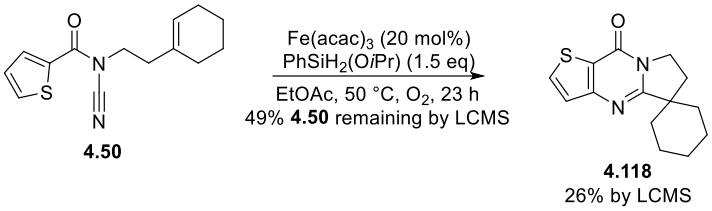
This result highlights one of the major challenges of this project; reaction conversion by LCMS often appeared superior to the isolated yields obtained. There are two plausible reasons for this phenomenon. Firstly, the desired heterocyclic products have stronger UV absorptions than the corresponding starting materials and side-products, as they have a larger extended array of π-electrons. Secondly, a proportion of the desired heterocycle is lost on purification possibly due to ligation with Fe.

The reaction of **4.50** was repeated under the optimised conditions of 10 mol% $Fe(acac)_3$ and the outcome is shown below in Scheme 109. The reaction profile (by LCMS) appeared inferior, with desired product **4.118** formed in lesser amounts (50% UV by LCMS *vs*. 65%) and more S.M. **4.50** remaining (29% UV by LCMS *vs*. 12%). However, on purification a slightly greater isolated yield of desired heterocycle **4.118** was obtained (25% *vs*. 19%). Tentatively this result is consistent with product loss by ligation with Fe, as though the conversion was lower than that of Scheme 108, the isolated yield was slightly increased as there is less Fe in the reaction mixture (10 mol% vs. 20 mol%). These results (Scheme 108 and Scheme 109) are also consistent with the earlier observation that 5 mol% Fe gave the same yield as 10 mol% despite apparent poorer conversion (Table 7, p. 69).



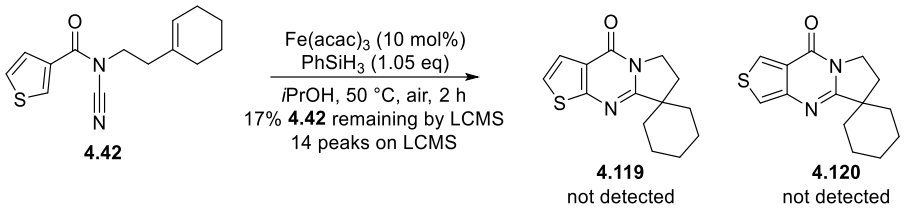
Scheme 109. *HAT-mediated domino reaction of **4.50** to give desired heterocycle **4.118**.*

For completeness, the more strongly oxidising optimised conditions were also employed on 2-substituted thiophene substrate **4.50**. However, the reaction profile obtained was inferior (Scheme 110).



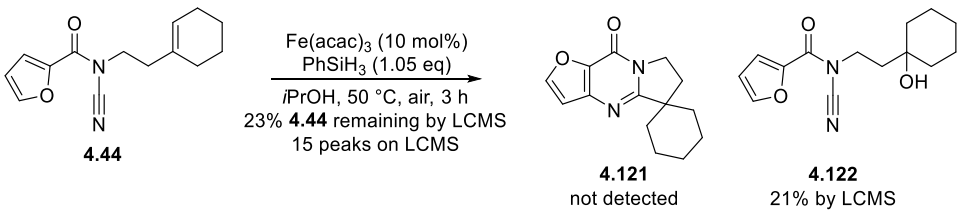
Scheme 110. *HAT-mediated domino reaction of **4.50** towards desired heterocycle **4.118**.*

The 3-substituted thiophene (**4.42**) was not tolerated (Scheme 111). The reaction profile was complex (14 peaks by LCMS). Neither desired heterocycle **4.119** nor **4.120** was observed and many of the peaks contained dimeric masses or other high mass unknown compounds.



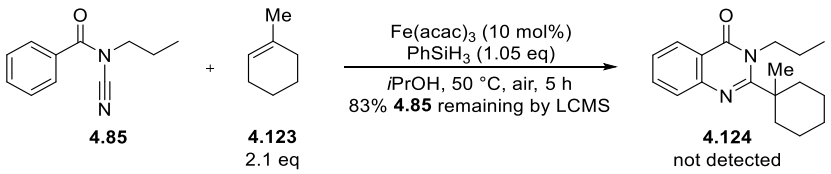
Scheme 111. *Unsuccessful HAT-mediated domino reaction of **4.42** to give desired heterocycles **4.119** and **4.120**.*

The HAT-mediated reaction of 2-substituted furan substrate **4.44** to heterocycle **4.121** was investigated (Scheme 112). Unfortunately, no desired product **4.121** was observed in the reaction mixture, while along with remaining S.M. **4.44** (23% UV by LCMS) the major peak in the reaction was the oxidised product **4.122** (21% UV by LCMS with correct MH^+). In combination with the efforts on the 2/3-substituted thiophene substrates (**4.42** and **4.50**), this result brought about the end of the heterocycle substrate scope investigations.



Scheme 112. *Unsuccessful HAT-mediated domino reaction of **4.44** towards desired quinazolinone **4.121**.*

Finally, to investigate the potential for an intermolecular variant of the domino reaction, substrate **4.85** and commonly used donor-alkene[66] **4.123** were subjected to the optimised HAT conditions as shown below in Scheme 113. Unfortunately, none of the desired addition product **4.124**, nor any other addition products, was observed after 5 hours. The major component of the reaction mixture was unreacted S.M. **4.85** (83% by LCMS).



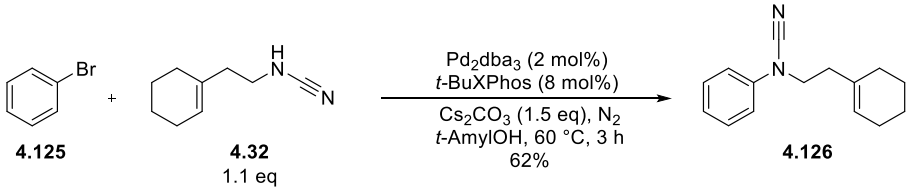
Scheme 113. *Unsuccessful intermolecular HAT-mediated cyclisation reaction towards quinazolinone **4.124**.*

4.2.5 – Removing Amide Moiety

To investigate the effect of removing the amide moiety on the HAT-mediated domino reaction, a series of substrates were made with the intention of synthesising amidines (mono-cyclisation) or benzimadazoles (domino reaction).

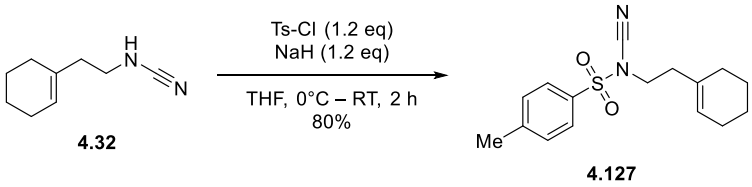
Synthesis of Starting Materials

Applying cross-coupling conditions from the literature,[144] phenylcyanamide **4.126** was synthesised in moderate yield (62%) (Scheme 114) from bromobenzene (**4.125**) and *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**).



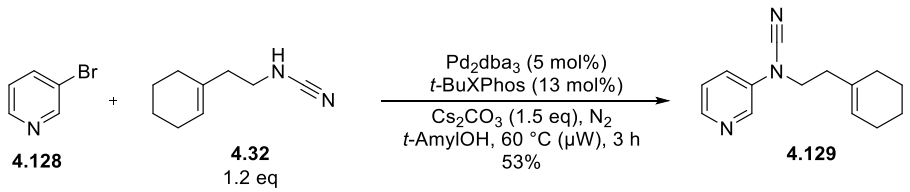
Scheme 114. *Palladium-catalysed cross-coupling of **4.125** and **4.32** to give **4.126**.*

Tosylation of *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**) afforded tosylcyanamide **4.127** in good yield (80%) (Scheme 115).[145]



Scheme 115. *Tosylation of N-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**) to give **4.127**.*

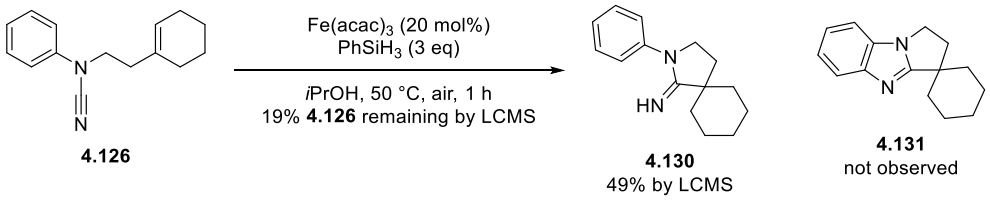
The same cross-coupling conditions that were successful in synthesising phenylcyanamide **4.126** were applied to the cross-coupling of 3-bromopyridine (**4.128**) and *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**). With increases in catalyst and ligand loading, pyridinylcyanamide **4.129** was also synthesised in reasonable yield (53%) (Scheme 116).



Scheme 116. *Palladium-catalysed cross-coupling of **4.128** and **4.32** to give **4.129**.*

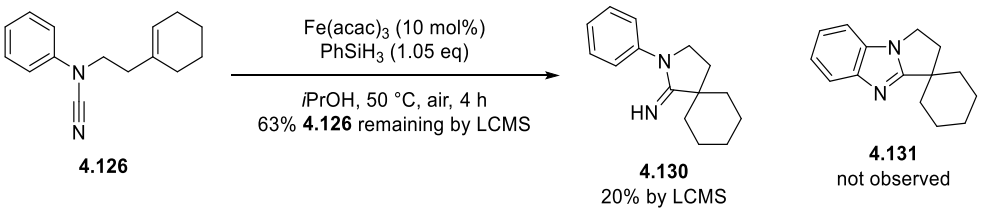
HAT Reactions

The HAT reaction of model phenyl-substrate **4.126** was studied (Scheme 117). The major observed product (by LCMS) was the mono-cyclised amidine **4.130**, whilst the domino product **4.131** was not observed. Purification of the concentrated reaction mixture by reverse-phase chromatography yielded only remaining S.M. **4.126**. The broad nature of the LCMS peak for amidine **4.130**, and the loss of material on the column, indicates that amidine **4.130** may have been complexing to iron.



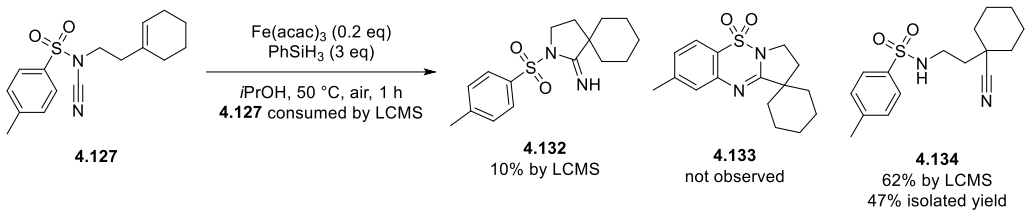
Scheme 117. *HAT reaction of N-cyanamide alkene **4.126.***

Repeating the reaction with the previously optimised catalyst and silane loading did not improve the reaction profile (Scheme 118). Unfortunately, lower conversion of **4.126** was obtained and none of the desired domino-product **4.131** was observed.



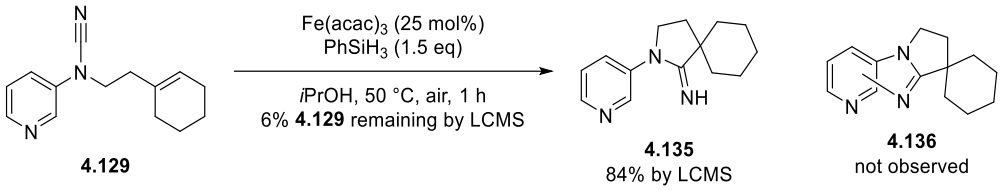
Scheme 118. *HAT reaction of N-cyanamide alkene **4.126.***

Tosyl-substrate **4.127** was investigated under HAT-conditions and the outcome is shown below in Scheme 119. Interestingly, nitrile-migration product **4.134** was the major product, alongside small amounts of amidine **4.132**. The S.M. **4.127** was fully consumed (by LCMS) and none of the domino-product **4.133** was observed. The β-scission event leading to the formation of nitrile-migrated product **4.134** is presumably favoured due to the extra stabilisation of the nitrogen radical, provided by the SO_2 group.



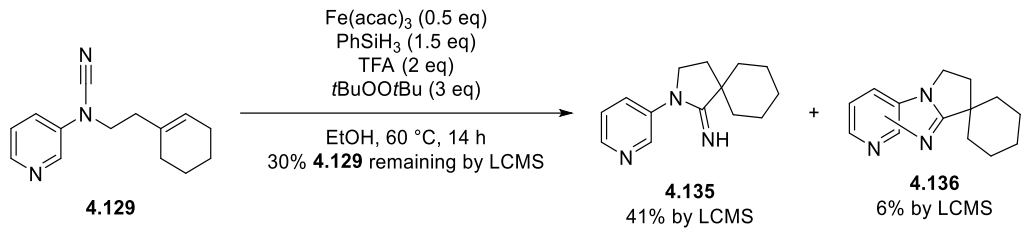
Scheme 119. *HAT reaction of N-cyanamide alkene* ***4.127.***

3-Pyridine substituted substrate **4.129** was subjected to HAT-conditions shown in Scheme 120. The reaction proceeded smoothly to the mono-cyclised amidine **4.135** (84% by LCMS), with none of domino-product **4.136** observed. As was the case with the phenyl-variant, purification of the amidine proved challenging and unfortunately **4.135** was not isolated.



Scheme 120. *HAT reaction of N-cyanamide alkene* ***4.129.***

Inspired by Starr's method for hydropyridylation of olefins,[129] the reaction was repeated under the conditions shown in Scheme 121. The major species remained amidine **4.135**, however a small amount of domino-product **4.136** was observed by LCMS. Unfortunately, due to incomplete conversion and only minor amounts of desired-product formed, the reaction and the exploration of further substrates was abandoned.



Scheme 121. *HAT reaction of N-cyanamide alkene* ***4.129.***

The amide moiety appears critical to the success of the HAT-mediated domino reaction. In its absence, the major product is often the mono-cyclised amidine which is challenging to purify. It is possible, the amide is required to rigidify the

conformation required for the second cyclisation step and also providing electronic activation of the aryl ring.

4.3 – Summary

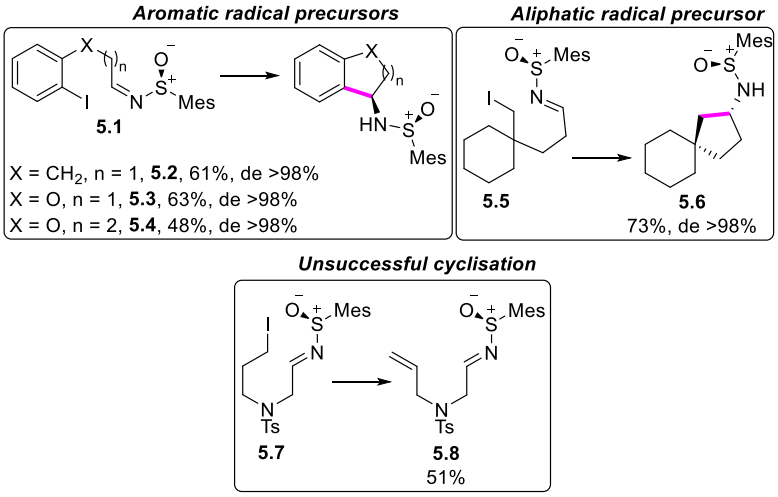
In summary, HAT methodology to enable the synthesis of (spiro)quinazolinone scaffolds from tractable *N*-cyanamide alkenes (synthesised from their acid and cyanamide counterparts) has been developed. The reaction has been shown to be scalable and has been optimised to tolerate challenging electron-deficient heterocycles. An oxidative step is believed to be the key event in the synthesis of the quinazolinone products and the mechanism of the transformation has been probed through a study of varying electronic properties of the accepting aryl ring. Hopefully this methodology will prove to be a general route to valuable quinazolinone scaffolds in the future. Highlights of the work discussed in Chapter 2 were published in Chemistry – A European Journal (2020, hot paper).[2]

5 – Side-Projects/Future Work

5.1 – Radical Cyclisations of Sulfinimines

5.1.1 – Background

Inspiration for this chapter of work regarding radical additions to imine derivatives was provided by Garcia,[146] Stockman,[147] Malacria,[148] and Clive.[149] Of particular note, Stockman reported that chiral amines can be formed by the highly diastereoselective intramolecular addition of alkyl and aryl radicals onto chiral mesityl sulfinimines (Scheme 122).[147]



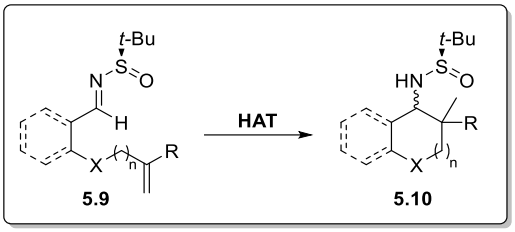
Scheme 122. *Aromatic and aliphatic radical cyclisations of sulfinimines. Reaction conditions: Bu_3SnH, AIBN, PhH, reflux.*

S-Mesitylsulfinimines are able radical acceptors and undergo radical cyclisations with excellent control of diastereoselectivity (de >98%). The product chiral sulfinamides (**5.2**–**5.4**) shown above in Scheme 122 are easily deprotected (4M HCl, quantitative yield) to give the corresponding chiral amines.

However, this work has limitations. Substrates such as **5.7** undergo elimination of the terminal iodide to form the corresponding alkene. Whilst tin-free conditions could be used, taken from Malacria–Curran's methodology,[150] yields were diminished dramatically in all cases as a consequence. In addition, it was reported that mesitylsulfinimine was required to promote the radical cyclisation (*tert*-butylsulfinimine was not active), as was the need for an iodide radical precursor.

5.1.2 – Methodology Outline

The aim of this project was to develop HAT-methodology based on the work shown previously in Scheme 122, to provide access to new (hetero)cyclic compounds (**5.10**) via radical cyclisation with templates bearing chiral sulfinimines (**5.9**) (Scheme 123). Such fused aryl/aliphatic ring systems would provide interesting chiral building blocks for biological screening collection enhancement.[151–155]



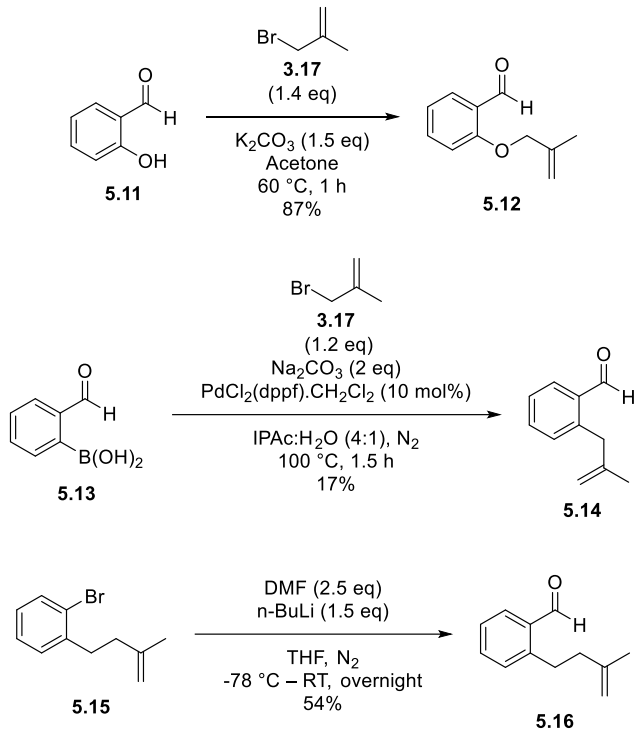
X = C, O, NH, NR
R = Me, F, BR_2, O, NR_2

Scheme 123. *Outline of the methodology proposed for this project.*

Initial reactions were carried out with the aim of exploring tolerance of ring size, along with heteroatoms at the X position, for the desired *exo-trig* radical cyclisation reactions. The R group remained as methyl for this preliminary work. *Tert*-butanesulfinamide was chosen as the chiral motif, as it is readily accessible.

5.1.3 – Synthesis of Starting Materials

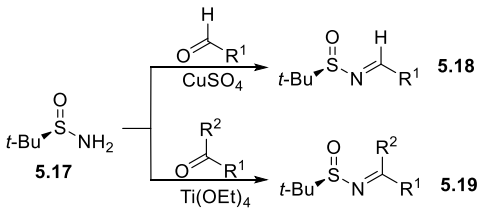
The starting materials for the desired HAT reactions were not commercially available. Therefore, precursor functionalised-aldehydes (**5.12**, **5.14**, and **5.16**) were synthesised as shown below in Scheme 124.



Scheme 124. *Unoptimised yields for the synthesis of starting materials **5.12**, **5.14** and **5.16**.*

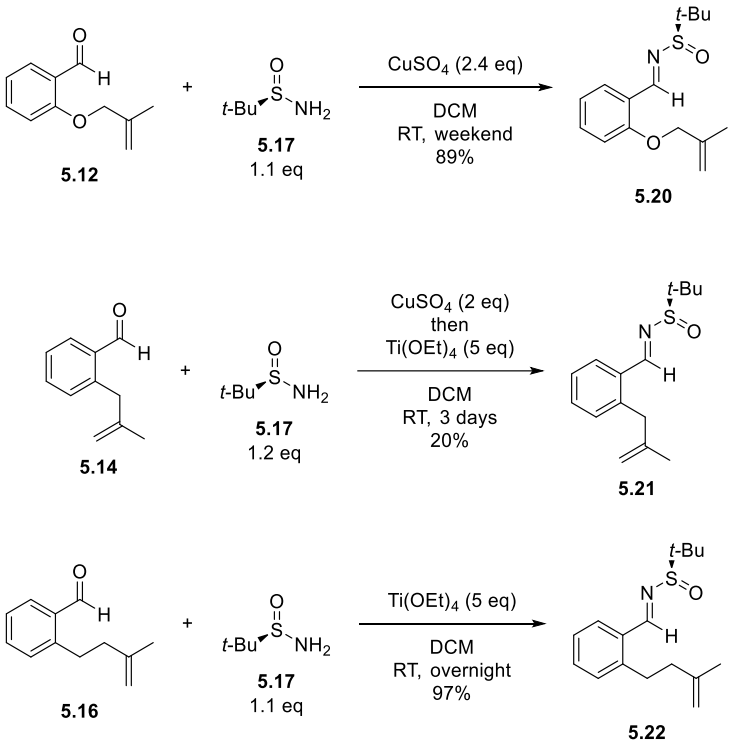
Substrate **5.12** was readily synthesised on a large scale (5 g) by alkylation[156] of the corresponding phenol **5.11** in high yield (87%). The Suzuki-Miyaura reaction of boronic acid **5.13** afforded desired substrate **5.14** in poor yield (17%); issues with protodeboronation and purification were likely attributed to loss of desired material. Nevertheless, sufficient material was isolated. Lithiation of bromide **5.15** followed by reaction with DMF provided aldehyde **5.16** in reasonable yield (54%).[157] This procedure should be used in future to access **5.14**.

Developed in 1997 by Ellman,[158] two high-yielding and general methods for the preparation of chiral *tert*-butanesulfinyl aldimines (**5.18**) and ketimines (**5.19**) are shown in Scheme 125 through reaction with *tert*-butanesulfinamide (**5.17**).



Scheme 125. *General methods for the synthesis of chiral tert-butanesulfinyl aldimines (**5.18**) and ketimines (**5.19**).*

The most straightforward method for the preparation of aldimines (**5.18**) is the condensation of aldehydes and *tert*-butanesulfinamide (**5.17**) using $CuSO_4$ as a Lewis acid catalyst and water scavenger.[158,159] For the preparation of ketimines (**5.19**), $Ti(OEt)_4$ is the preferred Lewis acid and water scavenger. Using this methodology, the aldehydes in hand (**5.12**, **5.14**, and **5.16**) were transformed into the desired *tert*-butanesulfinyl aldimines (**5.20**–**5.22**) shown below in Scheme 126. Pleasingly, *tert*-butanesulfinyl aldimines **5.20** and **5.22** were synthesised in high yield (89% and 97%). The formation of **5.21** proceeded sluggishly under $CuSO_4$ conditions, addition of $Ti(OEt)_4$ aided conversion, but a poor yield (20%) still resulted. Repetition of the experiment on a larger scale under $Ti(OEt)_4$ conditions from the outset would potentially yield **5.21** in an improved yield.

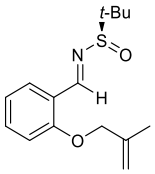
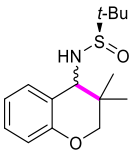
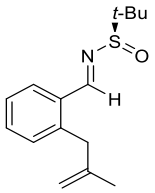
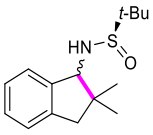
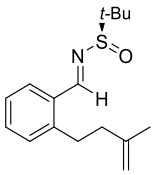
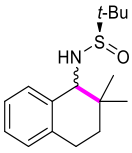


Scheme 126. *Synthesis of desired tert-butanesulfinyl aldimines **5.20–5.22**.*

5.1.4 – HAT-Mediated Cyclisations of Sulfinimines

Importantly, sufficient material was obtained to trial the HAT-mediated cyclisation reactions, the results of which are shown (Table 9). The d.r. of these reactions were determined using ^{1}H NMR; for **5.23** and **5.25** analysis of the crude reaction mixture (after citric acid washes to remove Fe species) was used. The d.r. of **5.24** was obtained after purification by MDAP as there was sparse material.

Table 9. *Isolated yields for the 5-6-exo-trig radical cyclisation reactions of chiral sulfinimines.*

Substrate	Product	Isolated Yield (%) / (d.r.)
 **5.20**	 **5.23**	**59 (68:32)**
 **5.21**	 **5.24**	**67 (57:43)***
 **5.22**	 **5.25**	**39 (68:32)**

Reaction conditions: Fe(acac)$_3$ 50 mol%, PhSiH$_3$ (3.0 eq), EtOH:HFIP (1:1), 50 ^{o}C, 1.5-2 h.
**d.r. obtained after isolation by MDAP.*

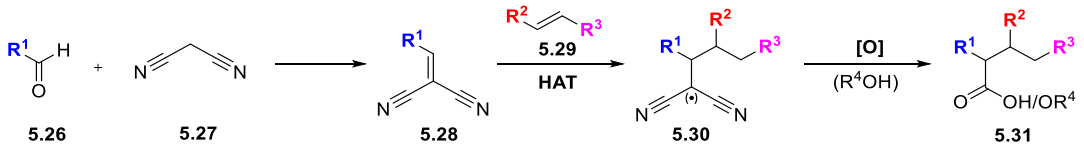
Interestingly, due to the increased electrophilicity of the *tert*-butanesulfinyl aldimine compared to the nitrile group, the desired cyclisation of oxygen-linked substrate **5.20** proceeded faster than the competing de-allylation side-reaction (which was only a minor side-reaction *cf.* nitrile substrate earlier, Scheme 72, p. 54) and sufficient quantities of **5.23** could be isolated (59%). Unfortunately, poor diastereoselectivity was observed (d.r. = 68:32, ^{1}H NMR). 5-*exo-trig* cyclisation of **5.21** also proceeded well to form **5.24** in good yield (67%) but again, poor diastereoselectivity (57:43) was

observed. The 6-*exo*-*trig* cyclisation of **5.22** proceeded well to the cyclic sulfinamide **5.25**, but problems in purification led to a diminished yield (39%). Poor diastereoselectivity (68:32), in agreement with **5.23**, was unfortunately seen once more. With the promise of the nitrile methodology at the time and the disappointing d.r.'s observed, future work on this project was halted. The relative stereochemistry of the major and minor diastereomers were not determined.

5.2 – HAT-Mediated Oxidative Multicomponent Reaction

5.2.1 – Background and Methodology Outline

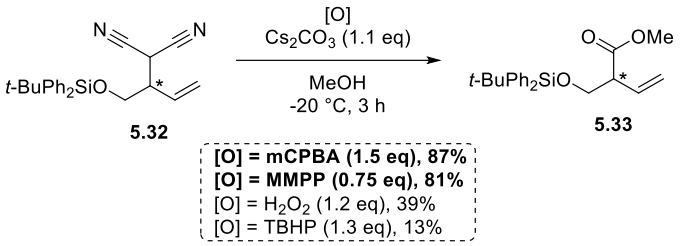
Shown below in Scheme 127 is the outline of the proposed strategy to achieve a HAT-mediated oxidative multicomponent reaction. If malononitrile (**5.27**) was condensed with an aldehyde (**5.28**), the corresponding C=C bond (**5.28**) could be utilised as an acceptor in a HAT-mediated cross-coupling reaction with an additional donor alkene (**5.29**). The intermediate cross-coupled malononitrile product (or radical intermediate) (**5.30**) could then undergo oxidation to the desired product as the functionalised ester or acid (**5.31**) (depending on the reaction solvent).



Scheme 127. *Outline of the proposed HAT-mediated oxidative multicomponent reaction, with the aim to optimise to a one-pot no addition methodology.*

The ultimate aim for this HAT-mediated oxidative multicomponent reaction was to optimise it into a one-pot, 'no addition' methodology. This would allow for the synthesis of highly functionalised acids/esters from simple tractable building blocks (malononitrile, aldehydes and alkenes).

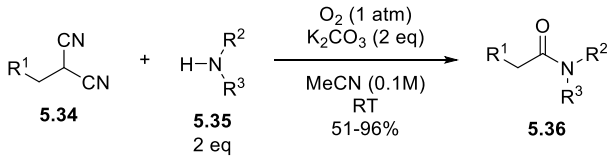
The inspiration for this investigation came from work by Helmchen and Hayashi, on the oxidation of malononitrile. The oxidation of malononitrile has been previously reported[160] but it was not until work by Helmchen *et al.* that the functional group interconversion became a synthetically viable transformation.[161] Optimisation of the oxidation of chiral malononitrile derivative **5.32**, accessed by iridium-catalysed allylic alkylation methodology, to methyl ester **5.33** is shown below in Scheme 128.



Scheme 128. *Oxidative degradation of chiral malononitrile derivative **5.32**.*

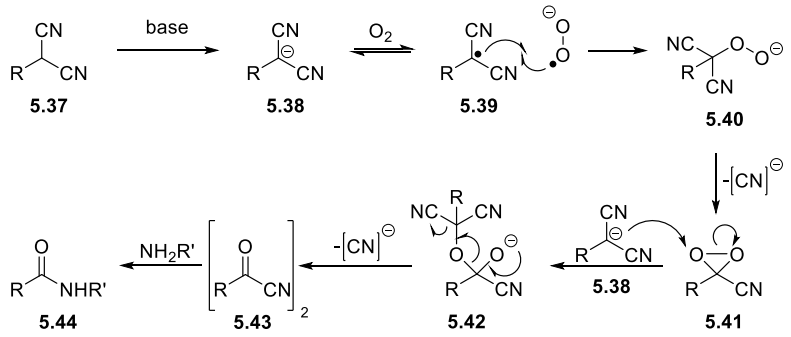
Two optimal oxidants were found to facilitate the desired transformation, with methyl ester **5.33** isolated in good yield with either *m*CPBA or magnesium monoperoxyphthalate (MMPP). It is to be noted that *m*CPBA was not found to epoxidise the double-bond (but isomerisation occurred at temperatures above 0 °C). The authors stated that they pursued MMPP for their methodology, as workup and purification were easier than with *m*CPBA.

Also of note is the work by Hayashi *et al.* who devised an efficient amidation method between readily available α-substituted malononitriles (**5.34**) and amines (**5.35**), simply with molecular oxygen and a carbonate base to afford the desired amide (**5.36**) (Scheme 129).[162]



Scheme 129. *Oxidative amidation of α-substituted malononitriles with amines using O_2.*

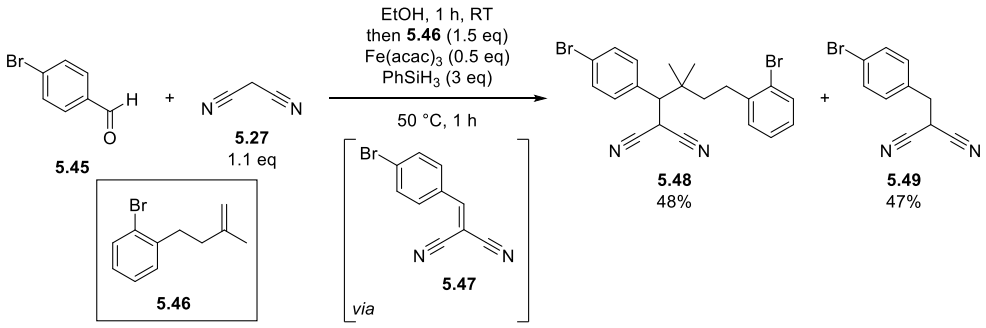
This oxidative protocol can be applied to both sterically and electronically challenging substrates in a highly chemoselective, practical, and rapid manner. The use of cyclopropyl and thioether substrates support the radical-mechanism outlined in Scheme 130. Radical formation of α-peroxy malononitrile species (**5.40**) through reaction of **5.38/5.39** with oxygen, forms dioxirane **5.41** via cyclisation of intermediate **5.40**. This can in term be opened with malononitrile α-carbanion **5.38** to afford two equivalents of activated acyl cyanide **5.43**, upon release of cyanide. The acyl cyanide may then react with amine nucleophiles to afford amide **5.44**.[162]



Scheme 130. *Proposed mechanism of amide formation via acyl cyanide **5.43**.*

5.2.2 – Results and Discussion

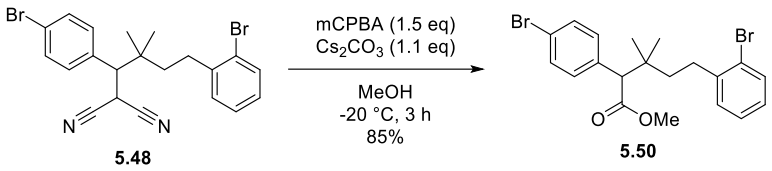
A proof-of-concept reaction was studied to investigate the HAT-mediated cross-coupling of malononitrile derived **5.47** and donor alkene **5.46** to give desired product **5.48** (Scheme 131). Firstly, formation of **5.47** by condensation of 4-bromobenzaldehyde (**5.45**) and malononitrile (**5.27**) was carried out. Bromine atoms were included to make the products of the reaction easier to monitor by LCMS due to the characteristic isotope pattern. After preformation of intermediate **5.47**, a slight excess of the donor alkene **5.46** was introduced under HAT conditions. Pleasingly, the desired cross-coupled product **5.48** was isolated in moderate yield (48%) along with the reduced malononitrile derivative (**5.49**, 47%) without any other major side-products. It was envisaged that the yield of the desired cross-coupled product **5.48** could be increased upon alteration of the donor:acceptor alkene ratio.



Scheme 131. *Proof of concept for the HAT-mediated cross-coupling of malononitrile derived **5.47** and donor alkene **5.46** to give desired product **5.49**.*

Subsequently, the desired cross-coupled product **5.48** was subjected to the optimised oxidation conditions shown earlier (Scheme 128, p.94). Pleasingly, the

desired methyl ester (**5.50**) was isolated in good yield (85%) when using *m*CBPA as the oxidant (Scheme 132).

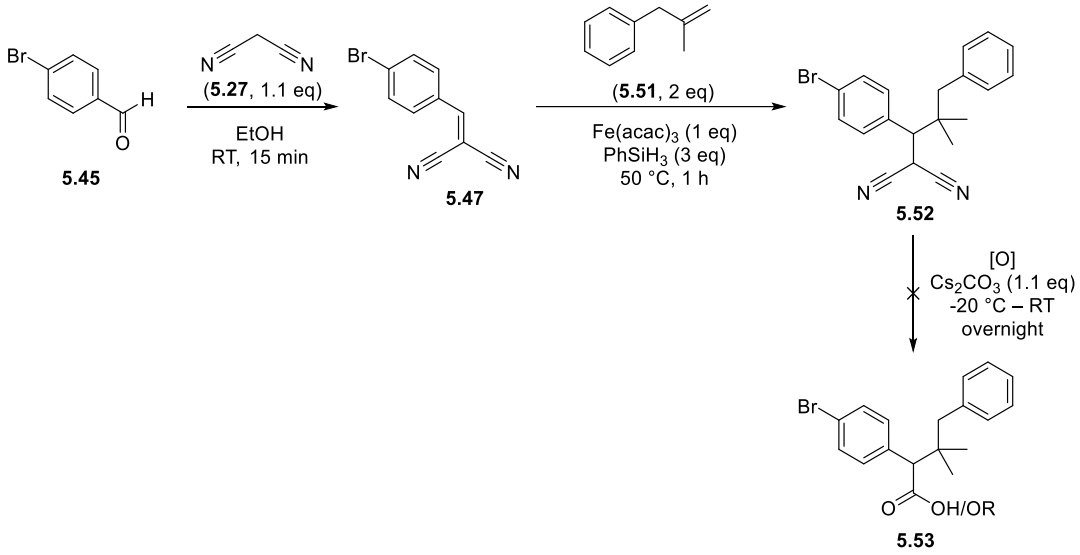


Scheme 132. *Oxidative degradation of malononitrile derivative **5.48** to give methyl ester **5.50**.*

These results proved that the desired functionalised ester could be accessed, in a step-wise fashion, and acted as a proof-of-concept for the HAT-mediated oxidative multicomponent reaction.

Some initial work was carried out to optimise the potential one-pot HAT cross-coupling/oxidation process (shown below in Table 10). Alkene **6.23** was used as it was more readily available and addition of HFIP was investigated since it had proved beneficial for the alkene-nitrile methodology. Three oxidants were chosen, as well as the inclusion of basic conditions under air, based on the work by Helmchen[161] and Hayashi[162] respectively.

Table 10. *Screening of oxidants for the one-pot HAT-mediated oxidative multicomponent reaction.*



HAT Reaction Solvent	5.52 (%UV by LCMS)	Oxidant [O] (eq)	5.53 (%UV by LCMS)
EtOH	47	TBHP (1.5 then 1.5)	0%
"	46	*m*CPBA (1.5 then 1.5)	0%
"	47	MMPP (0.75 then 0.75)	0%
EtOH:HFIP	60	Air	0%

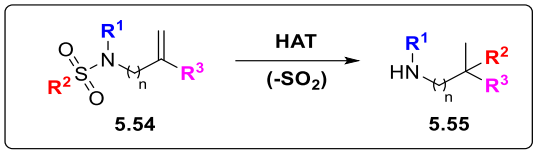
Addition of oxidant and base made at -20 °C, then run at RT overnight and 60°C for 4 h after second addition.

Disappointingly, none of the reactions showed any conversion to the desired ester or acid (**5.53**); the malononitrile-derived cross-coupled product **5.52** appeared unconsumed across all conditions (by LCMS). It is to be noted that intermediate **5.52** could not be isolated, though the mass and isotope pattern observed were consistent with its formation as the major product. Additionally, the inclusion of HFIP in the HAT step increased the conversion to **5.52** (60% *vs*. 46-47%).

5.3 – HAT-Mediated Migration Methodology

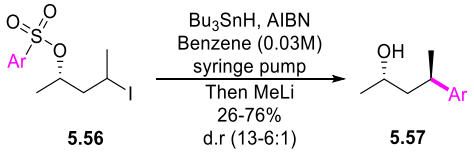
5.3.1 – Background and Methodology Outline

Exploitation of the observed 1,5-toyl migration reaction (shown earlier in Scheme 66, p.51) into a useful methodology for the synthesis of functionalised amines (**5.55**) from *N*-tosyl alkenes (**5.54**) was envisaged (Scheme 133). This work would be an addition to other radical Smiles methodologies (recently reviewed).[113]



Scheme 133. *HAT-mediated migration methodology to access functionalised amines via loss of sulfur dioxide.*

Studer *et al.* have previously reported stereoselective radical aryl migration reactions from silicon to carbon[163,164] and sulfur to carbon.[165,166] The 1,5-aryl migration of **5.56** from sulfur could be performed with high yields and selectivities to deliver alcohol **5.57**, as is shown below in Scheme 134. This work was partly inspired by Motherwell's biaryl synthesis, using both 1,4- and 1,5-aryl migrations from sulfur to aryl radicals.[167–169]

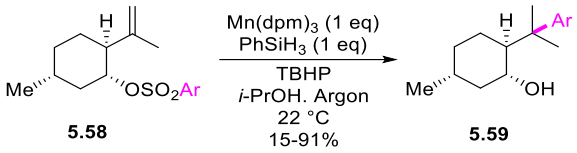


Scheme 134. *Stereoselective 1,5-aryl radical migration by Studer et al.*[166]

Attempts by Studer *et al.* to extend this methodology to sulfonamides were made, but it was found that the radical 1,5-aryl migration was not as efficient as in the sulfonate series described above and isolation of the desired amine proved elusive (reduction and elimination products were also reported).[166] It is worth noting that in the 1970s, Speckamp *et al.* reported moderate yields for the 1,4-aryl migration of sulfonamides derived from piperidines (using Bu_3SnH methodology).[170]

More recently, Shenvi *et al.* published the synthesis of the privileged 8-arylmenthol class by radical arylation of Isopulegol sulfonates (**5.58**) (Scheme 135).[171] They utilised

HAT methodology to facilitate the transfer of a range of aromatic groups by *ipso*-attack of the generated radical onto the sulfonate, liberating sulfur dioxide, to give their desired Isopulegol analogues (**5.59**) in a range of yields.

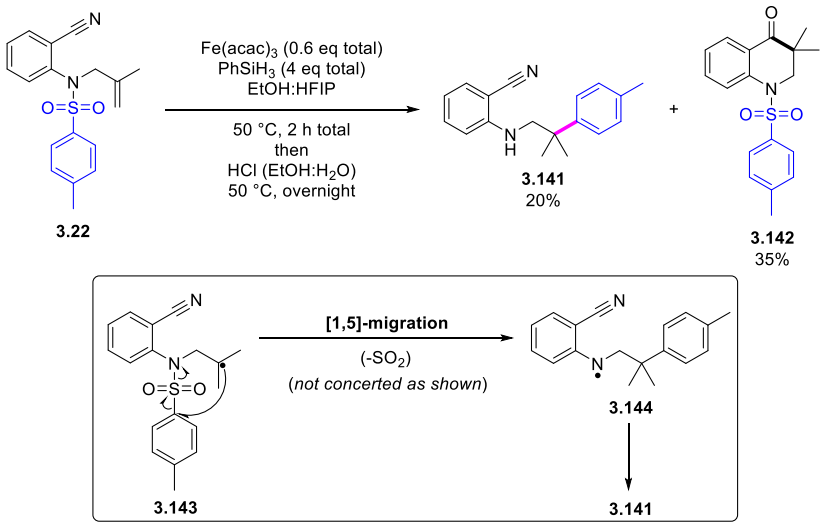


Scheme 135. *HAT-mediated 1,6-aryl migration reaction of Isopulegol analogues.*

Whilst this work bears a striking resemblance to the proposed methodology (Scheme 133, p.98), the scope is limited to 1,6-migration reactions and only concerns alcohol-derived sulfonates. Conversely, this HAT methodology aimed to focus on amine-derived sulfonamides and varied migration patterns.

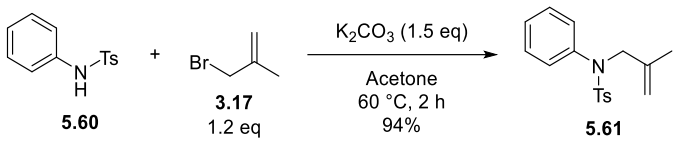
5.3.2 – Results and Discussion

The initial migration result came unexpectedly during the HAT-mediated cyclisation reaction of tosyl-protected substrate **3.22**, which has been discussed earlier in this report (see Scheme 66, p.51), but can be seen again below (Scheme 137),



Scheme 136. *Interesting [1,5] tolyl group migration reaction, upon release of sulphur dioxide.*

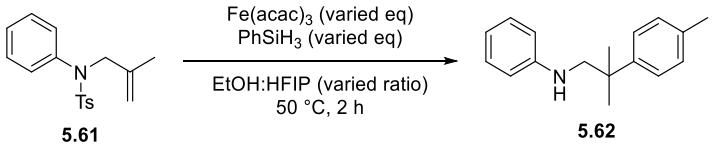
Firstly, the [1,5]-migration reaction was investigated without the interference of the nitrile-cyclisation reaction. Thus, sulfonamide **5.61** was prepared by alkylation of *N*-tosylaniline (**5.60**) in excellent yield (Scheme 137).



Scheme 137. *Synthesis of **5.61** via alkylation reaction.*

The HAT-mediated [1,5]-tolyl-migration reaction of **5.61** was investigated and the results are shown below in Table 11. Poor conversion to the desired product (**5.62**) was observed across all conditions tested (entries 1-4). The addition of HFIP did not appear to be beneficial (entry 1 vs. 2), neither did the concentration of the reaction (entry 1 vs. 3). The largest increase in conversion was seen with increased $Fe(acac)_3$ and $PhSiH_3$ loading (entry 4). Poor conversion may be rationalised by the absence of a strongly stabilising group on the nitrogen, which should help promote the desired reaction by stabilising the intermediate *N*-radical formed following tolyl-migration.

Table 11. *Investigation into the HAT-mediated [1,5] tolyl migration reaction of **5.61** towards **5.62**.*

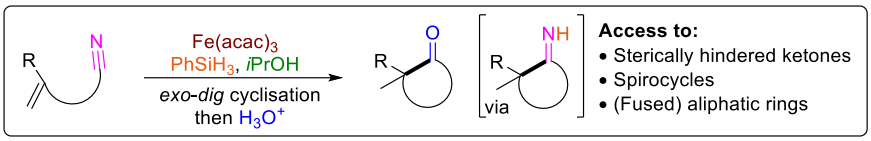


Entry	EtOH:HFIP (M)	$Fe(acac)_3$ (eq)	$PhSiH_3$ (eq)	5.62 by LCMS (%)
1	1:1 (0.17)	1	3	**9**
2	1:0 (0.17)	1	3	**8**
3	1:1 (0.06)	0.5	3	**10**
4	1:1 (0.17)	0.5	6	**17**

6 – Summary and Future Work

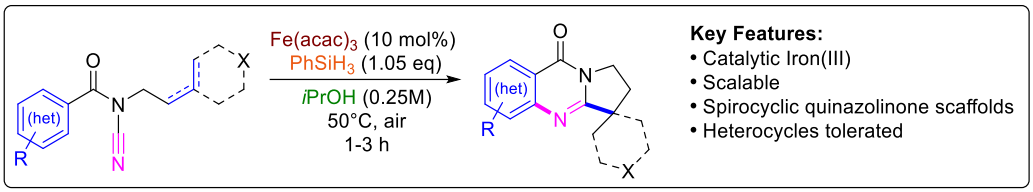
In summary, two new HAT-mediated intramolecular cyclisation methodologies were discovered and developed, utilising C≡N as the radical acceptor. The highlights of both pieces of work were published in Chemistry – A European Journal.[1,2]

The first methodology involves a HAT-mediated intramolecular C-C coupling reaction between alkenes and nitriles, using $PhSiH_3$ and catalytic $Fe(acac)_3$. Which introduces a new strategic bond disconnection for ring-closing reactions, forming ketones via imine intermediates. Of note is the scope of the reaction, including formation of sterically hindered ketones, spirocycles and fused aliphatic systems (Scheme 138).



Scheme 138. *Outline of HAT-mediated alkene-nitrile cyclisation methodology.*

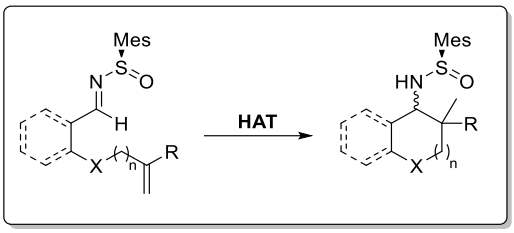
Following on from this, a radical domino cyclisation reaction of *N*-cyanamide alkenes, mediated by HAT was also developed (Scheme 139). This methodology allows for the synthesis of challenging (spiro)quinazolinone scaffolds from simple, tractable (hetero)aryl carboxylic acid and cyanamide building blocks.



Scheme 139. *Outline of HAT-mediated domino cyclisation methodology.*

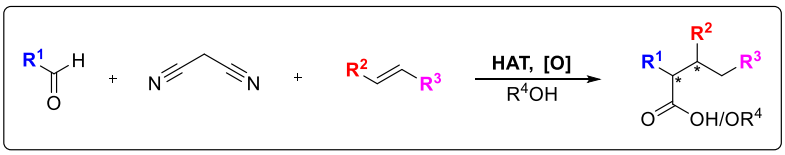
Future work of this thesis may be concentrated on developing the side-projects outlined in section 4.

In future, the use of mesitylsulfinimines (for HAT-mediated cyclisation) may yield improved d.r. over the previous investigation of *tert*-butylsulfinimines, based on the work by Stockman.[147]



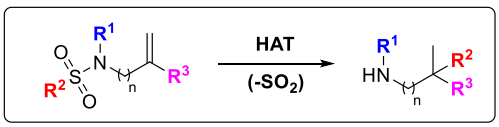
Scheme 140. *Use of mesitylene rather than tert-butyl on the chiral motif to improve d.r..*

There is scope for further work to optimise a one-pot oxidation method for the multicomponent HAT reaction (Scheme 141). First steps may be to carry out exclusion experiments to investigate whether one of the HAT reagents is inhibiting oxidation of the malononitrile. If a one-pot oxidation procedure were to be established, optimisation into a 'no addition' methodology might be made. With established reaction conditions in hand, aldehyde and alkene substrate scope could be investigated, with the potential for substrate or catalyst-controlled stereoselectivity.



Scheme 141. *Ultimate aim – one-pot 'no addition' HAT-mediated oxidative multicomponent reaction to access structurally diverse acids/esters.*

Finally, future studies may be aimed at the optimisation of the sulfonamide substrate to give the desired [1,5] or [1,6] HAT-mediated migration reaction (Scheme 142). Screening of a range of variables could be envisaged; metal source, ligands, additives, silane source, solvent and atmosphere. Once satisfied with the reaction conditions, substrate scope could be investigated to broaden the outlined methodology in Scheme 142 (electronics of the R^2 group may prove pivotal) .



Scheme 142. *HAT-mediated migration methodology to access functionalised amines via loss of sulfur dioxide.*

7 – References

1 O. J. Turner, J. A. Murphy, D. J. Hirst and E. P. A. Talbot, *Chem. Eur. J.*, 2018, **24**, 18658–18662.

2 J. Murphy, O. Turner and D. Hirst, *Chem. Eur. J.*, 2020, **26**, 3026–3029.

3 E. A. Mader, E. R. Davidson and J. M. Mayer, *J. Am. Chem. Soc.*, 2007, **129**, 5153–5166.

4 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, **18**, 734–736.

5 K. Gilmore and I. Alabugin, *Chem. Rev.*, 2011, **111**, 6513–6556.

6 K. Gilmore and I. V. Alabugin, *Chem. Rev.*, 2011, **111**, 6513–6556.

7 R. A. Jackson, *J. Organomet. Chem.*, 1979, **166**, 17–19.

8 I. J. Boyer, *Toxicology*, 1989, **55**, 253–298.

9 P. Renaud, E. Lacôte and L. Quaranta, *Tetrahedron Lett.*, 1998, **39**, 2123–2126.

10 D. S. Hays, M. Scholl and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 6751–6752.

11 C. Chatgilialoglu, *Chem. Eur. J.*, 2008, **14**, 2310–2320.

12 C. P. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237–1286.

13 J. Kwlatek, I. L. Mador and J. K. Seyler, *J. Am. Chem. Soc.*, 1962, **84**, 304–305.

14 J. Kwlatek and J. K. Seyler, *J. Organomet. Chem.*, 1965, **3**, 421–432.

15 T. Mukaiyama, S. Isayama, S. Inoki, K. Kato, T. Yamada and T. Takai, *Chem. Lett.*, 1989, 449–452.

16 S. Inoki, K. Kato, T. Takai, S. Isayama, T. Yamada and T. Mukaiyama, *Chem. Lett.*, 1989, 18, 515–518.

17 T. Mukaiyama and S. Isayama, *Chem. Lett.*, 1989, 1071–1074.

18 H. Ishikawa, D. a Colby, S. Seto, P. Va, A. Tam, H. Kakei, T. J. Rayl, I. Hwang and D. L. Boger, *J. Am. Chem. Soc.*, 2009, **131**, 4904–4916.

19 C. S. Schindler, C. R. J. Stephenson and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2008, **47**, 8852–8855.

20 R. A. Shenvi, C. A. Guerrero, J. Shi, C. Li and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7241–7243.

21 S. Isayama, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1305–1310.

22 H. Shigehisa, T. Aoki, S. Yamaguchi, N. Shimizu and K. Hiroya, *J. Am. Chem. Soc.*, 2013, **135**, 10306–10309.

23 T. Okamoto, K. Kobayashi, S. Oka and S. Tanimoto, *J. Org. Chem.*, 1987, **52**, 5089–5092.

24 J. Waser, B. Gaspar, H. Nambu and E. M. Carreira, *J. Am. Chem. Soc.*, 2006, **128**, 11693–11712.

25 H. Shigehisa, N. Koseki, N. Shimizu, M. Fujisawa, M. Niitsu and K. Hiroya, *J. Am. Chem. Soc.*, 2014, **136**, 13534–13537.

26 J. Hartung, M. E. Pulling, D. M. Smith, D. X. Yang and J. R. Norton, *Tetrahedron*, 2008, **64**, 11822–11830.

27 J. Shey, C. McGinley, K. McCauley, A. Dearth, B. A. Young and W. van der Donk, *J. Org. Chem.*, 2002, **67**, 837–846.

28 B. Gaspar and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2007, **46**, 4519–4522.

29 H. T. Dao, C. Li, Q. Michaudel, B. D. Maxwell and P. S. Baran, *J. Am. Chem. Soc.*, 2015, **137**, 8046–8049.

30 J. Zheng, D. Wang and S. Cui, *Org. Lett.*, 2015, **17**, 4572–4575.

31 S. W. M. Crossley, R. M. Martinez, S. Guevara-Zuluaga and R. A. Shenvi, *Org. Lett.*, 2016, **18**, 2620–2623.

32 J. C. Lo, Y. Yabe and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 1304–1307.

33 J. C. Lo, J. Gui, Y. Yabe, C.-M. Pan and P. S. Baran, *Nature*, 2014, **516**, 343–348.

34 T. J. Barker and D. L. Boger, *J. Am. Chem. Soc.*, 2012, **134**, 13588–13591.

35 H. Shigehisa, E. Nishi, M. Fujisawa and K. Hiroya, *Org. Lett.*, 2013, **15**, 5158–5161.

36 B. Gaspar and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2008, **47**, 5758–5760.

37 X. Ma and S. B. Herzon, *Chem. Sci.*, 2015, **6**, 6250–6255.

38 K. Iwasaki, K. K. Wan, A. Oppedisano, S. W. M. Crossley and R. A. Shenvi, *J . Am. Chem. Soc.*, 2014, **136**, 1300–1303.

39 V. Girijavallabhan, C. Alvarez and F. G. Njoroge, *J. Org. Chem.*, 2011, **76**, 6442–6446.

40 S. W. M. Crossley, C. Obradors, R. M. Martinez and R. A. Shenvi, *Chem. Rev.*, 2016, **116**, 8912–9000.

41 B. Gaspar and E. M. Carreira, *J. Am. Chem. Soc.*, 2009, **131**, 13214–13215.

42 J. Rô Me Waser and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 5676–5677.

43 S. Isayama and T. Mukaiyama, *Chem. Lett.*, 1989, **18**, 2005–2008.

44 B. Giese, J. A. González-Gómez and T. Witzel, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 69–70.

45 Hiroyoshi Noguchi, Kosho Hojo and M. Suginome, *J. Am. Chem. Soc.*, 2007, **129**, 758–759.

46 N. Miyaura, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2008, pp. 41–123.

47 J. Gui, C.-M. Pan, Y. Jin, T. Qin, J. C. Lo, B. J. Lee, S. H. Spergel, M. E.

Mertzmann, W. J. Pitts, T. E. La Cruz, M. A. Schmidt, N. Darvatkar, S. R. Natarajan and P. S. Baran, *Science.*, 2015, **348**, 6237.

48 K. Zhu, M. P. Shaver and S. P. Thomas, *Chem. Sci.*, 2016, **7**, 3031–3035.

49 K. Zhu, M. P. Shaver and S. P. Thomas, *Chem. Asian. J.*, 2016, **11**, 977–980.

50 C. Obradors, R. M. Martinez and R. A. Shenvi, *J. Am. Chem. Soc.*, 2016, **138**, 4962–4971.

51 K. Revunova and G. I. Nikonov, *Chem. Eur. J.*, 2014, **20**, 839–845.

52 S. A. Green, S. Vásquez-Céspedes and R. A. Shenvi, *J. Am. Chem. Soc.*, 2018, **140**, 11317–11324.

53 F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer and P. S. Baran, *Angew. Chem. Int. Ed.*, 2017, **56**, 3319–3323.

54 T. Zhang, N.-X. Wang and Y. Xing, *J. Org. Chem.*, 2018, **83**, 7559–7565.

55 M. Saladrigas, C. Bosch, G. V. Saborit, J. Bonjoch and B. Bradshaw, *Angew. Chem. Int. Ed.*, 2018, **57**, 182–186.

56 A. L. J. Beckwith and B. P. Hay, *J. Am. Chem. Soc.*, 2002, **111**, 230–234.

57 M. Saladrigas, G. Loren, J. Bonjoch and B. Bradshaw, *ACS Catal.*, 2018, **8**, 11699–11703.

58 J. Halpern and R. L. Sweany, *J. Am. Chem. Soc.*, 1977, **99**, 8335–8337.

59 J. Halpern and L.-Y. Wong, *J. Am. Chem. Soc.*, 1968, **90**, 6665–6669.

60 E. J. Moore, J. M. Sullivan and J. R. Norton, *J. Am. Chem. Soc.*, 1986, **108**, 2257–2263.

61 J. L. Elkind and P. B. Armentrout, *Inorg. Chem.*, 1986, **25**, 1078–1080.

62 S. W. Benson, *J. Chem. Educ.*, 1965, **42**, 502.

63 R. Sweany, S. C. Butler and J. Halpern, *J. Organomet. Chem.*, 1981, **213**, 213–487.

64 T. E. Nalesnik, J. H. Freudenberger and M. Orchin, *J. Mol. Catal.*, 1982, **16**, 43–49.

65 M. R. Bullock and E. G. Samsel, *J. Am. Chem. Soc.*, 1990, **112**, 6886–6898.

66 J. C. Lo, Y. Yabe and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 2484–2503.

67 M. G. Vinum, L. Voigt, C. Bell, D. Mihrin, R. W. Larsen, K. M. Clark and K. S. Pedersen, *Chem. Eur. J.*, 2020, **26**, 2143–2147.

68 D. P. Estes, D. C. Grills and J. R. Norton, *J. Am. Chem. Soc.*, 2014, **136**, 17362–17365.

69 D. Kim, S. M. W. Rahaman, B. Q. Mercado, R. Poli and P. L. Holland, *J . Am. Chem. Soc.*, 2019, **141**, 7473–7485.

70 D. P. Curran and W. Liu, *Synlett*, 1999, **1**, 117–119.

71 R. A. Alonso, C. S. Burgey, B. Venkateswara Rao, G. D. Vite, R. Vollerthun, M. A. Zottola and B. Fraser-Reid, *J . Am. Chem. Soc.*, 1993, **115**, 6666–6672.

72 D. L. J. Clive, P. L. Beaulieu and L. Set, *J. Org. Chem.*, 1984, **49**, 1313–1314.

73 Y. Yamamoto, D. Matsumi, R. Hattori and K. Itoh, *J. Org. Chem.*, 1999, **64**, 3224–3229.

74 B. B. Snider and B. O. Buckman, *J. Org. Chem.*, 1992, **57**, 322–326.

75 B.-W. Anissa Yeung, J. L. M. Contelles and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1989, 1160–1162.

76 B. Chenera, C.-P. Chuang, D. J. Hart and L.-Y. Hsu, *J. Org. Chem.*, 1985, **50**, 5409–5410.

77 J. D. Kilburn, *Tetrahedron Lett.*, 1990, **31**, 2193–2196.

78 D. Griller, P. Schmid and K. U. Ingold, *Can. J. Chem.*, 1979, **57**, 831–834.

79 E. L. Cochran, F. J. Adrian and V. A. Bowers, *J. Chem. Phys.*, 1962, **36**, 1938–1942.

80 R. Symons, *Tetrahedron*, 1973, **29**, 615–619.

81 R. F. Hudson, A. J. Lawson and K. A. F. Record, *J. Chem. Soc., Chem. Commun.*, 1974, 488–489.

82 M.-H. Le Tadic-Biadatti, A.-C. Callier-Dublanchet, J. H. Horner, B. Quiclet-Sire,

S. Z. Zard and M. Newcomb, *J. Org. Chem.*, 1997, **62**, 559–563.

83 W. Yin and X. Wang, *New J. Chem.*, 2019, **43**, 3254–3264.

84 D. Griller, G. D. Mendenhall, W. Van Hoof and K. U. Ingold, *J. Am. Chem. Soc.*, 2002, **96**, 6068–6070.

85 B. P. Roberts and J. N. Winter, *J. Chem. Soc. Perkin Trans. 2*, 1979, 1353–1361.

86 J. Boivin, E. Fouquet and S. Z. Zard, *J. Am. Chem. Soc.*, 2002, **113**, 1055–1057.

87 D. P. Curran and H. Liu, *J. Am. Chem. Soc.*, 2002, **113**, 2127–2132.

88 J. Davies, N. S. Sheikh and D. Leonori, *Angew. Chem. Int. Ed.*, 2017, **56**, 13361–13365.

89 E. M. Dauncey, S. P. Morcillo, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem. Int. Ed.*, 2018, **57**, 744–748.

90 E. P. A. Talbot, *GSK , 2016*.

91 M. P. Coogan, R. Haigh, A. Hall, L. D. Harris, D. E. Hibbs, R. L. Jenkins, C. L. Jones and N. C. O. Tomkinson, *Tetrahedron*, 2003, **59**, 7389–7395.

92 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 453–754.

93 H. Hikawa, T. Koike, K. Izumi, S. Kikkawa and I. Azumaya, *Adv. Synth. Catal.*,

2016, **358**, 784–791.

94 Jun Takagi, Kou Takahashi, T. Ishiyama and N. Miyaura, *J. Am. Chem. Soc.*, 2002, **124**, 8001–8006.

95 A. K. Podichetty, S. Wagner, S. Schröer, A. Faust, M. Schäfers, O. Schober, K. Kopka and G. Haufe, *J. Med. Chem.*, 2009, **52**, 3484–3495.

96 M. McMullan, A. Garc?a-Bea, P. Miranda-Azpiazu, L. F. Callado and I. Rozas, *Eur. J. Med. Chem.*, 2016, **123**, 48–57.

97 Z. Lim, P. J. Duggan, S. S. Wan, G. Lessene, A. G. Meyer and K. L. Tuck, *Tetrahedron*, 2016, **72**, 1151–1160.

98 L. Boymond, M. Rottländer, G. Cahiez and P. Knochel, *Angew. Chem. Int. Ed.*, 1998, **37**, 1701–1703.

99 S. Cren, P. Schär, P. Renaud and K. Schenk, *J. Org. Chem.*, 2009, **74**, 2942–2946.

100 H.-Y. Lee, Y. Jung, Y. Yoon, B. G. Kim and Y. Kim, *Org. Lett.*, 2010, **12**, 2672–2674.

101 B.-J. Wang, P. Xue and P. Gu, *Chem. Commun.*, 2015, **51**, 2277–2279.

102 Y. Schramm, M. Takeuchi, K. Semba, Y. Nakao and J. F. Hartwig, *J . Am. Chem. Soc.*, 2015, **137**, 12215–12218.

103 A. Fernández-Mateos, P. Herrero Teijón, L. Mateos Burón, A. R. Rabanedo

Clemente and R. R. González, *J. Org. Chem.*, 2007, **72**, 9973–9982.

104 G. Manolikakes, C. Muñoz Hernandez, M. A. Schade, A. Metzger and P. Knochel, *J. Org. Chem.*, 2008, **73**, 8422–8436.

105 L. E. Overman, E. Jon Jacobsen and R. J. Doedens, *J. Org. Chem.*, 2002, **48**, 3393–3400.

106 D. Das, M. T. Richers, L. Ma and D. Seidel, *Org. Lett.*, 2011, **13**, 6584–6587.

107 D. Lebœuf, L. Marin, B. Michelet, A. Perez-Luna, R. Guillot, E. Schulz and V. Gandon, *Chem. Eur. J.*, 2016, **22**, 16165–16171.

108 A. M. A. Dias, M. Freire, J. A. P. Coutinho and I. M. Marrucho, *Fluid Phase Equilib.*, 2004, **222**–**223**, 325–330.

109 W.-Y. Siau and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 17726–17729.

110 D. Vrubliauskas and C. D. Vanderwal, *Angew. Chem. Int. Ed.*, , DOI:doi:10.1002/anie.202000252.

111 X.-W. Lan, N.-X. Wang, C.-B. Bai, C.-L. Lan, T. Zhang, S.-L. Chen and Y. Xing, *Org. Lett.*, 2016, **18**, 5986–5989.

112 R. Bowman, C. Bridge and P. Brookes, *Tetrahedron Lett.*, 2000, **41**, 8989–8994.

113 I. Allart-Simon, S. Gérard and J. Sapi, *Molecules*, 2016, **21**, 878.

114 H. C. Brown, M. M. Rogic, H. Nambu and M. W. Rathke, *J. Am. Chem. Soc.*, 1969, **91**, 2147–2149.

115 D. Chen, X. Zhang, W.-Y. Qi, B. Xu and M.-H. Xu, *J. Am. Chem. Soc.*, 2015, **137**, 5268–5271.

116 B. Quiclet-Sire and S. Z. Zard, *J. Am. Chem. Soc.*, 2015, **137**, 6762–6765.

117 E. R. Altwicker, *Chem. Rev.*, 1967, **67**, 475–531.

118 J. Zheng, Z. Deng, Y. Zhang and S. Cui, *Adv. Synth. Catal.*, 2016, **358**, 746–751.

119 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930.

120 U. A. Kshirsagar, *Org. Biomol. Chem.*, 2015, **13**, 9336–9352.

121 A. Hameed, M. Al-Rashida, M. Uroos, S. A. Ali, Arshia, M. Ishtiaq and K. M. Khan, *Expert Opin. Ther. Pat.*, 2018, **28**, 281–297.

122 S. Von Niementowski, *J. Prakt. Chem.*, 1894, **51**, 564–572.

123 L. He, H. Li, J. Chen and X.-F. Wu, *RSC Adv.*, 2014, **4**, 12065–12077.

124 A. Servais, M. Azzouz, D. Lopes, C. Courillon and M. Malacria, *Angew. Chem. Int. Ed.*, 2007, **46**, 576–579.

125 G. Xu, C. Tong, S. Cui and L. Dai, *Org. Biomol. Chem.*, 2018, **16**, 5899–5906.

126 J. Zheng, Y. Zhang, D. Wang and S. Cui, *Org. Lett.*, 2016, **18**, 1768–1771.

127 P. Qian, Y. Deng, H. Mei, J. Han, J. Zhou and Y. Pan, *Org. Lett.*, 2017, **19**, 4798–4801.

128 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.

129 S. Bordi and J. T. Starr, *Org. Lett.*, 2017, **19**, 2290–2293.

130 E. Gößnitzer, R. Malli, S. Schuster, B. Favre and N. S. Ryder, *Arch. Pharm. (Weinheim).*, 2002, **335**, 535–546.

131 D. Meyer, E. Vin, B. Wyler, G. Lapointe and P. Renaud, *Synlett*, 2015, **27**, 745–748.

132 Z.-L. Zang, S. Zhao, S. Karnakanti, C.-L. Liu, P.-L. Shao and Y. He, *Org. Lett.*, 2016, **18**, 5014–5017.

133 R. F. Nystrom, *J . Am. Chem. Soc.*, 1955, **77**, 2544–2545.

134 A. Van der Bent, A. G. S. Blommaert, C. T. M. Melman, A. P. IJzerman, I. Van Wijngaarden and W. Soudijn, *J. Med. Chem.*, 2002, **35**, 1042–1049.

135 N. Brindani, G. Rassu, L. Dell'Amico, V. Zambrano, L. Pinna, C. Curti, A. Sartori, L. Battistini, G. Casiraghi, G. Pelosi, D. Greco and F. Zanardi, *Angew. Chem. Int. Ed.*, 2015, **54**, 7386–7390.

136 US2011112103, 2011, 20.

137 D. G. Hendry and D. Schuetzle, *J . Am. Chem. Soc.*, 1975, **97**, 7123–7127.

138 B. Maillard, K. U. Ingold and J. C. Scaiano, *J . Am. Chem. Soc.*, 1983, **105**, 5095–5099.

139 J. S. Wright, H. Shadnia and L. L. Chepelev, *J. Comput. Chem.*, 2009, **30**, 1016–1026.

140 J. Hofmann, T. Clark and M. R. Heinrich, *J. Org. Chem.*, 2016, **81**, 9785–9791.

141 M. Bietti, E. Cucinotta, G. A. DiLabio, O. Lanzalunga, A. Lapi, M. Mazzonna, E. Romero-Montalvo and M. Salamone, *J. Org. Chem.*, 2019, **84**, 1778–1786.

142 J. M. Mayer, D. A. Hrovat, J. L. Thomas and W. Thatcher Borden, *J. Am. Chem. Soc.*, 2002, **124**, 11142–11147.

143 A. Beaume, C. Courillon, E. Derat and M. Malacria, *Chem. Eur. J.*, 2008, **14**, 1238–1252.

144 R. M. Stolley, W. Guo and J. Louie, *Org. Lett.*, 2011, **14**, 322–325.

145 R. M. Stolley, M. T. Maczka and J. Louie, *Eur. J. Org. Chem.*, 2011, **2011**, 3815–3824.

146 J. Fernández-Salas, C. Maestro, M. Rodríguez-Fernández, J. García-Ruano and I. Alonso, *Org. Lett.*, 2013, **15**, 1658–1661.

147 E. M. Rochette, W. Lewis, A. G. Dossetter and R. A. Stockman, *Chem. Commun.*, 2013, **49**, 9395–9397.

148 E. Lacôte and M. Malacria, *C. R. Acad. Sci.*, 1998, **1**, 191–194.

149 D. L. J. Clive, M. P. Pham and R. Subedi, *J. Am. Chem. Soc.*, 2007, **129**, 2713–2717.

150 S.-H. Ueng, L. Fensterbank, E. Lacôte, M. Malacria and D. P. Curran, *Org. Lett.*, 2010, **12**, 3002–3005.

151 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.

152 W. P. Walters, J. Green, J. R. Weiss and M. A. Murcko, *J. Med. Chem.*, 2011, **54**, 6405–6416.

153 A. Nadin, C. Hattotuwagama and I. Churcher, *Angew. Chem. Int. Ed.*, 2012, **51**, 1114–1122.

154 P. Maclellan and A. Nelson, *Chem. Commun.*, 2013, **49**, 2383–2393.

155 F. Lovering, *Med.Chem.Commun.*, , DOI:10.1039/c2md20347b.

156 N. Monteiro and G. Balme, *Synlett*, 1998, **7**, 746–747.

157 I. D. G. Watson, S. Ritter and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 2056–2057.

158 Guangcheng Liu, Derek A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913–9914.

159 G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang and J. A. Ellman, *J. Org. Chem.*,

1999, **64**, 1278–1284.

160 S. Patai and S. Dayagi, *J. Chem. Soc.*, 1962, 716–723.

161 S. Förster, O. Tverskoy and G. Helmchen, *Synlett*, 2008, 2803–28061.

162 J. Li, M. J. Lear and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2016, **55**, 9060–9064.

163 S. Amrein, M. Bossart, T. Vasella and A. Studer, *J.Org.Chem*, 2000, **65**, 4281–4288.

164 A. Studer, M. Bossart and H. Steen, *Tetrahedron Lett.*, 1998, **39**, 8829–8832.

165 A. Studer and M. Bossart, *Chem. Commun.*, 1998, 2127–2128.

166 M. Bossart, R. Fässler, J. Schoenberger and A. Studer, *Eur. J. Org. Chem.*, 2002, **2002**, 2742–2757.

167 W. B. Motherwell, E. Bonfand, A. M. K. Pennell, M. K. Uddin and F. Ujjainwalla, *Heterocycles*, 1997, **46**, 523.

168 M. Lucllia, E. N. Da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 141–144.

169 M. Lueflia, E. N. Da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137–140.

170 W. N. Speckamp and J. J. Kohler, *J. Chem. Soc., Chem. Commun.*, 1978, **0**, 166–176.

171 S. W. M. Crossley, R. M. Martinez, S. Guevara-Zuluaga and R. A. Shenvi, *Org. Lett.*, 2016, **18**, 2620–2623.

172 H. Hikawa, T. Koike, K. Izumi, S. Kikkawa and I. Azumaya, *Adv. Synth. Catal.*, 2016, **358**, 784–791.

173 A. Fernández-Mateos, P. Herrero Teijón, L. Mateos Burón, A. R. Rabanedo Clemente and R. R. González, *J. Org. Chem.*, 2007, **72**, 9973–9982.

8 – Experimental

8.1 – General Information

Solvents and reagents

- Solvents (anhydrous) and reagents were purchased from commercial suppliers or obtained from GlaxoSmithKline's internal compound storage and used as received without further purification.

Where materials were synthesised, full procedures or literature references to procedures are provided.

Chromatography

Thin layer chromatography (TLC) was carried out using plastic-backed 50 precoated silica plates (particle size 0.2 mm). Spots were visualized by ultraviolet (UV) light (λ_{max} = 254 nm or 365 nm) and then stained where appropriate with potassium permanganate solution followed by gentle heating. Normal phase silica gel chromatography was carried out using the Teledyne ISCO CombiFlash® Rf+ apparatus with RediSep® silica and Biotage® SNAP KP-NH cartridges. Reverse phase chromatography was carried out using Teledyne ISCO CombiFlash® Rf+ apparatus with Biotage® SNAP KP-C18-HS cartridges.

Liquid chromatography mass spectrometry (LCMS)

LCMS analysis was carried out on an H_2Os Acquity UPLC instrument equipped with a BEH column (50 mm x 2.1 mm, 1.7 µm packing diameter) and H_2Os micromass ZQ MS using alternate-scan positive and negative electrospray. Analytes were detected as a summed UV wavelength of 210 – 350 nm. Two liquid phase methods were used:

High pH (HpH) – 40 ^{o}C, 1 mL/min flow rate. Gradient elution with the eluents as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile. Gradient conditions were

initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min.

Low pH (Formic) – 40 ^{o}C, 1 mL/min flow rate. Gradient elution with the eluents as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min.

Nuclear magnetic resonance (NMR) spectroscopy

Proton (^{1}H), carbon (^{13}C) and fluorine (^{19}F) spectra were recorded in $CDCl_3$ at ambient temperature using standard pulse methods on any of the following spectrometers and signal frequencies: Bruker AV-400 (^{1}H = 400 MHz, ^{13}C = 101 MHz, ^{19}F = 376 MHz) and Bruker AV-600 (^{1}H = 600 MHz, ^{13}C = 151 MHz). Chemical shifts (δ) are reported in ppm downfield from Me_4Si, in the absence of Me_4Si chemical shifts were referenced to the NMR solvent. Peak assignments were made on the basis of chemical shifts, integrations, and coupling constants using COSY, DEPT, HSQC, HMBC, NOESY and ROESY where appropriate. Coupling constants (*J*) are reported in, and quoted to the nearest 0.1 Hz for ^{1}H, ^{13}C and ^{19}F, and multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sxt), br. (broad), app. (apparent) and multiplet (m).

Infrared (IR) spectroscopy

IR spectra were recorded using a Perkin Elmer Spectrum 1 machine. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) to the nearest whole number.

Melting Points

Melting points were recorded for crystalline solids, using either a Buchi M-565 or Stuart SMP10 melting point apparatus. Melting points are given as a range, to the nearest whole numbers, in degrees Centigrade (^{o} C).

Mass directed automated preparation (MDAP)

MDAP was carried out using a Waters ZQ MS, using alternate-scan positive and negative electrospray and a summed UV wavelength of 210–350 nm. Three liquid phase methods were used:

Formic – Xselect C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution occurred at ambient temperature with the eluents as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid.

High pH (HpH) – Xselect C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution occurred at ambient temperature with the eluents as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with aqueous ammonia and (B) acetonitrile.

TFA – Xselect C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution occurred at ambient temperature with the eluents as (A) H_2O containing 0.1% volume/volume (v/v) trifluoroacetic acid and (B) acetonitrile containing 0.1% (v/v) trifluoroacetic acid.

The elution gradients used were at a flow rate of 40 mL/min over 20 or 30 min depending on separation:

Method A	0-25% B
Method B	15-55% B
Method C	30-85% B
Method D	50-99% B
Method E	80-99% B

High Resolution Mass Spectrometry (HRMS)

High-resolution mass spectra were recorded on a Waters XEVO G2-XS quadrupole time-of-flight mass spectrometer, with analytes separated using an Acquity UPLC CSH C18 column (100 mm x 2.1 mm, 1.7 µm packing diameter). UPLC conditions were 0.8 mL/min flow rate, 50 ^{o}C, injection volume 0.2 µL. Gradient elution with (A) water containing 0.1% (v/v) formic acid and (B) acetonitrile containing 0.1% (v/v) formic acid. Gradient conditions were initially 3% B, increasing linearly to 100% B over 8.5 min, remaining at 100% B for 0.5 min then decreasing linearly to 3% B over 0.5 min followed by an equilibration period of 0.5 min prior to the next injection. Mass to charge ratios (*m*/*z*) are reported in Daltons and error in ppm. An error of less than 5ppm is deemed to be consistent with the proposed molecular formula.

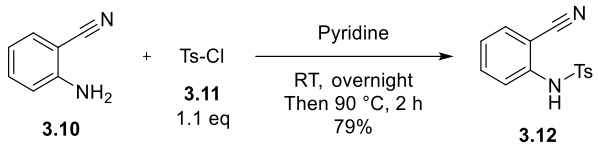
Significant Figures

Reagent quantities are quoted to the accuracy of the equipment used (e.g. balance, syringe etc.), which may vary, in all cases reaction yield is rounded up to the nearest percentage (%).

8.2 – Synthetic Procedures for Section 3

8.2.1 – Synthesis of Substrates

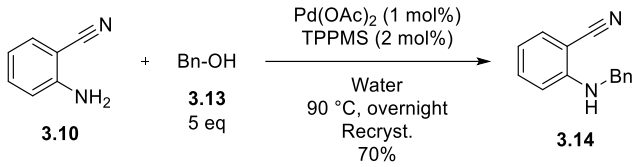
_N_-(2-cyanophenyl)-4-methylbenzenesulfonamide (3.12)



A solution of tosyl-Cl (**3.11**) (2.558 g, 13.42 mmol, 1.1 eq) and 2-aminobenzonitrile (**3.10**) (1.503 g, 12.72 mmol, 1 eq) in pyridine (13 mL) was stirred at RT overnight. The solution was then stirred at 90 ^{o}C for 2 h. The reaction was allowed to come to RT and EtOAc (50 mL) was added and the organic layer washed with $HCl_{(aq)}$ (2M, 4 x 50 mL). The organic layer was dried through a hydrophobic frit and concentrated *in vacuo* to yield a crude pale purple solid. The crude solid was recrystalised from ethanol, to remove starting material but bis-tosylated product remained. The resulting white solid was dissolved in DMSO and purified by automated reverse phase column chromatography on C18 silica gel (30-85% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.12** as a white solid (2.727 g, 10.02 mmol, 79%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.69-7.74 (3H, m), 7.52-7.57 (1H, m), 7.46-7.48 (1H, m), 7.25-7.28 (2H, m), 7.17 (1H, td, *J* = 7.6 and 1.0 Hz), 7.06 (1H, br. s), 2.39 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 144.8, 139.4, 135.5, 134.2, 132.7, 129.9, 127.4, 125.1, 121.6, 115.7, 104.2, 21.6. LCMS (Formic): t_R = 1.01 min, [M-H$^+$] 271.2.

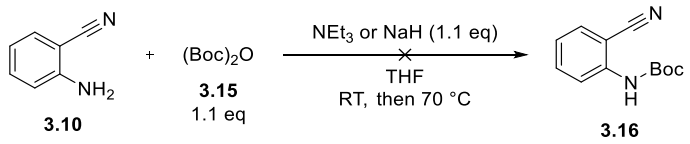
2-(Benzylamino)benzonitrile (3.14)[172]



A solution of benzyl alcohol (**3.13**) (6.6 mL, 63.5 mmol, 5 eq), 2-aminobenzonitrile (**3.10**) (1.5 g, 12.7 mmol, 1 eq), $Pd(OAc)_2$ (29 mg, 0.13 mmol, 1 mol%) and sodium 3-(diphenylphosphanyl)benzenesulfonate (TPPMS) (93 mg, 0.26 mmol, 2 mol%) in water (50 mL) was stirred at 90 ^{o}C overnight. The reaction was stopped and allowed to come to RT slowly. Then brine (50 mL) was added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The resulting crude yellow solid was dissolved in the minimum amount of hot EtOAc and then cyclohexane added until precipitation was observed. The flask was left in the fridge overnight to aid crystallisation, then the solids filtered and washed with cold cyclohexane. The procedure was then repeated for the remaining filtrate. After drying, **3.14** was afforded as an off white solid (1.85 g, 8.89 mmol, 70%).

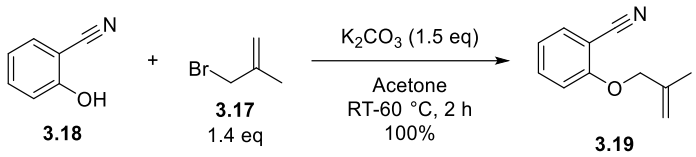
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.41 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.27-7.38 (6H, m), 6.66-6.70 (1H, m), 6.63 (1H, d, *J* = 8.3 Hz), 5.01 (1H, br. s), 4.43 (2H, d, *J* = 5.4 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.1, 137.7, 134.3, 132.8, 128.9, 127.7, 127.2, 117.9, 116.9, 111.1, 96.0, 47.5. LCMS (HpH): t_R = 1.19 min, [M-H^{+}] 209.1.

Failed synthesis of tert-butyl (2-cyanophenyl)carbamate (3.16)



To a stirred solution of 2-aminobenzonitrile (**3.10**) (1.5 g, 12.7 mmol, 1 eq) in THF (30 mL) was added *base* (NEt_3 or NaH, 1.1 eq), followed by Boc-anhydride (**3.15**) (3.3 mL, 14 mmol, 1.1 eq). The reaction stirred at RT overnight, then heated at 70 ^{o}C for 6 h. LCMS of crude reaction mixture showed no conversion of **3.10**, reaction abandoned.

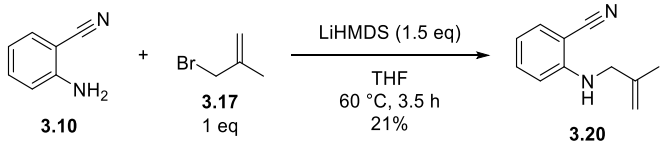
2-((2-Methylallyl)oxy)benzonitrile (3.19)



To a solution of 2-hydroxybenzonitrile (**3.18**) (251 mg, 2.11 mmol, 1 eq) and K_2CO_3 (436 mg, 3.15 mmol, 1.5 eq) in acetone (2 mL), 3-bromo-2-methylprop-1-ene (**3.17**) (398 mg, 2.95 mmol, 1.4 eq) was added. The reaction was stirred at RT for 1 h and then heated at 60 ^oC for 1 h. The reaction was allowed to cool to RT and water added (10 mL), the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (10 mL), dried through a hydrophobic frit and evaporated *in vacuo* to afford **3.19** as a pale brown oil (367 mg, 2.10 mmol, 100%).

^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.58 (1H, dd, *J* = 7.6 and 1.7 Hz), 7.48-7.52 (1H, m), 6.98-7.02 (1H, m), 6.96 (1H, d, *J* = 8.8 Hz), 5.14-5.15 (1H, m), 5.03-5.04 (1H, m), 4.55 (2H, s), 1.85 (3H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 160.4, 139.6, 134.2, 133.7, 120.9, 116.4, 113.4, 122.7, 102.3, 72.4, 19.2 LCMS (Formic): t_R = 1.12 min, $[M+H^+]$ 174.1.

Synthesis of 2-((2-methylallyl)amino)benzonitrile (3.20) by alkylation

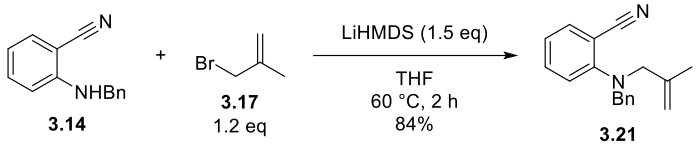


To a vial containing 2-aminobenzonitrile (**3.10**) (251 mg, 2.13 mmol, 1 eq) and 3-bromo-2-methylprop-1-ene (**3.17**) (211 µL, 2.09 mmol, 1 eq), LiHMDS (3.2 mL, 3.2 mmol, 1.5 eq) (1M, THF) was added. The reaction was stirred at 60 ^oC for 3.5 h, cooled to RT and water added (10 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), the combined organics dried through a hydrophobic frit and concentrated *in vacuo*. The crude brown oil was purified by automated reverse phase column chromatography on C18 silica gel (30-95% acetonitrile:water adjusted to *p*H 10 with

ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.20** as a light brown oil (75 mg, 0.44 mmol, 21%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.40 (2H, m), 6.65-6.69 (1H, m), 6.62 (1H, d, *J* = 8.3 Hz), 4.95-4.96 (1H, m), 4.91-4.93 (1H, m), 4.84 (1H, br. s), 3.77 (2H, d, *J* = 5.9 Hz), 1.79 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.3, 141.1, 134.1, 132.6, 117.9, 116.6, 111.6, 111.0, 95.7, 49.2, 20.2. LCMS (Formic): t_R = 1.15 min, [M+H$^+$] 173.1. HRMS: ($C_{11}H_{13}N_2$) [M+H$^+$] requires 173.1079, found [M+H$^+$] 173.1072 (error -4.0 ppm).

2-(Benzyl(2-methylallyl)amino)benzonitrile (3.14)

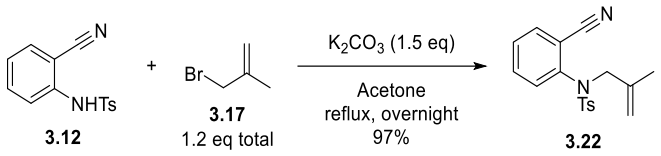


To 2-(benzylamino)benzonitrile (**3.14**) (248 mg, 1.19 mmol, 1 eq) and 3-bromo-2-methylprop-1-ene (**3.17**) (199 mg, 1.48 mmol, 1.2 eq), LiHMDS (1.8 mL, 1.8 mmol, 1.5 eq) (1M, THF) was added. The reaction was stirred at 60 ^{o}C for 2 h and then allowed to cool to RT. Water was then added (20 mL) and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-20% diethyl ether:cyclohexane). The resulting brown oil was re-purified by automated reverse phase column chromatography on C18 silica gel (50-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.21** as a yellow gum (262 mg, 1.00 mmol, 84%).

ν_{max} (neat): 3065, 3029, 2914, 2216, 1595, 1487, 1442, 749, 698 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.55 (1H, dd, *J* = 7.7 and 1.6 Hz), 7.33-7.38 (1H, m), 7.23-7.31 (5H, m), 6.88-6.93 (2H, m), 4.94-4.95 (1H, m), 4.90-4.91 (1H, m), 4.55 (2H, s), 3.87 (2H, s), 1.76 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 153.5, 141.2, 137.4, 135.1, 133.3, 128.5, 127.8, 127.3, 120.4, 119.9, 119.3, 113.1, 103.3, 58.1, 56.4, 20.3.

LCMS (HpH): t_R = 1.38 min, [M+H$^+$] 263.1. HRMS: ($C_{18}H_{18}N_2$) [M+H$^+$] requires 263.1548, found [M+H$^+$] 263.1553 (error 2.3 ppm).

_N_-(2-cyanophenyl)-4-methyl-_N_-(2-methylallyl)benzenesulfonamide (3.22)

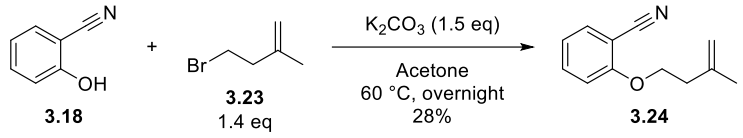


To a solution of *N*-(2-cyanophenyl)-4-methylbenzenesulfonamide (**3.12**) (249 mg, 0.92 mmol, 1 eq) in acetone (2 mL), K_2CO_3 (190 mg, 1.37 mmol, 1.5 eq) was added. Then 4-bromo-2-methylbut-1-ene (135 mg, 1.00 mmol, 1.1 eq) (**3.17**) was added slowly, and the reaction stirred at reflux overnight. Further 4-bromo-2-methylbut-1-ene (**3.17**) (12 mg, 0.10 mmol, 0.1 eq) was then added and the reaction stirred for a further 1 h at reflux. The reaction was allowed to cool to RT, water added (20 mL) and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The resulting crude yellow solid was purified by automated reverse phase column chromatography on C18 silica gel (50-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.22** as an off white solid (289 mg, 0.89 mmol, 97%).

M.pt.: 126-128 ^oC. ν_{max} (neat): 2920, 2237, 1347, 1155, 868, 573 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.61-7.64 (3H, m), 7.55 (1H, td, *J* = 7.8 and 1.5 Hz), 7.40 (1H, td, *J* = 7.6 and 1.0 Hz), 7.29-7.32 (1H, m), 7.24 (1H, dd, *J* = 8.3 and 1.0 Hz), 2.59 (2H, t, *J* = 6.8 Hz), 4.75-4.76 (1H, m), 4.69-4.70 (1H, m), 4.18 (2H, s), 2.45 (3H, s), 1.79 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 144.3, 141.4, 139.3, 134.9, 133.9, 133.1, 130.7, 129.8, 128.4, 128.1, 116.5, 116.4, 114.9, 57.2, 21.6, 20.0. LCMS (HpH): t_R = 1.22 min, [M+NH$_4^+$] 344.1. HRMS: ($C_{18}H_{18}N_2O_2S$) [M+H$^+$] requires 327.1167, found [M+H$^+$] 327.1171 (error 1.2 ppm).

2-((3-Methylbut-3-en-1-yl)oxy)benzonitrile (3.24)

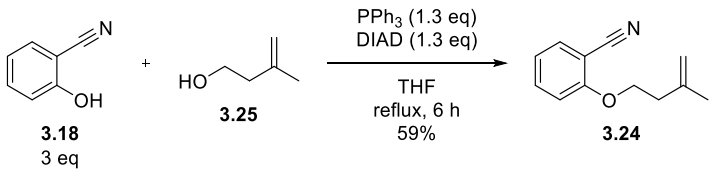
By Alkylation



To a solution of 2-hydroxybenzonitrile (**3.18**) (255 mg, 2.14 mmol, 1 eq) in acetone (2 mL), K_2CO_3 (445 mg, 3.25 mmol, 1.5 eq) was added. Then 4-bromo-2-methylbut-1-ene (**3.23**) (444 mg, 2.98 mmol, 1.4 eq) was added slowly, and the reaction stirred at 60 ^oC overnight. The reaction was allowed to cool to RT, water added (10 mL) and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The resulting brown oil was purified by automated reverse phase column chromatography on C18 silica gel (50-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.24** as a pale-yellow oil (111 mg, 0.59 mmol, 28%).

^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.49-7.56 (2H, m), 6.95-7.01 (2H, m), 4.87-4.88 (1H, m), 4.83-4.84 (1H, m), 4.18 (2H, t, *J* = 6.9 Hz), 2.57 (2H, t, *J* = 6.9 Hz), 1.84 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 160.6, 141.6, 134.2, 133.8, 120.7, 116.4, 112.6, 112.2, 102.3, 67.8, 36.9, 22.9. LCMS (Formic): t_R = 1.19 min, $[M+H^+]$ 188.1. HRMS: ($C_{12}H_{13}NO$) $[M+H^+]$ requires 188.1075, found $[M+H^+]$ 188.1073 (error -1.1 ppm).

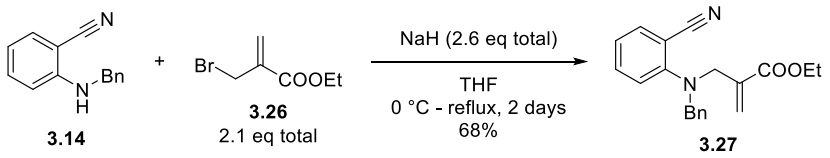
By Mitsunobu



To a solution of 2-hydroxybenzonitrile (**3.18**) (801 mg, 6.72 mmol, 3 eq), 3-methylbut-3-en-1-ol (193 mg, 2.24 mmol, 1 eq) (**3.25**) and PPh_3 (764 mg, 2.91 mmol, 1.3 eq) in

THF (8 mL), was added diisopropyl azodicarboxylate (DIAD) (0.57 mL, 2.93 mmol, 1.3 eq). The reaction was stirred at 70 ^{o}C (reflux) for 6 h. The reaction was stopped, allowed to cool to RT and then concentrated *in vacuo*. The resulting oil was purified by automated reverse phase column chromatography on C18 silica gel (30-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to yield the desired product as a colourless oil with 5% triphenylphosphine oxide impurity. The crude oil was dissolved in ether, loaded onto a short silica plug and eluted with further ether. The resulting organics were cooled over ice, resulting in precipitation of a white solid, which was removed by filtration. The filtrate was dried *in vacuo* to yield **3.24** as colourless oil (247 mg, 1.32 mmol, 59%). Spectroscopic data consistent with previously synthesised **3.24**.

Ethyl 2-((benzyl(2-cyanophenyl)amino)methyl)acrylate (3.27)

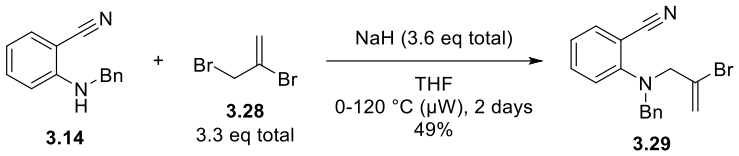


To a flask containing NaH (124 mg, 3.11 mmol, 1.6 eq) (60% dispersion in mineral oil) at 0 ^{o}C was added THF (2 mL). A solution of 2-(benzylamino)benzonitrile (**3.14**) (417 mg, 2.00 mmol, 1 eq) in THF (2 mL) was added dropwise, the reaction stirred for 5 min at 0 ^{o}C and 10 min at RT. The reaction was then returned to 0 ^{o}C and a solution of ethyl 2-(bromomethyl)acrylate (**3.26**) (426 mg, 2.21 mmol, 1.1 eq) in THF (2 mL) was added. The reaction was stirred for 2 h at 0 ^{o}C, 2 h at RT and then overnight at reflux. The reaction was allowed to come to RT and then further additions of NaH (80 mg, 2.00 mmol, 1 eq) (60% dispersion in mineral oil) and ethyl 2-(bromomethyl)acrylate (**3.26**) (386 mg, 2.00 mmol, 1 eq) were made. The reaction was stirred at reflux overnight. Water (50 mL) was then added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane).

Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.27** as a purple oil (434 mg, 1.35 mmol, 68%).

ν_{max} (neat): 3030, 2982, 2218, 1710, 1595, 1488, 1129, 737, 698 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.55 (1H, dd, *J* = 8.0 and 1.6 Hz), 7.33-7.38 (1H, m), 7.22-7.31 (5H, m), 6.90-6.94 (2H, m), 6.30-6.31 (1H, m), 5.75-5.76 (1H, m), 4.54 (2H, s), 4.21 (2H, s), 4.15 (2H, q, *J* = 7.2 Hz), 1.23 (3H, t, *J* = 7.2 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.3, 153.3, 137.2, 136.1, 134.9, 133.3, 128.6, 127.8, 127.4, 126.7, 120.9, 120.2, 119.0, 104.2, 60.9, 56.8, 52.3, 14.1. LCMS (HpH): t_R = 1.32 min, [M+H$^+$] 321.3. HRMS: ($C_{20}H_{20}N_2O_2$) [M+H$^+$] requires 321.1603, found [M+H$^+$] 321.1604 (error 0.3 ppm).

2-(Benzyl(2-bromoallyl)amino)benzonitrile (3.29)

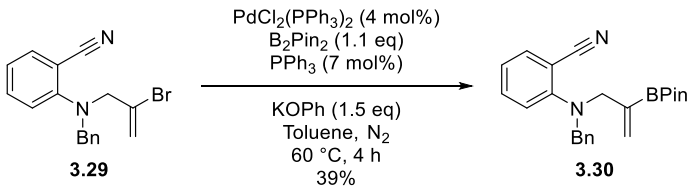


To a flask containing NaH (116 mg, 2.89 mmol, 1.2 eq) (60% dispersion in mineral oil) at 0 ^{o}C was added THF (5 mL). A solution of 2-(benzylamino)benzonitrile (**X**) (501 mg, 2.41 mmol, 1.0 eq) in THF (5 mL) was added dropwise, the reaction stirred for 5 min at 0 ^{o}C and 10 min at RT. The reaction was then returned to 0 ^{o}C and a solution of 2,3-dibromoprop-1-ene (**X**) (624 mg, 2.65 mmol, 1.1 eq) (85%, stabilised with Cu) in THF (1 mL) was added. The reaction was allowed to come to RT slowly and then stirred overnight. Further additions of NaH (116 mg, 2.90 mmol, 1.2 eq) (60% dispersion in mineral oil) and 2,3-dibromoprop-1-ene (**X**) (624 mg, 2.65 mmol, 1.1 eq) (85%, stabilised with Cu) were made. The reaction was stirred at reflux overnight. The reaction was allowed to come to RT slowly and then further NaH (116 mg, 2.90 mmol, 1.2 eq) (60% dispersion in mineral oil) was added. The reaction was heated at 120 ^{o}C in the microwave for 1 h. The reaction was allowed to come to RT slowly and then further additions of NaH (116 mg, 2.90 mmol, 1.2 eq) (60% dispersion in mineral oil) and 2,3-dibromoprop-1-ene (**X**) (624 mg, 2.65 mmol, 1.1 eq) (85%, stabilised with Cu) were made. The reaction was heated at 120 ^{o}C in the microwave for 4 h. The reaction

was allowed to cool to RT slowly, then water was added (40 mL) and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated reverse phase column chromatography on C18 silica gel (50-85% acetonitrile:water adjusted to *p*H 2 with TFA). Desired fractions were combined, and the solvent removed *in vacuo* to afford **X** as a brown oil (386 mg, 1.18 mmol, 49%)

ν_{max} (neat): 3063, 3029, 2852, 2218, 1595, 1488, 757, 698 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.56 (1H, dd, *J* = 7.7, 1.4 Hz), 7.40 (1H, ddd, *J* = 8.5, 7.2 and 1.7 Hz), 7.23-7.34 (5H, m), 7.01 (1H, dd, *J* = 8.6 and 0.5 Hz), 6.96 (1H, td, *J* = 7.5 and 1.0 Hz), 5.79-5.80 (1H, m), 5.59-5.60 (1H, m), 4.60 (2H, s), 4.20 (2H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.9, 136.8, 134.8, 133.4, 129.2, 128.6, 128.0, 127.6, 121.3, 120.8, 119.0, 118.9, 104.2, 59.5, 56.2. LCMS (Method B): t_R = 1.36 min, [M+H$^+$] 326.9/328.9. HRMS: ($C_{17}H_{16}BrN_2$) [M+H$^+$] requires 327.0497, found [M+H$^+$] 327.0496 (error -0.3 ppm).

2-(Benzyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)amino)benzonitrile (3.30)

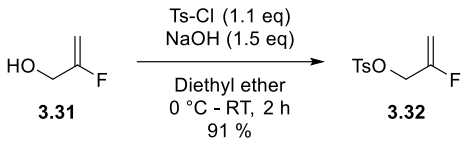


To a vial was added bis(pinacolato)diboron (B_2Pin_2) (44 mg, 0.17 mmol, 1.1 eq), PPh_3 (2.7 mg, 0.01 mmol, 7 mol%), $PdCl_2(PPh_3)_2$ (4.7 mg, 0.007 mmol, 4 mol%) and KOPh (31 mg, 0.24 mmol, 1.5 eq). The vial was sealed and degassed, filled with N_2 (procedure repeated x3) and then a degassed solution of 2-(benzyl(2-bromoallyl)amino)benzonitrile (**3.29**) (51 mg, 0.16 mmol, 1.0 eq) in toluene (1 mL) was added. The reaction was stirred at 60 ^{o}C for 4 h. The reaction was allowed to come to RT, then water was then added (10 mL) and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated

column chromatography on silica gel (0-10% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.30** as colourless gum (23 mg, 0.06 mmol, 39%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.49 (1H, dd, *J* = 7.8 and 1.7 Hz), 7.20-7.32 (6H, m), 6.82-6.86 (2H, m), 5.95-5.96 (1H, m), 5.76-5.77 (1H, m), 4.60 (2H, s), 4.09-4.10 (2H, m), 1.22 (12H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 153.2, 137.7, 135.1, 133.1, 130.8, 129.6, 128.5, 127.7, 127.1, 120.6, 119.6, 119.5, 115.3, 102.4, 83.6, 56.5, 55.1, 24.8. LCMS (Formic): t_R = 1.49 min, [M+H$^+$] 375.1.

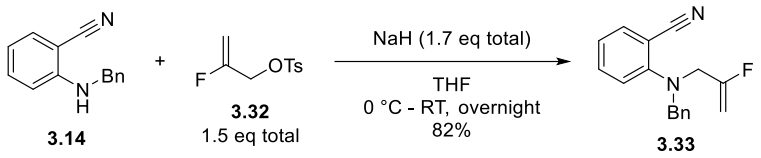
2-Fluoroallyl 4-methylbenzenesulfonate (3.32)



To a solution of tosyl-Cl (689 mg, 3.61 mmol, 1.1 eq) and NaOH (195 mg, 4.88 mmol, 1.5 eq) in ether (3 mL) at 0 ^{o}C, a solution of 2-fluoroprop-2-en-1-ol (**3.31**) (256 mg, 3.36 mmol, 1.0 eq) in ether (3 mL) was added. The reaction was allowed to come to RT slowly and stirred for 2 h. Water (25 mL) was added and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude oil was purified by automated column chromatography on silica gel (0-15% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.32** as a colourless oil (702 mg, 3.05 mmol, 91%).

ν_{max} (neat): 2958, 1361, 1174, 812, 668, 550 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.79-7.82 (2H, m Hz), 7.36 (2H, d, *J* = 7.8 Hz), 4.81 (1H, dd, *J* = 15.3 and 3.6 Hz), 4.64 (1H, dd, *J* = 46.5 and 3.4 Hz), 4.54 (2H, d, *J* = 14.2 Hz), 2.54 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 158.1 (d, *J* = 259.0 Hz), 145.2, 132.8, 129.9, 128.0, 96.2 (d, *J* = 16.1 Hz), 66.3 (d, *J* = 34.5 Hz), 21.7. ^{19}F{^{1}H} NMR (376 MHz, CHLOROFORM-d) δ = -106.16. LCMS (Formic): t_R = 1.08 min, [M+MeCN] 271.1. HRMS: ($C_{10}H_{11}FO_3S$) [M+H$^+$] requires 231.0491, found [M+H$^+$] 231.0492 (error 0.4 ppm).

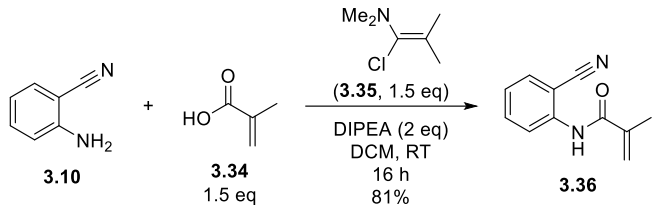
2-(Benzyl(2-fluoroallyl)amino)benzonitrile (3.33)



To a flask containing NaH (59 mg, 1.47 mmol, 1.2 eq) (60% dispersion in mineral oil) at 0 ^{o}C was added THF (3 mL). A solution of 2-(benzylamino)benzonitrile (**3.14**) (249 mg, 1.20 mmol, 1.0 eq) in THF (3 mL) was added dropwise, the reaction stirred for 5 min at 0 ^{o}C and 10 min at RT. The reaction was then returned to 0 ^{o}C and a solution of 2-fluoroallyl 4-methylbenzenesulfonate (**3.32**) (306 mg, 1.33 mmol, 1.1 eq) in THF (1 mL) was added. The reaction was allowed to come to RT slowly and stirred overnight at RT. Further additions of NaH (24 mg, 0.60 mmol, 0.5 eq) (60% dispersion in mineral oil) and 2-fluoroallyl 4-methylbenzenesulfonate (**3.32**) (70 mg, 0.30 mmol, 0.3 eq) were made. The reaction was stirred at RT for 2 h. Water was then added (25 mL) and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated reverse phase column chromatography on C18 silica gel (40-85% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.33** as a brown oil (261 mg, 0.98 mmol, 82%).

ν_{max} (neat): 3030, 2854, 2220, 1678, 1595, 1488, 1447, 761, 739, 697 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.57 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.40-7.44 (1H, m), 7.24-7.34 (5H, m), 7.07 (1H, d, *J* = 8.3 Hz), 6.99 (1H, td, *J* = 7.6 and 1.0 Hz), 4.69 (1H, dd, *J* = 17.0 and 3.1 Hz), 4.53 (2H, s), 4.32-4.45 (1H, m), 4.02 (2H, d, *J* = 13.9 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 161.9 (d, *J* = 261.9 Hz), 153.5, 137.0, 134.6, 133.4, 128.6, 128.2, 127.6, 121.9, 121.2, 118.6, 105.6, 93.5 (d, *J* = 16.9 Hz), 56.0, 52.5 (d, *J* = 30.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, CHLOROFORM-d) δ = -100.64. LCMS (HpH): t_R = 1.29 min, [M+H^{+}] 267.1. HRMS: ($C_{17}H_{16}FN_2$) [M+H^{+}] requires 267.1297, found [M+H^{+}] 267.1300 (error 1.1 ppm).

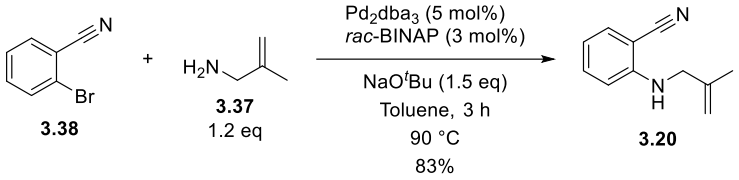
***N*-(2-cyanophenyl)methacrylamide (3.36)**



To methacrylic acid (**3.34**) (646 mg, 7.51 mmol, 1.5 eq) in DCM (20 mL) was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (**3.35**) (1 mL, 7.56 mmol, 1.5 eq) and the reaction stirred at RT for 5 mins. Then 2-aminobenzonitrile (**3.10**) (593 mg, 5.02 mmol, 1 eq) and DIPEA (1.75 mL, 10.02 mmol, 2 eq) added. The reaction stirred overnight (16 h) at RT, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-50% TBME:cyclohexane) to yield **3.36** (754 mg, 4.05 mmol, 81%) as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.50 (1H, d, *J* = 8.6 Hz), 8.08 (1H, br. s), 7.58-7.63 (2H, m), 7.18 (1H, td, *J* = 7.6 and 1.1 Hz), 5.94 (1H, d, *J* = 1.0 Hz), 5.58 (1H, q, *J* = 1.5 Hz), 2.11 (3H, dd, *J* = 1.6 and 0.9 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.2, 140.6, 139.9, 134.3, 132.1, 124.1, 121.7, 120.9, 116.3, 102.0, 18.5. LCMS (HpH): t_R = 0.75 min, [M+H$^+$] 187.2.

2-((2-Methylallyl)amino)benzonitrile (3.20) by Buchwald-Hartwig cross-coupling

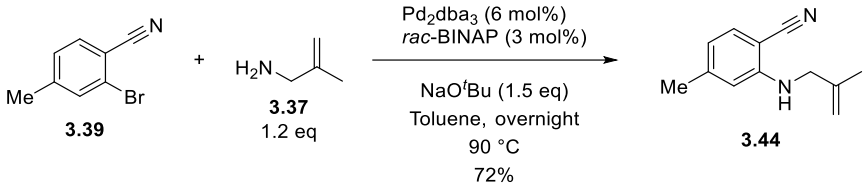


To a vial was added 2-bromobenzonitrile (**3.38**) (1.46 g, 8.02 mmol, 1 eq), $Pd_2(dba)_3$ (338 mg, 0.37 mmol, 5 mol%), *rac*-BINAP (150 mg, 0.24 mmol, 3 mol%) and NaO^{t}Bu (1.15 g, 11.98 mmol, 1.5 eq), the vial was sealed and purged with nitrogen. In a separate vial, a solution of 2-methylprop-2-en-1-amine (**3.37**) (704 mg, 9.89 mmol, 1.2 eq) in toluene (16 mL) was sealed and purged with nitrogen. The solution was transferred to the solids under nitrogen and the reaction stirred at 90 ^{o}C for 3 h. The

reaction was allowed to come to RT, then water added (75 mL) and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane) to afford **3.20** as a yellow solid (1.15 g, 6.68 mmol, 83%).

M.pt.: 57-59 ^{o}C. ν_{max} (neat): 3374, 3078, 2911, 2213, 748 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.39 (2H, m), 6.66 (1H, td, *J* = 7.8 and 1.0 Hz), 6.62 (1H, d, *J* = 8.6 Hz), 4.94-4.97 (1H, m), 4.90-4.93 (1H, m), 4.85 (1H, br. s), 3.77 (2H, d, *J* = 5.9 Hz), 1.78 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.3, 141.1, 134.1, 132.6, 117.9, 116.6, 111.7, 111.0, 95.7, 49.2, 20.2. LCMS (HpH): t_R = 1.14 min, [M+H$^+$] 173.1. HRMS: ($C_{11}H_{13}N_2$) [M+H$^+$] requires 173.1079, found [M+H$^+$] 173.1082 (error 1.7 ppm).

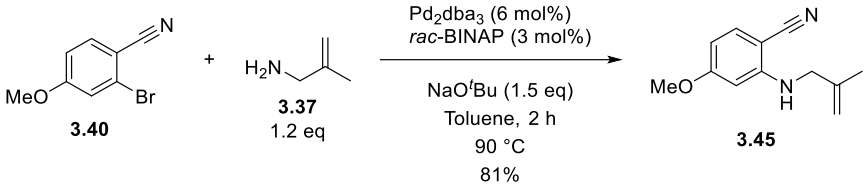
4-Methyl-2-((2-methylallyl)amino)benzonitrile (3.44)



To a vial was added 2-bromo-4-methylbenzonitrile (**3.39**) (480 mg, 2.45 mmol, 1.0 eq), $Pd_2(dba)_3$ (136 mg, 0.15 mmol, 6 mol%), *rac*-BINAP (47 mg, 0.08 mmol, 3 mol%) and NaO^{t}Bu (354 mg, 3.68 mmol, 1.5 eq), the vial was sealed and purged with N_2. In a separate vial, a solution of 2-methylprop-2-en-1-amine (**3.37**) (212 mg, 2.98 mmol, 1.2 eq) in toluene (10 mL) was sealed and purged with N_2. The solution was transferred to the solids under N_2 and the reaction stirred at 90 ^{o}C overnight. The reaction was allowed to come to RT, then water was added (50 mL) and the aqueous layer extracted with EtOAc (2 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) to afford **3.44** as an off-white solid (328 mg, 1.76 mmol, 72%).

M.pt.: 86-88 ^{o}C. ν_{max} (neat): 3357, 3086, 2976, 2918, 2219, 1612, 1576, 884, 789, 539 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.27 (1H, d, *J* = 8.1 Hz), 6.49 (1H, dd, *J* = 7.9 and 0.6 Hz), 6.42 (1H, s), 4.95 (1H, br. s), 4.92-4.91 (1H, m), 4.76 (1H, br. s), 3.76 (2H, d, *J* = 5.9 Hz), 2.30 (s, 3H), 1.79 (s, 3H).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.3, 145.2, 141.2, 132.4, 118.2, 118.0, 111.6, 111.4, 93.0, 49.2, 22.4, 20.2. LCMS (HpH): t_R = 1.21 min, [M+H$^+$] 187.2. HRMS: ($C_{12}H_{15}N_2$) [M+H$^+$] requires, 187.1235 found [M+H$^+$] 187.1239 (error 2.1 ppm).

4-Methoxy-2-((2-methylallyl)amino)benzonitrile (3.45)

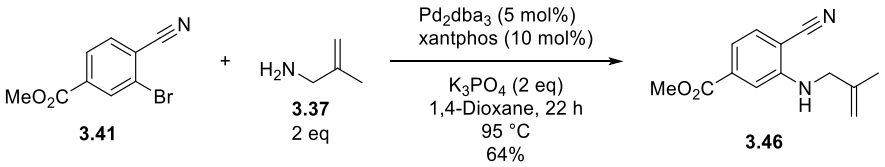


To a vial was added 2-bromo-4-methoxybenzonitrile (**3.40**) (1.067 g, 5.02 mmol, 1.0 eq), $Pd_2(dba)_3$ (278 mg, 0.30 mmol, 6 mol%), *rac*-BINAP (104 mg, 0.17 mmol, 3 mol%) and NaO^{t}Bu (725 mg, 7.55 mmol, 1.5 eq), the vial was sealed and purged with N_2. In a separate vial, a solution of 2-methylprop-2-en-1-amine (**3.37**) (432 mg, 6.08 mmol, 1.2 eq) in toluene (10 mL) was sealed and purged with N_2. The solution was transferred to the solids under nitrogen and the reaction stirred at 90 ^{o}C for 2 h. The reaction was allowed to come to RT, then water added (75 mL) and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) to afford **3.45** as a yellow solid (825 mg, 4.08 mmol, 81%).

M.pt.: 86-88 ^{o}C. ν_{max} (neat): 3371, 2916, 2842, 2207, 1611, 1568, 1521, 1306, 1214 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.31 (1H, d, *J* = 8.6 Hz), 6.24 (1H, dd, *J* = 8.6 and 2.4 Hz), 6.11 (1H, d, *J* = 2.2 Hz), 4.97 (1H, br. s), 4.93-4.94 (1H, m), 4.82 (1H, br. s), 3.79 (3H, s), 3.75 (2H, d, *J* = 5.9 Hz), 1.78 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 164.5, 152.1, 141.1, 134.2, 118.4, 111.8, 103.4, 96.4, 88.6, 55.3,

49.3, 20.1. LCMS (HpH): t_R = 1.13 min, [M+H$^+$] 203.1. HRMS: ($C_{12}H_{15}N_2O$) [M+H$^+$] requires 203.1184, found [M+H$^+$] 203.1188 (error 2.0 ppm).

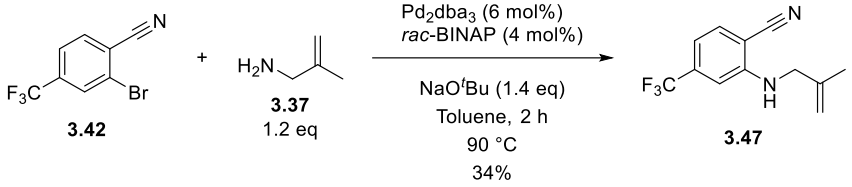
Ethyl 4-cyano-3-((2-methylallyl)amino)benzoate (3.46)



To a vial was added ethyl 3-bromo-4-cyanobenzoate (**3.41**) (1.264 g, 4.98 mmol, 1 eq), $Pd_2(dba)_3$ (220 mg, 0.24 mmol, 5 mol%), xantphos (285 mg, 0.49 mmol, 10 mol%) and K_3PO_4 (2.134 g, 10.05 mmol, 2 eq), the vial was sealed and purged with N_2. In a separate vial, a solution of 2-methylprop-2-en-1-amine (**3.37**) (728 mg, 10.23 mmol, 2 eq) in 1,4-dioxane (25 mL) was sealed and purged with N_2. The solution was transferred to the solids under nitrogen and the reaction stirred at 95 ^{o}C for 22 h. The reaction was allowed to come to RT, then water was added (150 mL) and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-20% TBME:cyclohexane, 1% NEt_3 additive) to afford **3.46** as a yellow solid (815 mg, 3.34 mmol, 64%).

M.pt.: 67-69 ^{o}C. ν_{max} (neat): 3298, 2967, 1600, 1229, 845 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.45 (1H, d, *J* = 8.6 Hz), 7.30-7.32 (2H, m), 4.94-4.98 (3H, m), 4.37 (2H, q, *J* = 7.1 Hz), 3.84 (2H, d, *J* = 5.9 Hz), 1.81 (3H, s), 1.39 (3H, t, *J* = 7.1 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.7, 150.2, 140.7, 135.5, 132.6, 117.1, 112.1, 112.0, 99.2, 61.5, 49.2, 20.2, 14.2. LCMS (HpH): t_R = 1.24 min, [M+H$^+$] 245.2. HRMS: ($C_{14}H_{17}N_2O_2$) [M+H$^+$] requires 245.1290, found [M+H$^+$] 245.1282 (error -3.3 ppm.

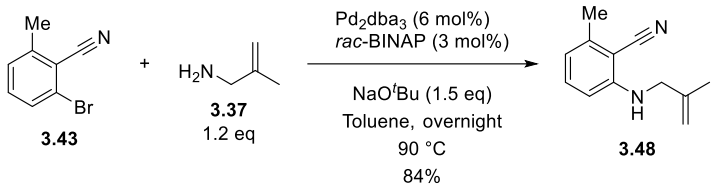
2-((2-Methylallyl)amino)-4-(trifluoromethyl)benzonitrile (3.47)



To a vial was added 2-bromo-4-(trifluoromethyl)benzonitrile (**3.42**) (1.27 g, 5.08 mmol, 1.0 eq), $Pd_2(dba)_3$ (281 mg, 0.31 mmol, 6 mol%), *rac*-BINAP (137 mg, 0.22 mmol, 4 mol%) and NaO^tBu (686 mg, 7.14 mmol, 1.4 eq), the vial was sealed and purged with N_2. In a separate vial, a solution of 2-methylprop-2-en-1-amine (**3.37**) (434 mg, 6.10 mmol, 1.2 eq) in toluene (10 mL) was sealed and purged with N_2. The solution was transferred to the solids under N_2 and the reaction stirred at 90 ^oC for 2 h. The reaction was allowed to come to RT, then water was added (75 mL) and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-5% EtOAc:cyclohexane, 1% NEt_3 additive) to afford **3.47** as a yellow solid (416 mg, 1.73 mmol, 34%).

M.pt.: 78-80 ^oC. ν_{max} (neat): 3379, 2970, 2218, 1329, 1116, 809 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.50 (1H, d, *J* = 8.1 Hz), 6.91 (1H, dd, *J* = 8.2 and 0.9 Hz), 6.84 (1H, s), 5.07 (1H, br. s), 4.97 (2H, s), 3.82 (2H, d, *J* = 5.9 Hz), 1.80 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.3, 140.2, 135.8 (q, *J* = 33.0 Hz), 133.3, 123.3 (q, *J* = 272.9 Hz) 116.6, 112.9 (q, *J* = 3.7 Hz), 112.3, 107.8 (q, *J* = 4.4 Hz), 98.7, 49.2, 20.1. $^{19}F\{^1H\}$ NMR (376 MHz, CHLOROFORM-d) δ = -64.0. LCMS (HpH): t_R = 1.28 min, [M-H^+] 239.2. HRMS: ($C_{12}H_{12}F_3N_2$) [M+H^+] requires 241.0952, found [M+H^+] 241.0953 (error 0.4 ppm).

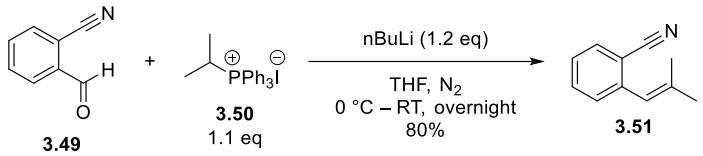
2-Methyl-6-((2-methylallyl)amino)benzonitrile (3.48)



To a vial was added 2-bromo-6-methylbenzonitrile (**3.43**) (487 mg, 2.48 mmol, 1.0 eq), $Pd_2(dba)_3$ (132 mg, 0.15 mmol, 6 mol%), *rac*-BINAP (48 mg, 0.08 mmol, 3 mol%) and NaO^tBu (359 mg, 3.74 mmol, 1.5 eq), the vial was sealed and purged with N_2. In a separate vial, a solution of 2-methylprop-2-en-1-amine (**3.37**) (213 mg, 3.00 mmol, 1.2 eq) in toluene (10 mL) was sealed and purged with N_2. The solution was transferred to the solids under N_2 and the reaction stirred at 90 ^oC overnight. The reaction was allowed to come to RT, then water added (50 mL) and the aqueous layer extracted with EtOAc (2 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) to afford **3.48** as a yellow solid (388 mg, 2.08 mmol, 84%).

M.pt.: 77-79 ^oC. ν_{max} (neat): 3372, 3075, 2912, 2210, 1580, 886, 777 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.22 (1H, t, *J* = 7.8 Hz), 6.53 (1H, d, *J* = 7.6 Hz), 6.44 (1H, d, *J* = 8.6 Hz), 4.94-4.95 (1H, m), 4.90-4.92 (1H, m), 4.82 (1H, br. s.), 3.76 (2H, s), 2.44 (3H, s), 1.78 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.7, 142.4, 141.2, 133.5, 117.9, 117.2, 111.6, 108.1, 96.6, 49.3, 20.8, 20.2. LCMS (HpH): t_R = 1.21 min, $[M+H^+]$ 187.0. HRMS: ($C_{12}H_{15}N_2$) $[M+H^+]$ requires 187.1235, found $[M+H^+]$ 187.1234 (error -0.5 ppm).

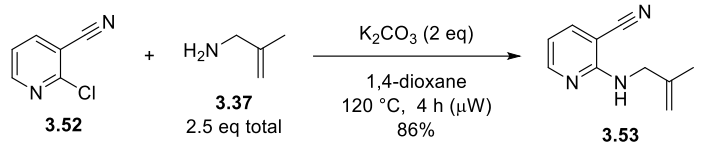
2-(2-Methylprop-1-en-1-yl)benzonitrile (3.51)



To a stirred solution of isopropyltriphenylphosphonium iodide (**3.50**) (1.816 g, 4.20 mmol, 1.1 eq) in THF (20 mL) at 0 ^{o}C, n-BuLi (1.8 mL, 4.6 mmol, 1.2 eq) (2.5M, hexanes) was added slowly under N_2. A solution of 2-formylbenzonitrile (**X**) (501 mg, 3.82 mmol, 1.0 eq) in THF (5 mL) was then added dropwise and the reaction was allowed to come to RT slowly and stirred overnight. Water (50 mL) was then added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude brown oil was purified by automated column chromatography on silica gel (0-10% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **X** as a colourless oil (483 mg, 3.07 mmol, **80%**).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.61 (1H, dd, *J* = 7.7 and 1.3 Hz), 7.52 (1H, td, *J* = 7.7 and 1.2 Hz), 7.35 (1H, d, *J* = 7.8 Hz), 7.27 (1H, td, *J* = 7.6 and 1.2 Hz), 6.43 (1H, s), 1.96 (3H, d, *J* = 1.5 Hz), 1.81 (3H, d, *J* = 1.5 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 142.3, 140.4, 132.6, 132.1, 129.7, 126.3, 121.6, 118.3, 112.2, 26.5, 19.6. LCMS (HpH): t_R = 1.17 min, [M+H^{+}] 158.0.

2-((2-Methylallyl)amino)nicotinonitrile (3.53)

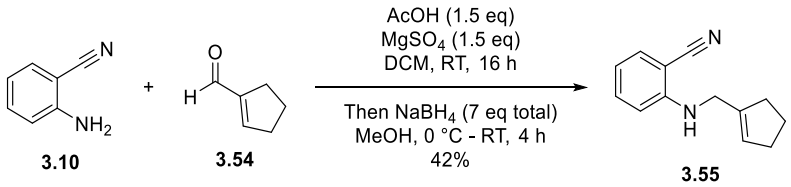


To 2-chloronicotinonitrile (**3.52**) (1.385 g, 10.00 mmol, 1.0 eq) and 2-methylprop-2-en-1-amine (**3.37**) (1.075 g, 15.12 mmol, 1.5 eq) dissolved in 1,4-dioxane (20 mL), was added K_2CO_3 (2.784 g, 20.14 mmol, 2 eq). The reaction was stirred in the microwave at 120 ^{o}C for 2 h. Then further 2-methylprop-2-en-1-amine (**3.37**) (0.7144 g, 10.04 mmol, 1.0 eq) was added and the reaction resumed in the microwave at 120 ^{o}C for 2

h. Water (100 mL) was added and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-20% EtOAc:cyclohexane, 1% NEt_3 additive) to afford **3.53** as a white solid (1.492 g, 8.61 mmol, 86%).

M.pt.: 56-58 ^{o}C. ν_{max} (neat): 3368, 2969, 2217, 1580, 1523, 757 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.28 (1H, dd, *J* = 5.0 and 1.8 Hz), 7.65 (1H, dd, *J* = 7.6 and 2.0 Hz), 6.60 (1H, dd, *J* = 7.7 and 5.0 Hz), 5.29 (1H, br. s), 4.91-4.92 (1H, m), 4.88-4.89 (1H, m), 4.10 (2H, d, *J* = 5.9 Hz), 1.80 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 158.4, 152.8, 142.0, 141.3, 116.7, 112.1, 110.9, 91.5, 46.6, 20.5. LCMS (HpH): t_R = 0.97 min, [M+H$^+$] 174.2. HRMS: ($C_{10}H_{12}N_3$) [M+H$^+$] requires 174.1031, found [M+H$^+$] 174.1036 (error 2.9 ppm).

2-((Cyclopent-1-en-1-ylmethyl)amino)benzonitrile (3.55)

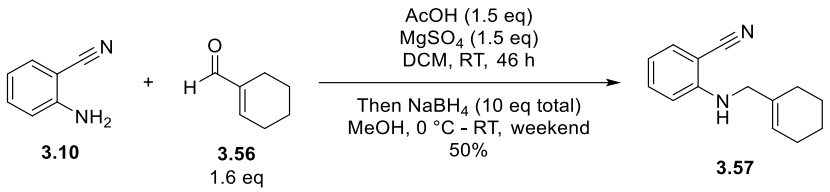


To 2-aminobenzonitrile (**3.10**) (766 mg, 6.48 mmol, 1 eq) and cyclopent-1-ene-1-carbaldehyde (**3.54**) (626 mg, 6.51 mmol, 1 eq) dissolved in DCM (13 mL), was added acetic acid (AcOH) (0.56 mL, 9.72 mmol, 1.5 eq) and $MgSO_4$ (1.17 g, 9.72 mmol, 1.5 eq). The reaction was stirred at RT for 16 h, then filtered and the filtrate concentrated *in vacuo*. The crude imine was re-dissolved in methanol (13 mL) and then sodium borohydride ($NaBH_4$) (494 mg, 13.06 mmol, 2 eq) was added portion-wise over ice and the reaction stirred for 2 h at RT. Further $NaBH_4$ (1.264 g, 33.40 mmol, 5 eq) was added portion-wise over ice and the reaction stirred at RT for a further 2 h. Water was added (100 mL) and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column

chromatography on silica gel (0-10% EtOAc:cyclohexane, 1% NEt_3 additive) to afford **3.55** as an off-white solid (545 mg, 2.75 mmol, 42%).

M.pt.: 46-49 ^{o}C. ν_{max} (neat): 3369, 3060, 2922, 2842, 2217, 1607, 1521, 744 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.39 (2H, m), 6.64-6.68 (2H, m), 5.60-5.62 (1H, m), 4.76 (1H, br. s), 3.87 (2H, s), 2.30-2.38 (4H, m), 1.89-1.96 (2H, m).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.4, 140.4, 134.1, 132.6, 126.7, 117.9, 116.5, 110.9, 95.7, 44.0, 33.5, 32.3, 23.3. LCMS (HpH): t_R = 1.31 min, [M-H$^+$] 197.1. HRMS: ($C_{13}H_{15}N_2$) [M+H$^+$] requires 199.1235, found [M+H$^+$] 199.1228 (error -3.5 ppm).

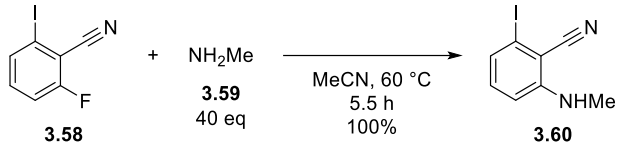
2-((Cyclohex-1-en-1-ylmethyl)amino)benzonitrile (3.57)



To 2-aminobenzonitrile (**3.10**) (1.178 g, 9.97 mmol, 1 eq) and cyclohex-1-ene-1-carbaldehyde (**3.56**) (1.756 g, 15.94 mmol, 1.6 eq) dissolved in DCM (20 mL), was added acetic acid (AcOH) (0.86 mL, 14.96 mmol, 1.5 eq) and $MgSO_4$ (1.801 g, 14.96 mmol, 1.5 eq). The reaction was stirred at RT for 48 h, then filtered and the filtrate concentrated *in vacuo*. The crude imine was re-dissolved in methanol (20 mL) and then sodium borohydride ($NaBH_4$) (770 mg, 20.34 mmol, 2 eq) was added portion-wise over ice and the reaction stirred for 2 h at RT. Further $NaBH_4$ (1.885 g, 49.80 mmol, 5 eq) was added portion-wise over ice and the reaction stirred at RT for a further 1 h. A final addition of $NaBH_4$ (1.141 g, 30.20 mmol, 3 eq) was added portion-wise over ice and the reaction stirred at RT over the weekend. Water (150mL) was added and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10 EtOAc:cyclohexane, 1% NEt_3 additive) to afford **3.57** as an off-white solid (1.064 g, 5.01 mmol, 50%).

M.pt.: 73-75 °C. ν_{max} (neat): 3371, 3026, 2926, 2852, 2214, 1606, 1572, 746 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.38 (2H, m), 6.63-6.66 (2H, m), 5.67-5.69 (1H, m), 4.70 (1H, br. s), 3.70 (2H, d, *J* = 4.9 Hz), 1.98-2.07 (4H, m), 1.55-1.69 (4H, m).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.6, 134.1, 133.6, 132.6, 123.9, 118.0, 116.3, 111.0, 95.5, 49.6, 26.5, 25.0, 22.6, 22.3. LCMS (HpH): t_R = 1.39 min, [M-H^+] 211.3. HRMS: ($C_{14}H_{17}N_2$) [M+H^+] requires 213.1386, found [M+H^+] 213.1379 (error -3.4 ppm).

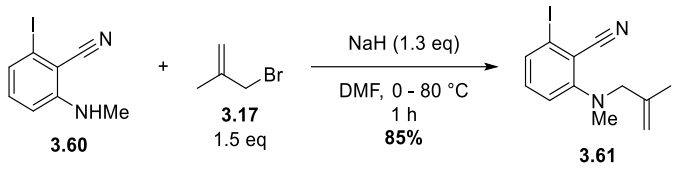
2-Iodo-6-(methylamino)benzonitrile (3.60)



To 2-fluoro-6-iodobenzonitrile (**3.58**) (3.057 g, 12.38 mmol, 1.0 eq) dissolved in MeCN (25 mL), was added methylamine (**3.59**) (43 mL, 495 mmol, 40 eq) (40% wt. in H_2O) and the reaction was stirred at 60 °C for 5.5 h. The reaction was allowed to come to RT slowly and then EtOAc (125 mL) added, the organic layer washed with sat. $NaHCO_{3(aq)}$ (2 x 200 mL). The organics were passed through a hydrophobic frit and dried *in vacuo* to afford **3.60** as an off-white solid (3.197 g, 12.39 mmol, 100%).

M.pt.: 120-121 °C. ν_{max} (neat): 3367, 2217, 1595, 1559, 1459, 1061, 759 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.05-7.13 (2H, m), 6.61 (1H, d, *J* = 8.3 Hz), 4.78 (1H, br. s), 2.91 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.9, 134.7, 126.6, 118.7, 109.3, 103.5, 98.4, 30.1. LCMS (HpH): t_R = 1.12 min, [M-H^+] 257.0. HRMS: ($C_8H_8IN_2$) [M+H^+] requires 258.9732, found [M+H^+] 258.9723 (error -3.5 ppm).

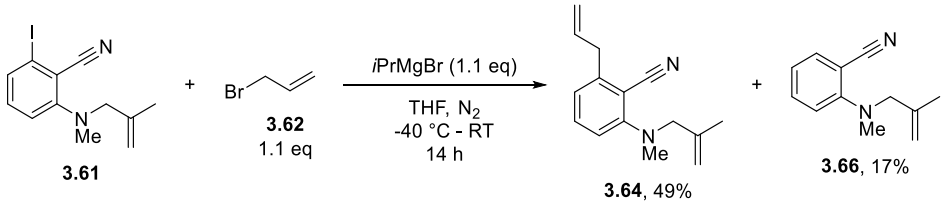
2-Iodo-6-(methyl(2-methylallyl)amino)benzonitrile (3.61)



To a suspension of NaH (623 mg, 15.59 mmol, 1.3 eq) (60% dispersion in mineral oil) in DMF (12 mL) at 0 ^{o}C, was added dropwise a solution of **3.60** (3.130 g, 12.13 mmol, 1.0 eq) in DMF (12 mL). The reaction was stirred at RT for 15 mins, cooled back to 0 ^{o}C and then 3-bromo-2-methylprop-1-ene (**3.17**) (2.471 g, 18.30 mmol, 1.5 eq) was added dropwise. The resulting mixture was heated at 80 ^{o}C for 1 h, allowed to cool to RT and then water (200 mL) added. The aqueous layer was extracted with EtOAc (2 x 100 mL), the combined organics passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane) to afford **3.61** as a yellow oil (3.228 g, 10.34 mmol, 85%).

ν_{max} (neat): 3077, 2937, 2212, 1579, 1539, 1440 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.35 (1H, dd, *J* = 7.8 and 1.0 Hz), 7.01-7.05 (1H, m), 6.88-6.91 (1H, m), 4.94-4.95 (1H, m), 4.88-4.89 (1H, m), 3.83 (2H, s), 2.98 (3H, s), 1.73 (3H, s) .^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 157.1, 140.7, 133.6, 130.2, 119.9, 117.5, 113.0, 190.2, 101.5, 61.1, 40.5, 20.0. LCMS (HpH): t_R = 1.34 min, [M+H^{+}] 313.1. HRMS: ($C_{12}H_{14}IN_2$) [M+H^{+}] requires 313.0202, found [M+H^{+}] 313.0195 (error -2.2 ppm).

2-Allyl-6-(methyl(2-methylallyl)amino)benzonitrile (3.64)



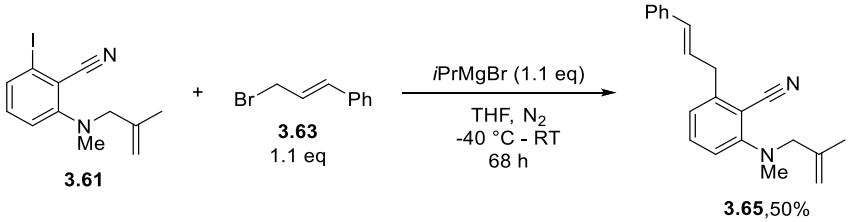
A solution of **3.61** (1.567 g, 5.02 mmol, 1.0 eq) in THF (50 mL), under N_2, was cooled over a bath of dry ice/MeCN. To this was added isopropylmagnesium bromide (5.5 mL, 5.5 mmol, 1.1 eq) (1M in THF) dropwise and the reaction stirred for 30 mins. Then

3-bromoprop-1-ene (**3.62**) (692 mg, 5.72 mmol, 1.1 eq) in THF (1 mL) was added and the reaction left to warm to RT slowly and stirred overnight (14 h). The reaction mixture was concentrated *in vacuo* to remove THF, then water (200 mL with 5 mL 2M $HCl_{(aq)}$ additive) was added and the aqueous layer extracted with EtOAc (3 x 75 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-10 TBME:cyclohexane) to afford a mixture of **3.64** and *des*-iodo starting material **3.66**. Further purification by automated reverse phase column chromatography on C18 silica gel (40-85% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate) afforded **3.64** as a brown oil (560 mg, 2.48 mmol, 49%).

3.64: ν_{max} (neat): 3078, 2919, 2227, 1598, 1492, 1450, 1289, 1258, 752 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.26-7.34 (1H, m), 6.77-6.82 (2H, m), 5.91-6.01 (1H, m), 5.14 (1H, dq, *J* = 7.6 and 1.6 Hz), 5.11 (1H, t, *J* = 1.5 Hz), 4.93-4.94 (2H, m), 3.81 (2H, s), 3.55-3.57 (2H, m), 2.94 (3H, s), 1.76 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 156.2, 145.8, 141.5, 135.3, 132.8, 120.6, 117.9, 117.0, 116.0, 112.8, 103.1, 61.7, 40.4, 39.0, 20.1. LCMS (HpH): t_R = 1.37 min, $[M+H^+]$ 227.4. HRMS: ($C_{15}H_{19}N_2$) $[M+H^+]$ requires 227.1548 found $[M+H^+]$ 227.1550 (error 0.8 ppm).

3.66 (159 mg, 0.85 mmol, 17%) was isolated as a brown oil also. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.49 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.38 (1H, ddd, *J* = 8.7, 7.2 and 1.7 Hz), 6.88 (1H, d, *J* = 8.8 Hz), 6.80-6.83 (1H, m), 4.93-4.94 (1H, m), 4.89-4.90 (1H, m), 3.88 (2H, s), 3.01 (3H, s), 1.76 (3H, s). LCMS (HpH): t_R = 1.21 min, $[M+H^+]$ 187.3.

2-Cinnamyl-6-(methyl(2-methylallyl)amino)benzonitrile (3.65)

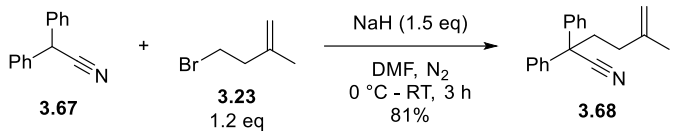


A solution of **3.61** (624 mg, 2.00 mmol, 1.0 eq) in THF (20 mL), under N_2, was cooled over a bath of dry ice/MeCN. To this was added isopropylmagnesium bromide (2.1

mL, 2.1 mmol, 1.1 eq) (1M in THF) dropwise and the reaction stirred for 30 mins. Then 3-bromo-1-phenyl-1-propene (**3.63**) (423 mg, 2.15 mmol, 1.1 eq) in THF (2 mL) was added and the reaction left to warm to RT slowly and stirred over the weekend (68 h). The reaction mixture was concentrated *in vacuo* to remove THF, then water (100 mL with 2.5 mL 2M $HCl_{(aq)}$ additive) was added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-10 TBME:cyclohexane) to afford a mixture of **3.65** and *des*-iodo starting material. Further purification by automated reverse phase column chromatography on C18 silica gel (40-85% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate) afforded **3.65** as a brown oil (302 mg, 1.00 mmol, 50%).

ν_{max} (neat): 2968, 2213, 1586, 1574, 1449 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.34-7.37 (2H, m), 7.26-7.32 (3H, m), 7.18-7.22 (1H, m), 6.82 (2H, t, *J* = 7.1 Hz), 6.50-6.54 (1H, m), 6.29-6.36 (1H, m), 4.93-4.94 (1H, m), 3.82 (2H, s), 3.71 (2H, dd, *J* = 6.9 and 1.0 Hz), 2.95 (3H, s), 1.76 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 156.3, 146.0, 141.5, 137.2, 132.9, 132.2, 128.5, 127.3, 127.0, 126.3, 120.6, 118.0, 116.1, 112.8, 102.9, 61.7, 40.4, 38.2, 20.1. LCMS (HpH): t_R = 1.53 min, $[M+H^+]$ 303.1. HRMS: ($C_{21}H_{23}N_2$) $[M+H^+]$ requires 303.1861 found $[M+H^+]$ 303.1861 (error 0.0 ppm).

5-Methyl-2,2-diphenylhex-5-enenitrile (3.68)

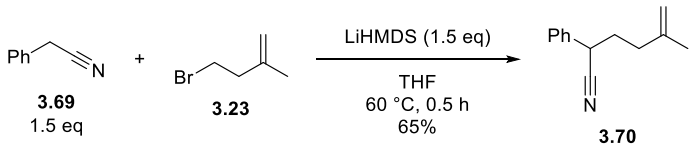


To a N_2 flushed flask containing NaH (187 mg, 4.69 mmol, 1.5 eq) (60% dispersion in mineral oil) at 0 °C was added DMF (2 mL). A solution of 2,2-diphenylacetonitrile (**3.67**) (587 mg, 3.04 mmol, 1 eq) in DMF (2 mL) was added dropwise, the reaction stirred for 5 min at 0 °C and 10 min at RT. The reaction was then returned to 0 °C and a solution of 4-bromo-2-methylbut-1-ene (**3.23**) (546 mg, 3.66 mmol, 1.2 eq) in DMF (2 mL) was added. The reaction was allowed to come to RT slowly and then stirred for 3 h under N_2. Water was then added (50 mL) and the aqueous layer extracted with

EtOAc (3 x 25 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated reverse phase column chromatography on C18 silica gel (40-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.68** as a colourless oil (646 mg, 2.47 mmol, 81%).

ν_{max} (neat): 3063, 2936, 2236, 1449, 751, 695 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.41 (8H, m), 7.26-7.30 (2H, m), 4.75 (1H, br. s), 4.71 (1H, br. s), 2.49-2.53 (2H, m), 2.10-2.15 (2H, m), 1.72 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 144.3, 140.1, 128.9, 127.9, 126.9, 122.2, 110.6, 51.6, 38.0, 33.6, 22.7. LCMS (Formic): t_R = 1.43 min, $[M+H^+]$ 262.3. HRMS: ($C_{19}H_{19}N$) $[M+H^+]$ requires 262.1596, found $[M+H^+]$ 262.1598 (error 0.8 ppm).

5-Methyl-2-phenylhex-5-enenitrile (3.70)

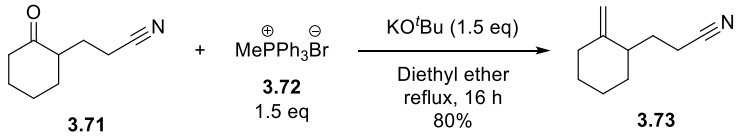


To a nitrogen-flushed flask containing 2-phenylacetonitrile (**3.69**) (1.499 g, 12.80 mmol, 1.5 eq) was added LiHMDS (13.2 mL, 13.20 mmol, 1.5 eq) (1M, THF), and the reaction stirred for 5 min at 60 ^{o}C. Then a solution of 4-bromo-2-methylbut-1-ene (**3.23**) (1.310 g, 8.79 mmol, 1.0 eq) in THF (15 mL) was added. The reaction was stirred for 30 min at 60 ^{o}C. Then water (100 mL) was added and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane) to afford a mixture of mono and bis alkylated products. Re-purification by TFA MDAP (method C) afforded **3.70** as a colourless oil (1.062 g, 5.73 mmol, 65%).

ν_{max} (neat): 3074, 3032, 2936, 2241, 1650, 1454, 892, 754, 697 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.29-7.40 (5H, m), 4.81 (1H, br. s), 4.75 (1H, br. s), 3.77

(1H, dd, *J* = 8.7 and 6.1 Hz), 2.18-2.22 (2H, t, *J* = 7.5 Hz), 1.95-2.10 (2H, m), 1.72 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 143.3, 135.9, 129.1, 128.1, 127.3, 120.7, 111.6, 36.7, 34.9, 33.8, 22.3. LCMS (HpH): t_R = 1.24 min, [M-H$^+$] 184.2. HRMS: ($C_{13}H_{16}N$) [M+H$^+$] requires 186.1283, found [M+H$^+$] 186.1288 (error 2.7 ppm).

3-(2-Methylenecyclohexyl)propanenitrile[99] (3.73)

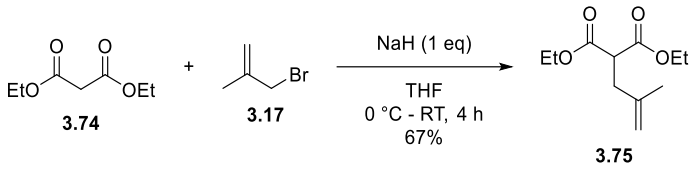


3.71 3.73

A solution of KO^{t}Bu (1.684 g, 15.01 mmol, 1.5 eq) and methyltriphenylphosphonium bromide (**3.72**) (5.371 g, 15.04 mmol, 1.5 eq) in diethyl ether (40 mL) were stirred for 30 mins. Then 3-(2-oxocyclohexyl)propanenitrile (**3.71**) (1.526 g, 10.09 mmol, 1 eq) in diethyl ether (5 mL) was added dropwise. The resulting solution stirred at reflux overnight (*ca.* 16 hrs). The reaction stopped, water (100 mL) added and the aqueous layer extracted with diethyl ether (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-6% EtOAc:cyclohexane) **3.73** (1.203 g, 8.06 mmol, 80%) as a colourless oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.74-4.75 (1H, m), 4.60 (1H, s), 2.28-2.40 (2H, m), 2.14-2.24 (2H, m), 2.03-2.09 (1H, m), 1.93-2.01 (1H, m), 1.76 (1H, ddt, *J* = 12.7, 8.4 and 4.3 Hz), 1.48-1.69 (5H, m), 1.31-1.39 (1H, m).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.2, 119.9, 107.3, 42.0, 33.9, 33.3, 28.4, 27.6, 23.5, 15.2.

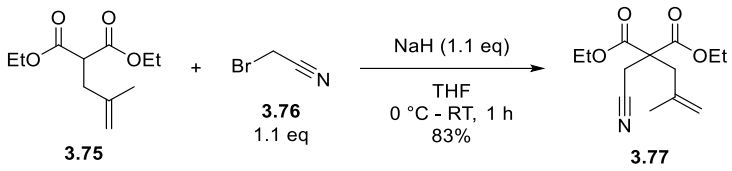
Diethyl 2-(2-methylallyl)malonate[100] (3.75)



To a suspension of NaH (400 mg, 10.01 mmol, 1 eq) (60% dispersion in mineral oil) in THF (20 mL) was added diethyl malonate (**3.74**) (1.61 g, 10.05 mmol, 1 eq) in THF (5 mL) over ice. After stirring for 30 mins, 3-bromo-2-methylprop-1-ene (**3.17**) (1.426 g, 10.56 mmol, 1 eq) was added. The reaction mixture was allowed to warm to RT and stirred for 4 h. The reaction mixture was quenched with sat. $NH4Cl_{(aq)}$ (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined and dried via hydrophobic frit. The filtrate was concentrated *in vacuo*, and the residue was purified by automated column chromatography on silica gel (0-15% EtOAc:cyclohexane) to yield **3.75** (1.438 g, 6.71 mmol, 67%) as a colourless oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.78-4.79 (1H, m), 4.73 (1H, br. s), 4.19 (4H, q, *J* = 7.3 Hz), 3.57 (1H, t, *J* = 7.8 Hz), 2.62 (2H, d, *J* = 7.8 Hz), 1.75 (3H, s), 1.26 (6H, t, *J* = 7.3 Hz).

Diethyl 2-(cyanomethyl)-2-(2-methylallyl)malonate (3.77)

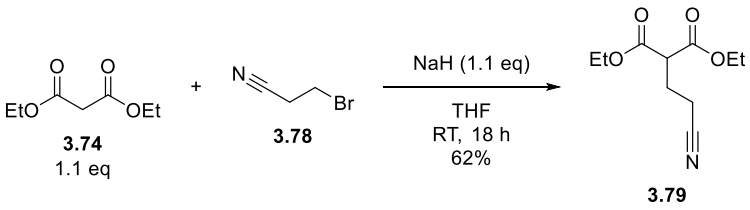


To a nitrogen-flushed flask containing NaH (113 mg, 2.82 mmol, 1.1 eq) (60% dispersion in mineral oil) over ice was added THF (5 mL). A solution of diethyl 2-(2-methylallyl)malonate (**3.75**) (536 mg, 2.50 mmol, 1 eq) in THF (2.5 mL) was added dropwise, the reaction stirred for 0.5 h at 0 ^{o}C. Then a solution of 2-bromoacetonitrile (**3.76**) (330 mg, 2.75 mmol, 1.1 eq) in THF (2.5 mL) was added. The reaction was allowed to come to RT slowly and then stirred for 1 h. Water (75 mL) was then added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were

passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-20 EtOAc:cyclohexane) to afford **3.77** as a colourless oil (525 mg, 2.07 mmol, 83%).

ν_{max} (neat): 2983, 1732, 1187 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.98-4.99 (1H, m), 4.92-4.93 (1H, m), 4.19-4.32 (4H, m), 2.95 (2H, s), 2.89 (2H, s), 1.66 (3H, s), 1.29 (6H, t, *J* = 7.1 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.8, 138.9, 117.5, 116.5, 62.5, 54.6, 40.5, 22.9, 21.7, 13.9. HRMS: ($C_{13}H_{20}NO_4$) [M+H^+] requires 254.1392, found [M+H^+] 254.1393 (error 0.4 ppm).

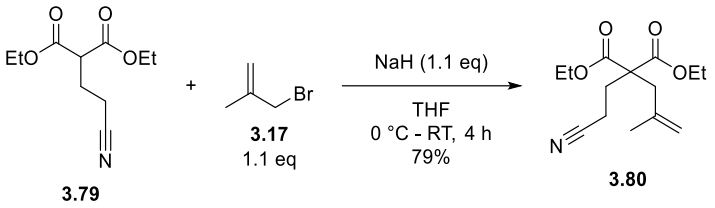
Diethyl 2-(2-cyanoethyl)malonate[101] **(3.79)**



To a stirred solution of diethyl malonate (**3.74**) (3.523 g, 21.99 mmol, 1.1 eq) in THF (20 mL) was added NaH (847 mg, 21.17 mmol, 1.1 eq) (60% dispersion in mineral oil) in several portions at RT, and the mixture was kept for 10 mins. Then bromopropanenitrile (**3.78**) (2.681 g, 20.01 mmol, 1 eq) was added dropwise and the reaction stirred at RT for 18 h. The reaction mixture was quenched with sat. $NH4Cl_{(aq)}$ (5 mL), water added (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-25% EtOAc:cyclohexane) to yield **3.79** as a colourless oil (2.638 g, 12.37 mmol, 62%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.17-4.29 (4H, m), 3.50 (1H, t, *J* = 7.4 Hz), 2.51 (2H, t, *J* = 7.4 Hz), 2.25 (2H, q, *J* = 7.4 Hz), 1.29 (6H, t, *J* = 7.1 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.1, 118.5, 61.9, 50.2, 24.5, 15.1, 14.0.

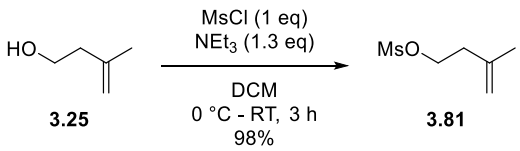
Diethyl 2-(2-cyanoethyl)-2-(2-methylallyl)malonate (3.80)



To a nitrogen-flushed flask containing NaH (432 mg, 10.80 mmol, 1.1 eq) (60% dispersion in mineral oil) over ice was added THF (20 mL). A solution of **3.79** (2.138 g, 10.03 mmol, 1.0 eq) in THF (5 mL) was added dropwise, the reaction brought to RT and stirred for 15 mins. Then a solution of 3-bromo-2-methylprop-1-ene (**3.17**) (1.502 g, 11.12 mmol, 1.1 eq) in THF (5 mL) was added over ice. The reaction was allowed to come to RT slowly and then stirred for 4 h. Water (75 mL) was then added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-20 EtOAc:cyclohexane) to afford **3.80** as a colourless oil (2.126 g, 7.95 mmol, 79%).

ν_{max} (neat): 2982, 1725, 1183 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.90-4.92 (1H, m), 4.76-4.77 (1H, m), 4.22 (4H, q, *J* = 7.4 Hz), 2.73 (2H, s), 2.39-2.43 (2H, m), 2.21-2.25 (2H, m), 1.65 (3H, s), 1.28 (6H, t, *J* = 6.9 Hz).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 170.4, 139.8, 119.0, 116.4, 61.8, 55.7, 41.2, 28.8, 22.9, 13.9, 13.0. HRMS: ($C_{14}H_{22}NO_4$) [M+H$^+$] requires 268.1549, found [M+H$^+$] 268.1552 (error 1.1 ppm).

3-Methylbut-3-en-1-yl methanesulfonate[102] (3.81)

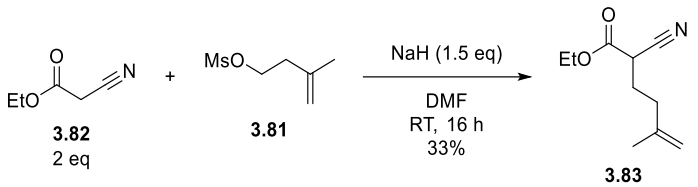


To 3-methylbut-3-en-1-ol (**3.25**) (2.159 g, 25.07 mmol, 1 eq) and MsCl (2.971 g, 25.9 mmol, 1 eq) in DCM (25 mL) over ice, was added NEt_3 (4.4 mL, 31.6 mmol, 1.3 eq). The reaction stirred at RT for 3 h, then quenched with water (150 mL) and extracted

with EtOAc (3 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to yield **3.81** as a crude colourless oil (4.054 g, 24.69 mmol, 98%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.88 (1H, br. s), 4.80 (1H, br. s), 4.33 (2H, t, *J* = 6.9 Hz), 3.00 (3H, s), 2.46 (2H, t, *J* = 6.9 Hz), 1.78 (3H, s).

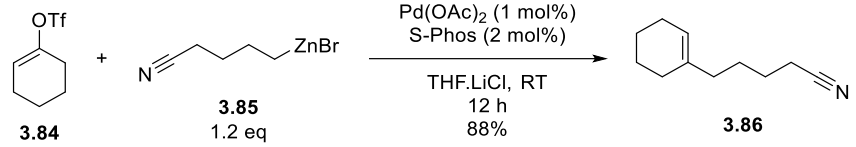
Ethyl 2-cyano-5-methylhex-5-enoate[173] **(3.83)**



To a suspension of NaH (1.383 g, 34.6 mmol, 1.5 eq) (60% dispersion in mineral oil) in DMF (50 mL) was added ethyl 2-cyanoacetate (**3.82**) (5.227 g, 46.2 mmol, 2 eq) in DMF (10 mL) dropwise. The resulting solution stirred at RT until clear (15 mins). Then 3-methylbut-3-en-1-yl methanesulfonate (**3.81**) (3.795 g, 23.11 mmol, 1 eq) was added in one portion, the reaction left to stir overnight (16 h) at RT. Then the reaction quenched with $HCl_{(aq)}$ (2M) (100 mL) and extracted EtOAc (2 x 50 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-15% EtOAc:cyclohexane) to yield **3.83** as colourless oil (1.381 g, 7.62 mmol, 33%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.82-4.83 (1H, m), 4.77-4.78 (1H, m), 4.27 (2H, q, *J* = 7.0 Hz), 3.50 (1H, dd, *J* = 8.6 and 5.6 Hz), 2.22-2.26 (2H, m), 2.02-2.17 (2H, m), 1.74 (3H, s), 1.33 (3H, t, *J* = 7.3 Hz).

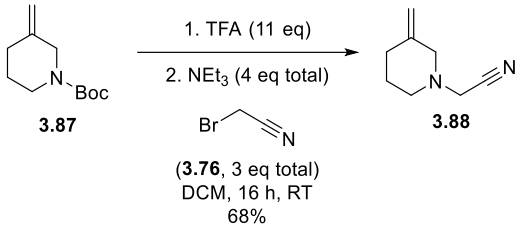
5-(Cyclohex-1-en-1-yl)pentanenitrile (3.86)



To a flame dried vial was added $Pd_2(OAc)_2$ (7 mg, 0.03 mmol, 1 mol%), cyclohex-1-en-1-yl trifluoromethanesulfonate (**3.84**) (711 mg, 3.09 mmol, 1 eq) and S-Phos (25 mg, 0.06 mmol, 2 mol%). The vial was sealed and evacuated (refilled with N_2 x 3), then lithium chloride (6.2 mL, 3.10 mmol, 1 eq) (0.5M in THF) was added and the solution stirred at RT for 5 mins. Then 4-cyanobutylzinc bromide (7.2 mL, 3.6 mmol, 1.2 eq) (0.5M in THF) was added and the reaction stirred at RT overnight (12 h). The reaction mixture was quenched by addition of sat. $NH_4Cl_{(aq)}$ (50 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic phases were washed with $thiourea_{(aq)}$ (10%, 50 mL), passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-20% EtOAc:cyclohexane) to afford **3.86** (446 mg, 2.73 mmol, 88%) as a colourless oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.40-5.41 (1H, m), 2.34 (2H, t, *J* = 8.3 Hz), 1.95-2.00 (4H, m), 1.88-1.92 (2H, m), 1.51-1.67 (8H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 136.6, 121.8, 119.8, 37.0, 28.1, 26.5, 25.2, 24.9, 23.0, 22.5, 17.0.

2-(3-Methylenepiperidin-1-yl)acetonitrile (3.88)

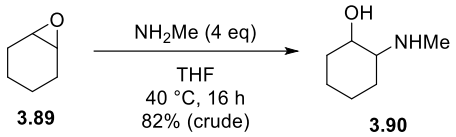


To *tert*-butyl 3-methylenepiperidine-1-carboxylate (**3.87**) (961 mg, 4.87 mmol, 1 eq) was added TFA (4 mL, 52 mmol, 11 eq) at RT. After stirring for 15 mins, excess TFA was removed *in vacuo*. Then DCM (20 mL) was added, followed by NEt_3 (1.36 mL, 9.76 mmol, 2 eq) and 2-bromoacetonitrile (**X**) (0.4 mL, 5.74 mmol, 1.2 eq). The mixture was stirred for 4 h, then further NEt_3 (1.36 mL, 9.76 mmol, 2 eq) and 2-

bromoacetonitrile (**3.76**) (0.6 mL, 8.61 mmol, 1.8 eq) added. The mixture was stirred overnight at RT (16 h). Reaction mixture then concentrated *in vacuo*, water (75 mL) added and extracted EtOAc (3 x 25mL). The combined organics were passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-20% EtOAc:cyclohexane) to yield **3.88** as a colourless oil (453 mg, 3.33 mmol, 68%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.82 (2H, d, *J* = 3.4 Hz), 3.56 (2H, s), 3.07 (2H, s), 2.64 (2H, t, *J* = 5.4 Hz), 2.18 (2H, t, *J* = 6.1 Hz), 1.70-1.76 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 143.1, 114.5, 110.3, 58.9, 52.4, 46.1, 31.7, 26.1.

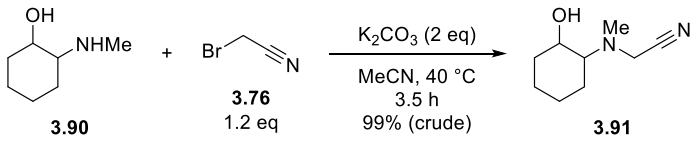
2-(Methylamino)cyclohexan-1-ol (3.90)



To a vial was added cyclohexene oxide (**3.89**) (2.017 g, 20.55 mmol, 1 eq) and methylamine (40 mL, 80 mmol, 4 eq) (2M in THF), the reaction sealed and stirred at 40 ^{o}C for 16 h. The reaction mixture was dried *in vacuo* to yield **3.90** as a crude colourless oil (2.188 g, 16.93 mmol, 82%).

^{1}H NMR not reported due to overlapping impurities. ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 73.6, 65.1, 33.6, 33.2, 29.7, 25.0, 24.4.

2-((2-Hydroxycyclohexyl)(methyl)amino)acetonitrile (3.91)

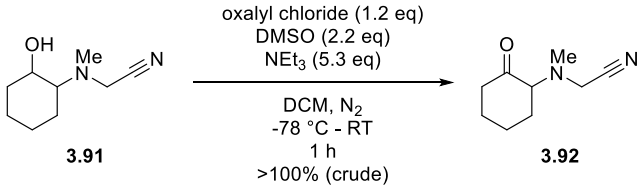


To a flask containing 2-(methylamino)cyclohexan-1-ol (**3.90**) (2.28 g, 17.65 mmol, 1 eq) in MeCN (35 mL) was added 2-bromoacetonitrile (**3.76**) (2.532 g, 21.10 mmol, 1.2 eq) and K_2CO_3 (4.885 g, 35.3 mmol, 2 eq). The reaction was stirred at 40 ^{o}C for 3.5 h, then water (100 mL) was added and the aqueous layer extracted with EtOAc (2 x

50mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to yield **3.91** as a crude orange oil (2.929 g, 17.41 mmol, 99%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 3.56-3.57 (2H, m), 3.32-3.38 (1H, m), 3.20 (1H, s), 2.45 (3H, s), 2.33-2.39 (1H, m), 2.09-2.14 (1H, m), 1.99-2.04 (1H, m), 1.79-1.84 (1H, m), 1.72-1.74 (1H, m), 1.21-1.32 (4H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 116.9, 69.8, 69.5, 42.8, 36.4, 33.2, 25.2, 23.9, 23.1.

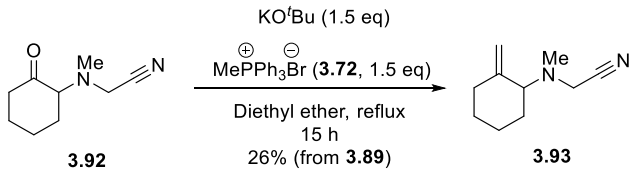
2-(Methyl(2-oxocyclohexyl)amino)acetonitrile[105] (3.92)



A solution of DMSO (2.1 mL, 29.6 mmol, 2.2 eq) in DCM (3 mL) was added dropwise oxalyl chloride (1.4 mL, 15.99 mmol, 1.2 eq) in DCM (3 mL) at -78 ^{o}C, under N_2. The resulting solution was stirred for 10 mins and **3.91** (2.28 g, 13.55 mmol, 1 eq) in DCM (9 mL) added dropwise. After 15 mins, NEt_3 (10 mL, 71.7 mmol, 5.3 eq) was added and the reaction mixture warmed to RT slowly and stirred for 1 h. Then sat. $Na_2SO_{4(aq)}$ (250 mL) added and the aqueous layer extracted with EtOAc (3 x 75 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo* to yield **3.92** as a crude brown oil (2.772 g, 16.68 mmol, >100%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 3.70-3.71 (2H, m), 3.21-3.25 (1H, m), 2.45-2.53 (4H, m), 2.23-2.36 (2H, m), 1.94-2.05 (2H, m), 1.68-1.77 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 209.8, 115.9, 70.1, 42.7, 41.4, 39.6, 31.5, 27.9, 23.9.

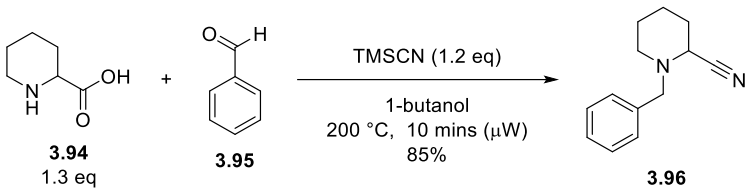
2-(Methyl(2-methylenecyclohexyl)amino)acetonitrile (X) (N66300-61-1)



A solution of KO^{t}Bu (2.804 g, 24.99 mmol, 1.5 eq) and methyltriphenylphosphonium bromide (**3.72**) (8.938 g, 25.02 mmol, 1.5 eq) in diethyl ether (55 mL) were stirred for 30 mins at RT, the solution turned bright yellow. Then 2-(methyl(2-oxocyclohexyl)amino)acetonitrile (**3.92**) (2.77 g, 16.66 mmol, 1 eq) in diethyl ether (7.5 mL) was added dropwise. The resulting solution stirred at reflux overnight (15 h). The reaction allowed to cool to RT, then water (150 mL) added and extracted with diethyl ether (3 x 50 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-10% TBME:cyclohexane) to afford **3.93** as a colourless oil (862 mg, 5.25 mmol, 26% from **3.89**).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.92 (1H, br. s), 4.81-4.82 (1H, m), 3.49-3.58 (2H, m), 2.92 (1H, t, *J* = 3.2 Hz), 2.35 (3H, s), 2.16-2.23 (1H, s), 2.06-2.11 (1H, m), 1.94-2.01 (1H, m), 1.74-1.80 (1H, m), 1.60-1.67 (1H, m), 1.32-1.56 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 148.7, 115.1, 110.8, 65.0, 43.5, 39.5, 31.3, 30.5, 28.3, 20.4.

1-Benzylpiperidine-2-carbonitrile[106] (3.96)

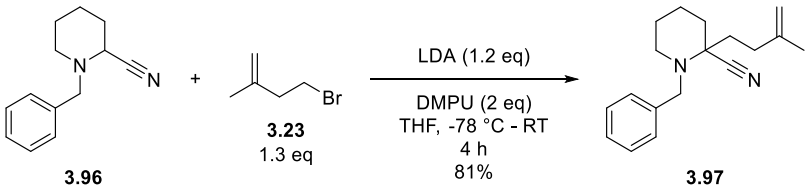


To a vial was added piperidine-2-carboxylic acid (**3.94**) (1.259 g, 9.75 mmol, 1.3 eq), benzaldehyde (**3.95**) (798 mg, 7.52 mmol, 1 eq) in 1-butanol (15 mL), then trimethylsilyl cyanide (TMSCN) (1.2 mL, 8.95 mmol, 1.2 eq) added. The reaction stirred at 200 ^{o}C in the microwave for 10 mins. Then the reaction was concentrated *in vacuo* and purified by automated reverse phase column chromatography on C18

silica gel (20-70% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate) to yield **3.96** as a pale-yellow oil (1.29 g, 6.44 mmol, 85%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.25-7.35 (5H, m), 3.72-3.73 (1H, m), 3.51-3.70 (2H, m), 2.76-2.81 (1H, m), 2.40-2.46 (1H, m), 1.54-1.88 (6H, m). LCMS (HpH): t_R = 1.19 min, [M+H$^+$] 201.2.

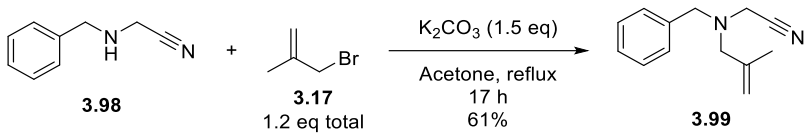
1-Benzyl-2-(3-methylbut-3-en-1-yl)piperidine-2-carbonitrile (3.97)



To a solution of diisopropylamine (0.64 mL, 4.49 mmol, 1.2 eq) in THF (30 mL) at -78 ^{o}C was added nBuLi (1.8 mL, 4.50 mmol, 1.2 eq). After stirring for 1 h, a solution of 1,3-dimethyltetrahydropyrimidin-2(1H)-one (DMPU) (0.91 mL, 7.53 mmol, 2 eq) and **3.96** (752 mg, 3.75 mmol, 1 eq) in THF (5 mL) was added. After 1 h, a solution of 4-bromo-2-methylbut-1-ene (**3.23**) (707 mg, 4.75 mmol, 1.3 eq) in THF (3 mL) was added slowly. The reaction was stirred for 2 h at -78 ^{o}C and then 2 h at RT. Water (100 mL) was added and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on basic Alumina (0-2% EtOAc:cyclohexane) to afford **3.97** as a colourless oil (815 mg, 3.03 mmol, 81%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.23-7.34 (5H, m), 4.73 (1H, br. s), 4.68-4.69 (1H, m), 4.11-4.15 (1H, m), 3.11-3.15 (1H, m), 2.74-2.78 (1H, m), 2.15-2.28 (3H, m), 2.01-2.12 (2H, m), 1.91-1.94 (1H, m), 1.76-1.80 (1H, m), 1.73 (3H, s), 1.55-1.67 (3H, m), 1.38-1.43 (1H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 144.5, 138.6, 128.4, 128.3, 127.1, 119.0, 110.6, 61.7, 55.3, 49.5, 36.3, 34.5, 30.8, 25.1, 22.6, 21.9. LCMS (HpH): t_R = 1.49 min, [M+H$^+$] 269.2.

2-(Benzyl(2-methylallyl)amino)acetonitrile (3.99)

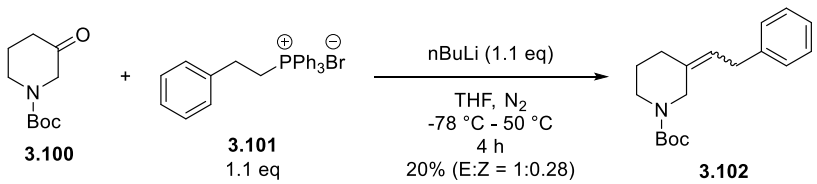


To a solution of 2-(benzylamino)acetonitrile* (**3.98**) (313 mg, 2.14 mmol, 1 eq) and 3-bromo-2-methylprop-1-ene (**3.17**) (312 mg, 2.31 mmol, 1.1 eq) in acetone (4 mL), was added K_2CO_3 (443 mg, 3.21 mmol, 1.5 eq). The reaction was stirred at 60 ^oC (reflux) overnight (16 h). Further 3-bromo-2-methylprop-1-ene (**3.17**) (22 µL, 0.21 mmol, 0.1 eq) was added, and reaction stirred at 60 ^oC (reflux) for a further 1 h. The reaction was allowed to cool to RT and water (20 mL) added, the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-10 EtOAc:cyclohexane) to yield **X** as a colourless oil (262 mg, 1.31 mmol, **61%**).

*80% pure by LCMS.

^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.25-7.36 (5H, m), 5.04-5.05 (1H, m), 4.96-4.97 (1H, m), 3.66 (2H, s), 3.41 (2H, m), 3.13 (2H, s), 1.77 (3H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 141.4, 137.3, 128.9, 128.6, 127.7, 114.9, 114.7, 60.8, 58.0, 40.8, 20.4. LCMS (Formic): t_R = 1.28 min, $[M+H^+]$ 201.1.

***Tert*-butyl 3-(2-phenylethylidene)piperidine-1-carboxylate (3.102)**

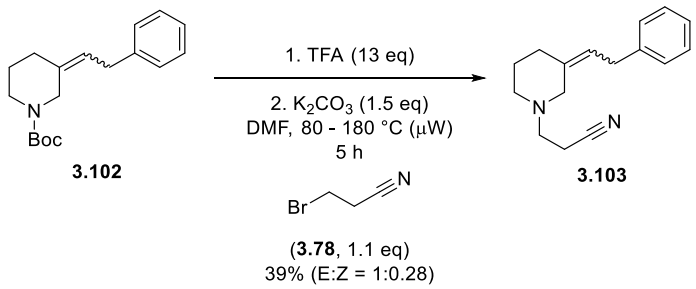


To phenethyltriphenylphosphonium bromide (**3.101**) (973 mg, 2.18 mmol, 1.1 eq) in THF (5 mL), nBuLi (0.87 mL, 2.18 mmol, 1.1 eq) was added dropwise (under N_2) at -78 ^oC and then stirred at RT for 10 mins. Then *tert*-butyl 3-oxopiperidine-1-carboxylate (**3.100**) (395 mg, 1.98 mmol, 1 eq) in THF (5 mL) was added dropwise, stirred for 3 h at RT and then 1 h at 50 ^oC. Reaction cooled to RT, water (75 mL) added and the

aqueous later extracted EtOAc (3 x 25 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-10% EtOAc:cyclohexane) to yield **3.102** as a colourless oil (111 mg, 0.39 mmol, 20%) (E:Z = 1:0.28).

The spectra reported are a mix of E/Z isomers. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.29-7.32 (2H, m), 7.18-7.23 (3H, m), 5.54 (0.2H, br. t, *J* = 7.2 Hz), 5.40 (0.8H, tt, *J* = 7.6 Hz), 4.11 (1.6H, s), 3.91 (0.5H, s), 3.50-3.54 (2H, m), 3.47 (1.6H, d, *J* = 7.6 Hz), 3.40 (0.5H, d, *J* = 7.6 Hz), 2.41 (0.5H, t, *J* = 6.2 Hz), 2.29 (1.6H, t, *J* = 6.2 Hz), 1.63-1.70 (2H, m), 1.48-1.49 (9H, m).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 154.8, 154.6, 141.0, 140.9, 134.2, 128.43, 128.41, 128.3, 123.3, 122.9, 79.5, 79.4, 44.7, 34.4, 33.6, 33.3, 28.5, 27.1, 26.6, 26.2. LCMS (HpH): t_R = 1.43 and 1.44 min, [MH^+-Boc] 188.2. HRMS: ($C_{13}H_{18}N$) [MH^+-Boc] requires 188.1439, found [$M+H^+$] 188.1436 (error -1.6 ppm).

3-(3-(2-Phenylethylidene)piperidin-1-yl)propanenitrile (3.103)



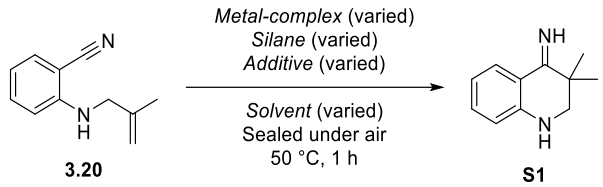
TFA (0.4 mL, 5.2 mmol, 13 eq) was added to **3.102** (114 mg, 0.40 mmol, 1 eq) and the reaction stirred for 30 mins at RT. Then excess TFA removed *in vacuo* and DMF (1.5 mL) added. Then K_2CO_3 (82 mg, 0.59 mmol, 1.5 eq) added, followed by 3-bromopropane nitrile (**3.78**) (36 µL, 0.44 mmol, 1.1 eq). The reaction heated at 80 ^{o}C for 3 h and then at 180 ^{o}C for 2 h (microwave). Reaction cooled to RT, water (15 mL) added and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organics passed through a hydrophobic frit, concentrated *in vacuo* and purified by MDAP (HpH, method C). The desired fractions were combined and dried *in vacuo* to yield **3.103** as a colourless gum (37 mg, 0.15 mmol, 39%).

The spectra reported are a mix of E/Z isomers. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.29-7.34 (2H, m), 7.19-7.23 (3H, m), 5.43-5.51 (1H, m), 3.42 (2H, d, *J* = 7.6 Hz), 3.18 (1.6H, s), 3.01 (0.5H, s), 2.73-2.80 (2H, m), 2.62-2.66 (2H, m), 2.53 (2H, t, *J* = 7.1 Hz), 2.31 (0.5H, td, *J* = 6.2 and 1.2 Hz), 2.19 (1.6H, td, *J* = 6.3 and 0.9 Hz), 1.68-1.75 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 141.0, 140.9, 134.82, 134.77, 128.47, 128.45, 128.38, 128.35, 126.0, 125.92, 122.3, 122.7, 118.9, 61.7, 53.9, 53.7, 53.5, 53.3, 34.2, 33.42, 33.40, 26.4, 25.7, 16.0, 15.9. LCMS (HpH): t_R = 1.19 min, [MH^+] 241.2. HRMS: ($C_{16}H_{21}N_2$) [MH^+] requires 241.1704, found [$M+H^+$] 241.1704 (error 0.0 ppm).

8.2.2 – Scoping of Reaction Conditions

To a vial was added **3.20** (22 mg, 0.13 mmol, 1 eq) and *metal-complex* (varied), then a solution of *silane* (varied) in *solvent(s)* (varied) was added, along with *additive* (on occasion). The vial sealed under air and the reaction stirred at 50 °C for 1 h. The reaction sampled for LCMS analysis and abandoned.

Table 12. *Exploration of reaction conditions for HAT-mediated cyclisation of **3.20** to **S1**.*



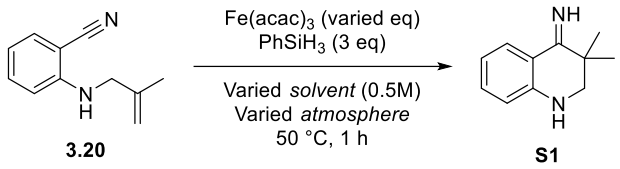
Entry	[M] (eq)	Solvent (M)	[Silane] (eq)	Additive (eq)	LCMS peak area (%UV)	
					3.20	S1
1	$Fe(acac)_3$ (0.5)	EtOH:HFIP (1:1, 0.5M)	$PhSiH_3$ (3)	-	5	68
2	"	"	"	TBHP (3)	4	41
3	$Fe(acac)_3$ (0.2)	"	"	"	6	35
4	$Fe(acac)_3$ (0.5)	"	"	DTBP (3)	4	69
5	$Fe(acac)_3$ (0.2)	"	"	"	9	67
6	"	"	"	-	16	60
7	$Fe(acac)_3$ (0.5)	EtOH:HFIP (1:1, 0.25M)	"	-	4	68
8	$Fe(acac)_3$ (0.2)	EtOH:HFIP (1:1, 0.5M)	$PhSiH_3$ (3.5)	-	9	60
9	$Fe(acac)_3$ (0.5)	"	$PhSiH_3$ (3.5)	DTBP (3.5)	4	68
10	$Fe(acac)_3$ (0.2)	"	"	DTBP (1)	9	68
11	$Fe(acac)_3$ (0.5)	"	"	$BF_3.OEt_2$ (2)	45	4

12	$Fe(acac)_3$ (0.2)	"	"	$BF_3.OEt_2$ (2)	50	3
13	$Fe(acac)_3$ (0.05)	"	"	-	27	47
14	"	"	"	DTBP (3)	18	52
15	"	"	"	DTBP (1)	18	53
16	$Fe(acac)_3$ (0.5)	"	PMHS (3)	-	13	34
17	"	"	Et_3SiH (3)	-	100	0
18	$Mn(dpm)_3$	"	$PhSiH_3$ (3)	-	9	47
19	$Fe(acac)_3$ (0.5)	O-*i*Pr (0.5M)	"	-	4	75
20	$Fe(acac)_3$ (0.5)	O-*i*Pr:HFIP (1:1, 0.5M)	"	-	23	55

Conclusion: *i*PrOH (entry 19) appears optimal reaction solvent

To a vial was added **3.20** (86 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (varied eq), then a solution of $PhSiH_3$ (162 mg, 1.50 mmol, 3 eq) in *solvent(s)* (varied, 0.5M) was added. The reaction stirred (atmosphere varied) at 50 °C for 1 h. The reaction sampled for LCMS analysis and abandoned.

Table 13. *Exploration of reaction conditions for HAT-mediated cyclisation of **3.20** to **S1**.*



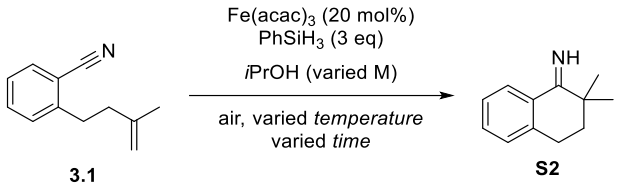
Entry	$Fe(acac)_3$ (mol%)	Solvent (0.5M)	Atmosphere	LCMS peak area (%UV)	
				3.20	**S1**
1	50	EtOH	N_2	34	53
2	"	EtOH:HFIP (1:1)	"	27	53
3	"	*i*PrOH	"	32	52
4	"	*i*PrOH:HFIP (1:1)	"	39	44
5	"	EtOH	Open to Air	2	77
6	"	EtOH:HFIP (1:1)	"	20	66
7	"	*i*PrOH	"	2	77
8	"	*i*PrOH:HFIP (1:1)	"	28	49
9	20	*i*PrOH	"	1	81
10	10	"	"	7	74
11	5	"	"	11	68
12*	20	"	"	2	19

* Reaction performed at RT.

Conclusion: Reaction poor under N_2 (entries 1-4), HFIP not needed when under air (entry 7 *vs*. 8) and 20 mol% Fe tolerated (entry 9).

To a vial was added **3.1** (86 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq), then a solution of $PhSiH_3$ (162 mg, 1.50 mmol, 3 eq) in *i*PrOH (varied M) was added. The reaction stirred open to air at varied *temperature* and *time*. The reaction sampled for LCMS analysis and abandoned.

Table 14. *Exploration of reaction molarity, temperature and time for conversion of **3.1** to **S2**.*



3.1 S2

Entry	*i*PrOH (M)	Temp (°C)	Time (mins)	LCMS peak area (%UV)	
				3.1	S2
1	0.25	50	60	<1	68
2	0.5	"	"	<1	58
3	0.1	"	"	7	61
4	0.05	"	"	<1	55
5	0.25	20 (RT)	"	20	26
6	"	50	15	31	55
7	"	"	30	12	53
8	"	"	60	4	64
9	"	"	90	1	59
10	"	"	120	<1	58
11	"	60	15	22	59
12	"	"	30	9	64
13	"	"	60	4	57
14	"	"	90	3	58
15	"	"	120	3	52
16	"	75	15	22	47
17	"	"	30	17	58
18	"	"	60	12	52
19	"	"	90	9	53

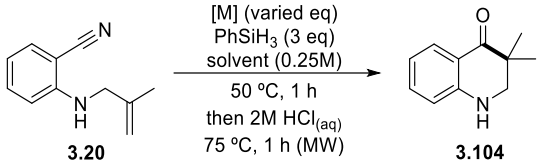
20	“	“	120	8	49

Conclusion: 0.25M optimal concentration (entry 1), 1 h at 50 ^{o}C optimal time/temperature (entry 8).

8.2.3 – Optimisation of Reaction Conditions

Alkene-nitrile (0.10 mmol, 1.0 eq) and *metal-complex* (varied) were added to a vial. Then a solution of $PhSiH_3$ (3.0 eq) in *solvent* (varied, 0.25M) was added. The reaction stirred for 1 h (under varied atmospheres) at 50 °C. Then $HCl_{(aq)}$ (2M, 0.4 mL) was added and the reaction heated at 75 °C for 1 h in the microwave. The reaction stopped, diluted with a solution of internal standard (anisole) (0.1 mmol, 1 eq) in MeCN (10 mL) and sampled for HPLC analysis.

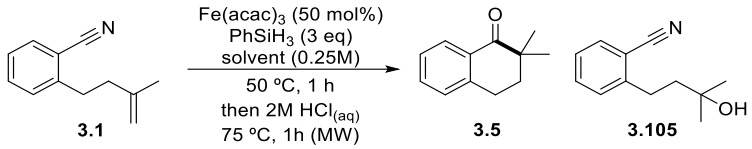
Table 15. *Screening of reaction conditions for conversion of **3.20** to **3.104**.*



Entry[a]	[M] (mol %)	Solvent	Conditions	Yield (%)	
				3.20	3.104
1	$Fe(acac)_3$ (50)	EtOH	Headspace (air)	3	81
2	$Mn(dpm)_3$ (50)	EtOH	Headspace (air)	14	66
3	$Fe(acac)_3$ (50)	EtOH:HFIP	Headspace (air)	9	61
4	$Fe(acac)_3$ (50)	EtOH:HFIP	N_2	24	65
5	$Fe(acac)_3$ (50)	*i*PrOH	Open (air)	<1	70
6	$Fe(acac)_3$ (20)	*i*PrOH	Open (air)	<1	57
7[b]	$Fe(acac)_3$ (20)	*i*PrOH	Open (air)	21	11
8[c]	$Fe(acac)_3$ (20)	*i*PrOH	Open (air)	<1	13
9[d]	$Fe(acac)_3$ (20)	*i*PrOH	Headspace (air)	19	71
10[d]	$Fe(acac)_3$ (20)	iPrOH	Open (air)	n.d.	94

[a] HAT: 0.1 mmol; solution yield quoted, quantified by HPLC using an internal standard. [b] HAT conducted at RT. [c] 1.5 eq $PhSiH_3$ used. [d] 0.5 mmol scale, isolated yields quoted.

Table 16. *Screening of reaction conditions for conversion of **3.1** to **3.5**.*



***Entry*[a]**	***Solvent***	***Conditions***	**Yield (%)**		
			3.1	**3.5**	**3.105**
1	EtOH	Headspace (air)	3	59	8
2	EtOH:HFIP	Headspace (air)	<1	77	5
3	EtOH:HFIP	N_2	4	86	3
(repeat)	″	″	4	85	2
4	*i*PrOH	Open (air)	<1	52	18
5[b]	*i*PrOH	Open (air)	21	11	51
6[c]	*i*PrOH	Open (air)	3	46	37
7	*i*PrOH	N_2	21	50	10
8[d]	*i*PrOH	N_2	11	61	5
9[e]	EtOH:HFIP	N_2	5	80	2
10[f*]	*i*PrOH	Open (air)	n.d.	74	n.d.
11[f]	EtOH:HFIP	N_2	n.d.	83	n.d.
12[e*]	EtOH	N_2	n.d.	33	n.d.
13[g]	EtOH:HFIP	N_2	n.d.	70	n.d.
14[g*]	EtOH:HFIP	N_2	n.d.	54	n.d.

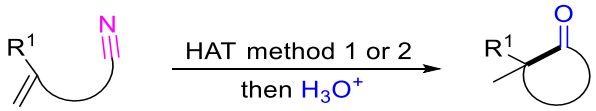
[a] HAT: 0.1 mmol; solution yield quoted, quantified by HPLC using an internal standard. [b] HAT conducted at RT. [c] 1.5 eq $PhSiH_3$ used. [d] 1.5 eq di-tert-butyl peroxide added. [e] Nitrogen bubbled through solvent prior to use. [f] 0.5 mmol scale, isolated yields quoted. *20 mol% $Fe(acac)_3$. [e] 0.5 mmol scale, NMR yield quoted as **3.1** and **3.5** co-elute. [g] Reactions performed with degassed solvents (via freeze-pump-thaw method).

The importance of HFIP when running the HAT reaction under inert conditions is highlighted below in Figure 13: in the absence of HFIP the iron catalyst precipitates out of solution during the course of the reaction (presumably in its inactive Fe^{II} form) whereas in the presence of HFIP the reaction remains homogeneous.

Figure 13. EtOH (Table 16, Entry 12) on the left (heterogeneous) and EtOH:HFIP (Table 16, Entry 11) on the right (homogeneous).

8.2.4 – Substrate Scope

HAT General Methods

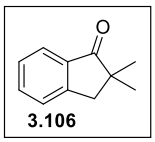


Method 1: To a vial containing *alkene-nitrile* (0.50 mmol, 1.0 eq) and $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq), was added a solution of $PhSiH_3$ (162 mg, 1.50 mmol, 3.0 eq) in *i*PrOH (2 mL, 0.25 M). The reaction moderately stirred open to air at 50 °C for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 °C for 1 h in the microwave (thermal hydrolysis is also suitable). The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel to afford the cyclised product.

Method 2: A vial containing *alkene-nitrile* (0.50 mmol, 1.0 eq) and $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) was sealed and purged with N_2. In a separate vial was added a solution of $PhSiH_3$ (162 mg, 1.50 mmol, 3.0 eq) in EtOH:HFIP (1:1, 2 mL, 0.25 M), the vial was also sealed and purged with N_2. The solution was then added to the solids and the reaction was moderately stirred at 50 °C for 1 h.* Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 °C for 1 h in the microwave (thermal hydrolysis is also suitable). The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel to afford the cyclised product.

*Venting of gas formed during the reaction (presumably H_2) was sometimes necessary, this was performed with a needle attached to a nitrogen line.

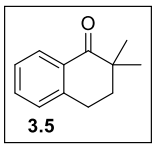
2,2-Dimethyl-2,3-dihydro-1*H*-inden-1-one (3.106)



The title compound was prepared according to general method 1* using alkene-nitrile **3.9** (80 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (37 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (165 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane) afforded **3.106** as a colourless oil (74 mg, 0.46 mmol, 91%). *****Method 1 with 5 mol% $Fe(acac)_3$ yielded 78% on 5 mmol scale.

ν_{max} (neat): 2960, 2926, 2866, 1712, 1609, 734 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.76 (1H, d, *J* = 7.8 Hz), 7.57-7.61 (1H, m), 7.41-7.43 (1H, m), 7.35-7.38 (1H, m), 3.00 (2H, s), 1.24 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 211.3, 152.2, 135.4, 134.8, 127.4, 126.6, 124.5, 45.5, 42.9, 25.3. LCMS (HpH): t_R = 1.03 min, $[M+H^+]$ 161.1. HRMS: ($C_{11}H_{13}O$) $[M+H^+]$ requires 161.0966, found $[M+H^+]$ 161.0968 (error 1.2 ppm).

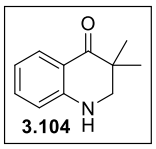
2,2-Dimethyl-3,4-dihydronaphthalen-1(2H)-one (3.5)



The title compound was prepared according to general method 2* using alkene-nitrile **3.1** (88 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (165 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane) afforded **3.5** as a colourless oil (74 mg, 0.42 mmol, 83%). *Method 1 yielded 74%.

ν_{max} (neat): 2962, 2926, 2854, 1682, 1602, 739 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.04 (1H, dd, *J* = 7.8 and 1.0 Hz), 7.44 (1H, td, *J* = 7.3 and 1.5 Hz), 7.27-7.31 (1H, m), 7.21 (1H, d, *J* = 7.6 Hz), 2.98 (2H, t, *J* = 6.4 Hz), 1.98 (2H, t, *J* = 6.4 Hz), 1.22 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 202.8, 143.4, 133.0, 131.5, 128.6, 128.0, 128.0, 126.6, 41.6, 36.6, 25.7, 24.4. LCMS (HpH): t_R = 1.18 min, $[M+H^+]$ 175.0. HRMS: ($C_{12}H_{14}O$) $[M+H^+]$ requires 175.1123, found $[M+H^+]$ 175.1124 (error 0.6 ppm).

3,3-Dimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.104)

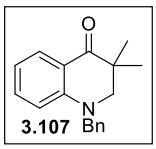


3.104

The title compound was prepared according to general method 1* using alkene-nitrile **3.20** (86 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (166 mg, 1.53 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.104** as a yellow solid (82 mg, 0.47 mmol, 94%). *Method 1 yielded 94% yield on 1g (5.8 mmol) scale.

M.pt.: 54-58 ^oC. ν_{max} (neat): 3349, 2961, 2931, 2816, 1651, 1607, 1506, 1339, 751 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.86 (1H, dd, *J* = 8.0 and 1.6 Hz), 7.28 (1H, ddd, *J* = 8.4, 6.9 and 1.6 Hz), 6.72 (1H, ddd, *J* = 8.0, 7.0 and 1.1 Hz), 6.63-6.66 (1H, m), 4.51 (1H, br. s), 3.26 (2H, d, *J* = 2.2 Hz), 1.18 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.7, 151.0, 134.7, 128.3, 117.8, 117.6, 115.4, 53.8, 41.4, 21.9. LCMS (HpH): t_R = 0.94 min, $[M+H^+]$ 176.0. HRMS: ($C_{11}H_{13}NO$) $[M+H^+]$ requires 176.1075, found $[M+H^+]$ 176.1081 (error 3.4 ppm).

1-Benzyl-3,3-dimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.107)

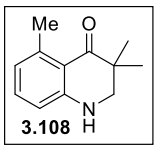


3.107

The title compound was prepared according to general method 1 using alkene-nitrile **3.21** (131 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (37 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane) afforded **3.107** as a yellow solid (100 mg, 0.38 mmol, 75%).

M.pt.: 93-102 ^oC. ν_{max} (neat): 3060, 2927, 2870, 2178, 1657, 1599, 1501, 1343 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.94-7.95 (1H, m), 7.27-7.35 (6H, m), 6.70-6.74 (2H, m), 4.56 (2H, s), 3.27 (2H, s), 1.17 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.5, 150.9, 137.5, 135.1, 129.0, 128.8, 127.4, 126.9, 118.0, 117.1, 113.1, 61.5, 55.4, 41.6, 22.1. LCMS (HpH): t_R = 1.31 min, $[M+H^+]$ 266.2. HRMS: ($C_{18}H_{20}NO$) $[M+H^+]$ requires 266.1545, found 266.1542 $[M+H^+]$ (error -1.1 ppm).

3,3,5-Trimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.108)

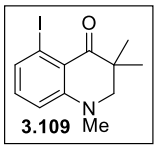


3.108

The title compound was prepared according to general method 1 using alkene-nitrile **3.48** (92 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (165 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.108** as a yellow solid (75.7 mg, 0.40 mmol, 81%).

M.pt.: 96-100 ^oC. ν_{max} (neat): 3361, 2958, 2923, 2826, 1651, 1603, 1525, 1340 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.10 (1H, t, *J* = 7.6 Hz), 6.47-6.49 (2H, m), 4.55 (1H, br. s), 3.22 (2H, s), 2.59 (3H, s), 1.15 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 200.3, 152.1, 142.9, 133.5, 121.1, 116.0, 113.6, 53.3, 41.7, 23.6, 22.2. LCMS (HpH): t_R = 1.06 min, [M-H^+] 188.2. HRMS: ($C_{12}H_{16}NO$) [M+H^+] requires 190.1232, found [M+H^+] 190.1227 (error -2.6 ppm).

5-Iodo-1,3,3-trimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.109)

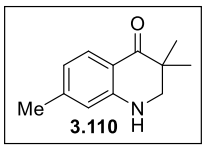


3.109

The title compound was prepared according to general method 1 using alkene-nitrile **3.61** (157 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq). Purification by automated reverse phase column chromatography on C18 silica gel (40-75% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate) afforded **3.109** as a yellow solid (118 mg, 0.37 mmol, 75%).

M.pt.: 114-120 ^oC. ν_{max} (neat): 2962, 1672, 1587, 1426, 768 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.40-7.42 (1H, m), 6.89-6.94 (1H, m), 6.67-6.69 (1H, m), 3.20 (2H, s), 3.03 (3H, s), 1.17 (6H s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 196.7, 152.4, 134.4, 131.9, 116.4, 113.2, 94.9, 62.6, 41.1, 40.0, 22.1. LCMS (HpH): t_R = 1.26 min, [M+H^+] 315.9. HRMS: ($C_{12}H_{15}INO$) [M+H^+] requires 316.0198, found [M+H^+] 316.0189 (error -2.8 ppm).

3,3,7-Trimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.110)

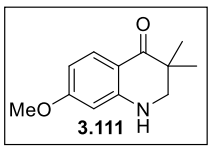


3.110

The title compound was prepared according to general method 1 using alkene-nitrile **3.44** (92 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (163 mg, 1.50 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.110** as a yellow solid (72 mg, 0.38 mmol, 77%).

M.pt.: 108-119 ^{o}C. ν_{max} (neat): 3323, 2956, 2921, 2851, 1641, 1614 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.76 (1H, d, *J* = 8.3 Hz), 6.54 (1H, dd, *J* = 8.1 and 1.2 Hz), 6.45 (1H, s), 4.49 (1H, br. s), 3.23 (2H, s), 2.26 (3H, s), 1.16 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.4, 151.1, 145.7, 128.3, 119.5, 115.5, 115.4, 53.9, 41.3, 22.0, 21.8. LCMS (HpH): t_R = 0.99 min, [M+H$^+$] 190.2. HRMS: ($C_{12}H_{16}NO$) [M+H$^+$] requires 190.1232, found [M+H$^+$] 190.1229 (error -1.6 ppm).

7-Methoxy-3,3-dimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.111)

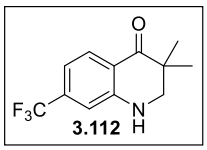


3.111

The title compound was prepared according to general method 1* using alkene-nitrile **3.45** (101 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (163 mg, 1.51 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-70% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.111** as an off white solid (70 mg, 0.34 mmol, 69%). *Hydrolysis performed for 5 h.

M.pt.: 151-156 ^{o}C. ν_{max} (neat): 3298, 2967, 1630, 1600, 1578, 1229, 845 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.81 (1H, d, *J* = 8.8 Hz), 6.32 (1H, dd, *J* = 8.8 and 2.5 Hz), 6.07 (1H, d, *J* = 2.5 Hz), 4.64 (1H, br. s), 3.78 (3H, s), 3.24 (2H, d, *J* = 2.0 Hz), 1.16 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 197.5, 165.0, 152.9, 130.4, 111.9, 106.7, 97.6, 55.3, 54.0, 41.1, 22.1. LCMS (HpH): t_R = 0.89 min, [M+H$^+$] 206.1. HRMS: ($C_{12}H_{16}NO_2$) [M+H$^+$] requires 206.1181, found [M+H$^+$] 206.1185 (error 1.9 ppm).

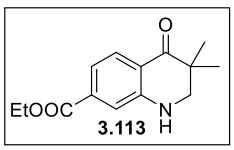
3,3-Dimethyl-7-(trifluoromethyl)-2,3-dihydroquinolin-4(1*H*)-one (3.112)



The title compound was prepared according to general method 1 using alkene-nitrile **3.47** (122 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (166 mg, 1.53 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.112** as a yellow solid (94 mg, 0.39 mmol, 76%).

M.pt.: 109-122 ^{o}C. ν_{max} (neat): 3369, 2979, 1661, 1131, 1065 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.94 (1H, d, *J* = 8.3 Hz), 6.90-6.93 (2H, m), 4.91 (1H, br. s), 3.30 (2H, d, *J* = 2.5 Hz), 1.18 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.1, 150.5, 135.9 (q, *J* = 32.3 Hz), 129.3, 123.6 (q, *J* = 272.9 Hz), 119.2, 113.6 (q, *J* = 3.2 Hz), 112.6 (q, *J* = 3.9 Hz), 53.4, 41.3, 21.7. ^{19}F{^{1}H} NMR (376 MHz, CHLOROFORM-d) δ = -63.8. LCMS (HpH): t_R = 1.19 min, [M-H$^+$] 242.1. HRMS: ($C_{12}H_{13}F_3NO$) [M+H$^+$] requires 244.0949, found [M+H$^+$] 244.0952 (error 1.2 ppm).

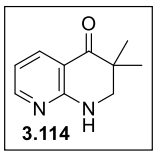
Ethyl 3,3-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-7-carboxylate (3.113)



The title compound was prepared according to general method 1 using alkene-nitrile **3.46** (125 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (38 mg, 0.11 mmol, 0.2 eq) and $PhSiH_3$ (166 mg, 1.53 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.113** as a yellow gum (111 mg, 0.45 mmol, 88%).

ν_{max} (neat): 3366, 2979, 1718, 1662, 1619, 1333 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.90 (1H, d, *J* = 8.3 Hz), 7.36 (1H, d, *J* = 1.5 Hz), 7.33 (1H, dd, *J* = 8.3 and 1.5 Hz), 4.62 (1H, br. s), 4.36 (2H, q, *J* = 7.0 Hz), 3.29 (2H, s), 1.38 (3H, t, *J* = 6.9 Hz), 1.18 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.3, 166.0, 150.4, 135.7, 128.5, 120.0, 118.0, 117.0, 61.3, 53.6, 41.4, 21.8, 14.3. LCMS (HpH): t_R = 1.12 min, [M-H$^+$] 246.1. HRMS: ($C_{14}H_{18}NO_3$) [M+H$^+$] requires 248.1287, found [M+H$^+$] 248.1285 (error -0.8 ppm).

3,3-Dimethyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (3.114)

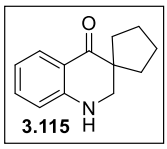


3.114

The title compound was prepared according to general method 1* using alkene-nitrile **3.53** (88 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-50 EtOAc:cyclohexane, 1% NEt_3 additive) afforded **3.114** as an off white solid (69 mg, 0.39 mmol, 77%). *Reaction worked-up using $NaHCO_{3(aq)}$ instead of water.

M.pt.: 111-113 ^oC. ν_{max} (neat): 3213, 2963, 1668, 1580, 776 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.24 (1H, dd, *J* = 4.9 and 2.0 Hz), 8.11 (1H, dd, *J* = 7.9 and 2.0 Hz), 6.70 (1H, dd, *J* = 7.9 and 4.4 Hz), 6.13 (1H, br. s), 3.33 (2H, d, *J* = 2.0 Hz), 1.19 (6H, s) .^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.4, 160.1, 154.3, 137.2, 114.1, 112.3, 51.9, 41.0, 21.8. LCMS (HpH): t_R = 0.74 min, $[M+H^+]$ 177.2. HRMS: ($C_{10}H_{13}N_2O$) $[M+H^+]$ requires 177.1028, found $[M+H^+]$ 177.1024 (error -2.3 ppm).

1',2'-Dihydro-4'*H*-spiro[cyclopentane-1,3'-quinolin]-4'-one (3.115)

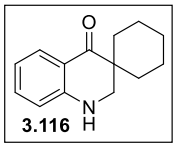


3.115

The title compound was prepared according to general method 1* using alkene-nitrile **3.55** (100 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (39 mg, 0.11 mmol, 0.2 eq) and $PhSiH_3$ (165 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.115** as a yellow solid (73 mg, 0.36 mmol, 72%). *Hydrolysis for 1.5 h.

M.pt.: 62-65 ^oC. ν_{max} (neat): 3368, 3330, 2947, 2864, 1639, 1609, 1343, 753 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.86 (1H, dd, *J* = 8.1 and 1.7 Hz), 7.26 (1H, ddd, *J* = 8.4, 7.0 and 1.7 Hz), 6.70 (1H, ddd, *J* = 8.0, 7.0 and 1.2 Hz), 6.63 (1H, d, *J* = 8.3 Hz), 4.61 (1H, br. s), 3.29 (2H, s), 1.98-2.05 (2H, m), 1.56-1.80 (6H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.2, 151.2, 134.6, 128.3, 118.0, 117.5, 115.4, 52.6, 51.7, 33.0, 25.8. LCMS (HpH): t_R = 1.07 min, $[M-H^+]$ 200.2. HRMS: ($C_{13}H_{16}NO$) $[M+H^+]$ requires 202.1232, found 202.1230 $[M+H^+]$ (error -1.0 ppm).

1',2'-Dihydro-4'*H*-spiro[cyclohexane-1,3'-quinolin]-4'-one (3.116)

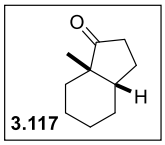


3.116

The title compound was prepared according to general method 1 using alkene-nitrile **3.56** (105 mg, 0.49 mmol, 1 eq), $Fe(acac)_3$ (37 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane, 1% NEt_3 additive) afforded **3.116** as a yellow solid (87 mg, 0.40 mmol, 82%).

M.pt.: 108-113 ^oC. ν_{max} (neat): 3337, 2919, 2845, 1639, 1612, 1523, 1348, 746 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.86 (1H, dd, *J* = 8.3 and 1.5 Hz), 7.25-7.29 (1H, m), 6.72 (1H, ddd, *J* = 7.8, 6.9 and 1.0 Hz), 6.63 (1H, d, *J* = 8.3 Hz), 4.41 (1H, br. s), 3.39 (2H, d, *J* = 2.0 Hz), 1.66-1.79 (4H, m), 1.52-1.60 (3H, m) 1.33-1.46 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.9, 150.5, 134.5, 128.5, 118.1, 117.8, 115.2, 48.9, 44.2, 29.2, 25.9, 21.6. LCMS (HpH): t_R = 1.16 min, $[M+H^+]$ 216.2. HRMS: ($C_{14}H_{18}NO$) $[M+H^+]$ requires 216.1388, found $[M+H^+]$ 216.1387 (error -0.5 ppm).

(+-)-7a-Methyl-*cis*-hexahydro-indan-1-one (3.117)



3.117

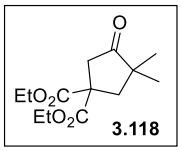
The title compound was prepared according to general method 2 using alkene-nitrile **3.73** (75 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (167 mg, 1.54 mmol, 3 eq). Purification by automated column chromatography on aminopropyl silica gel (0-10 TBME:cyclohexane) afforded **3.117** as a colourless gum (56 mg, 0.37 mmol, 73%).

ν_{max} (neat): 2925, 2858, 1733, 1447 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 2.32-2.41 (1H, m), 2.19-2.28 (1H, m), 1.90-1.98 (2H, m), 1.62-1.81 (3H, m), 1.26-1.53 (5H, m), 1.11-1.17 (1H, m), 1.04 (3H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 222.5, 48.3, 42.6, 35.0, 29.6, 26.8, 23.1, 22.4, 22.2, 21.4. HRMS: ($C_{10}H_{17}O$) $[M+H^+]$ requires 153.1279, found $[M+H^+]$ 153.1274 (error -3.3 ppm).

NMR yield: A vial containing alkene-nitrile **3.73** (75 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (91 mg, 0.26 mmol, 0.5 eq) was sealed and purged with nitrogen. In a separate vial was added a solution of $PhSiH_3$ (169 mg, 1.56 mmol, 3 eq) in EtOH:HFIP (1:1, 2 mL, 0.25 M), the vial was also sealed and purged with nitrogen. The solution

was then added to the solids and the reaction was moderately stirred at 50 °C for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 °C for 1 h in the microwave. The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. Then internal standard, 1,3,5-trimethoxybenzene (41 mg, 0.24 mmol, 0.5 eq), added and the reaction mixture diluted in $CDCl_3$. Analysis by ^1H NMR showed **3.117** in an 89% yield.

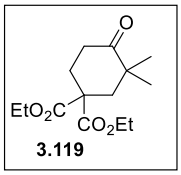
Diethyl 3,3-dimethyl-4-oxocyclopentane-1,1-dicarboxylate (3.118)



The title compound was prepared according to general method 2* using alkene-nitrile **3.77** (127 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **3.118** as a colourless oil (120 mg, 0.47 mmol, 93%). ***Method 1 yielded 70%.

ν_{max} (neat): 2977, 1728, 1182 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 4.17-4.29 (4H, m), 2.97 (2H, s), 2.51 (2H, s), 1.27 (6H, t, *J* = 7.1 Hz), 1.06 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 218.4, 171.4, 62.1, 53.9, 45.2, 44.4, 43.9, 25.2, 14.0. HRMS: ($C_{13}H_{21}O_5$) [M+H^+] requires 257.1389, found [M+H^+] 257.1390 (error 0.4 ppm).

Diethyl 3,3-dimethyl-4-oxocyclohexane-1,1-dicarboxylate (3.119)

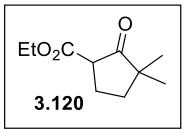


The title compound was prepared according to general method 2 using alkene-nitrile **3.80** (135 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (163 mg, 1.51 mmol, 3 eq). Purification by automated column chromatography on aminopropyl silica gel (0-20% TBME:cyclohexane) afforded **3.119** as a colourless oil (56 mg, 0.21 mmol, 41%).

ν_{max} (neat): 2979, 1728, 1712, 1228, 1152 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 4.23 (4H, q, *J* = 7.2 Hz), 2.62 (2H, t, *J* = 6.9 Hz), 2.38 (2H, s), 2.32 (2H, *J* = 7.1 Hz), 1.28 (6H, t, *J* = 7.1 Hz), 1.09 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 214.1, 171.3, 61.8, 52.6, 44.0, 43.5, 34.9, 31.3, 25.9, 14.0. HRMS: ($C_{14}H_{23}O_5$) [M+H^+] requires 271.1546, found [M+H^+] 271.1550 (error 1.5 ppm).

NMR yield: A vial containing alkene-nitrile **3.80** (135 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) was sealed and purged with nitrogen. In a separate vial was added a solution of $PhSiH_3$ (163 mg, 1.51 mmol, 3 eq) in EtOH:HFIP (1:1, 2 mL, 0.25 M), the vial was also sealed and purged with nitrogen. The solution was then added to the solids and the reaction was moderately stirred at 50 ^oC for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 ^oC for 1 h in the microwave. The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. Then internal standard, 1,3,5-trimethoxybenzene (41 mg, 0.25 mmol, 0.5 eq), added and the reaction mixture diluted in $CDCl_3$. Analysis by ^1H NMR showed **3.119** in a 65% yield, along with 30% of hydrogenated starting material.

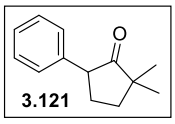
Ethyl 3,3-dimethyl-2-oxocyclopentane-1-carboxylate (3.120)



The title compound was prepared according to general method 2 using alkene-nitrile **3.83** (91 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (88 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (163 mg, 1.50 mmol, 3 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **3.120** as a colourless oil (56 mg, 0.30 mmol, 61%).

ν_{max} (neat): 2965, 1750, 1722, 1059 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 4.16-4.23 (2H, m), 3.23 (1H, t, *J* = 9.1 Hz), 2.14-2.34 (2H, m), 1.92-1.98 (1H, m), 1.70-1.77 (1H, m), 1.28 (3H, t, *J* = 7.1 Hz), 1.09 (3H, s), 1.09 (3H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 215.8, 169.7, 61.3, 54.2, 45.7, 36.5, 24.1, 23.6, 23.3, 14.1. HRMS: ($C_{10}H_{17}O_3$) [M+H$^+$] requires 185.1178, found [M+H$^+$] 185.1178 (error 0 ppm).

2,2-Dimethyl-5-phenylcyclopentan-1-one (3.121)



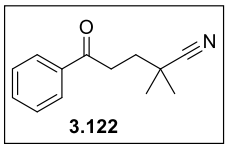
The title compound was prepared according to general method 2 using alkene-nitrile **3.70** (93 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (166 mg, 1.54 mmol, 3 eq). Purification by automated

column chromatography on silica gel (0-5% TBME:cyclohexane) afforded **3.121** as a colourless oil (66 mg, 0.35 mmol, 70%).

ν_{max} (neat): 2960, 1736, 696 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.30-7.34 (2H, m), 7.21-7.25 (1H, m), 7.17-7.19 (2H, m), 3.41 (1H, dd, *J* = 11.2 and 8.8 Hz), 2.39 (1H, dddd, *J* = 12.7, 8.7, 6.5, and 2.3 Hz), 2.04-2.14 (1H, m), 1.94-1.99 (1H, m), 1.79-1.86 (1H, m), 1.17 (3H, s), 1.09 (3H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 221.2, 139.0, 128.6, 128.1, 126.8, 54.9, 45.2, 36.6, 28.1, 24.9, 23.7. LCMS (HpH): t_R = 1.20 min, [M-H^+] 187.2. HRMS: ($C_{13}H_{17}O$) [M+H^+] requires 189.1279, found 189.1275 [M+H^+] (error -2.1 ppm).

NMR yield: A vial containing alkene-nitrile **3.70** (93 mg, 0.50 mmol, 1.0 eq) and $Fe(acac)_3$ (87 mg, 0.25 mmol, 0.5 eq) was sealed and purged with nitrogen. In a separate vial was added a solution of $PhSiH_3$ (168 mg, 1.56 mmol, 3 eq) in EtOH:HFIP (1:1, 2 mL, 0.25 M), the vial was also sealed and purged with nitrogen. The solution was then added to the solids and the reaction was moderately stirred at 50 ^{o}C for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 ^{o}C for 1 h in the microwave. The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. Then internal standard, 1,3,5-trimethoxybenzene (43 mg, 0.25 mmol, 0.5 eq), added and the reaction mixture diluted in $CDCl_3$. Analysis by ^{1}H NMR showed **3.121** in a 73% yield.

2,2-Dimethyl-5-oxo-5-phenylpentanenitrile (3.122)



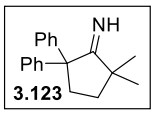
3.122

To a vial containing alkene-nitrile **3.70** (93 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq), was added a solution of $PhSiH_3$ (161 mg, 1.48 mmol, 3 eq) in *i*PrOH (2 mL, 0.25 M). The reaction was moderately stirred open to air at 50 ^{o}C for 0.5 h, then the reaction mixture concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-10 TBME:cyclohexane) afforded **3.122** as an impure colourless gum (42 mg, 0.21 mmol, 42%, ~90% purity).

ν_{max} (neat): 2979, 2939, 2232, 1685, 749 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.97-8.00 (2H, m), 7.56-7.60 (1H, m), 7.46-7.50 (2H, m), 3.18-3.22 (2H, m), 2.00-2.04 (2H, m), 1.41 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 198.3, 136.6, 133.3, 128.7, 128.0, 124.6, 34.9, 34.6, 32.1, 26.7. LCMS (Formic): t_R = 1.02 min, $[M+H^+]$ 202.1 (90% purity by UV). HRMS: ($C_{13}H_{16}NO$) $[M+H^+]$ requires 202.1232, found $[M+H^+]$ 202.1230 (error -1.0 ppm).

NMR yield: To a vial containing alkene-nitrile **3.70** (96 mg, 0.52 mmol, 1 eq) and $Fe(acac)_3$ (37 mg, 0.10 mmol, 0.2 eq), was added a solution of $PhSiH_3$ (166 mg, 1.54 mmol, 3 eq) in *i*PrOH (2 mL, 0.25 M). The reaction was moderately stirred open to air at 50 °C for 0.5 h, then the reaction mixture concentrated *in* vacuo. Then internal standard, 1,3,5-trimethoxybenzene (26 mg, 0.16 mmol, 0.3 eq), added and the reaction mixture diluted in $CDCl_3$. Analysis by ^{1}H NMR showed **3.122** in a 37% yield.

2,2-Dimethyl-5,5-diphenylcyclopentan-1-imine (3.123)

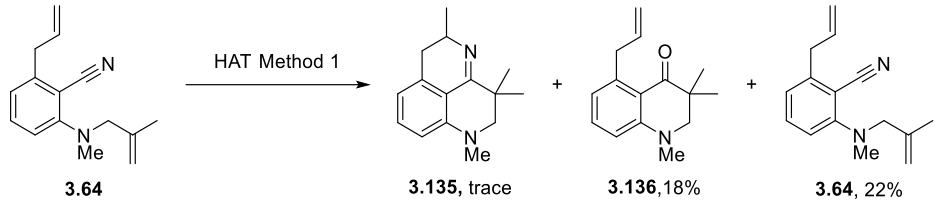


A vial containing alkene-nitrile **3.68** (107 mg, 0.41 mmol, 1.0 eq) and $Fe(acac)_3$ (108 mg, 0.31 mmol, 0.75 eq) was sealed and purged with nitrogen. In a separate vial was added a solution of $PhSiH_3$ (198 mg, 1.83 mmol, 4.5 eq) in EtOH:HFIP (1:1, 2 mL, 0.21M), the vial was also sealed and purged with nitrogen. The solution was then added to the solids and the reaction was moderately stirred at 50 °C for 1 h. The reaction was stopped, concentrated *in vacuo* and the resulting mixture purified by High pH MDAP (method D) to afford **3.123** as a brown gum (32 mg, 0.12 mmol, 29%).

ν_{max} (neat): 2966, 2870, 1667, 1599, 1501, 758 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.28-7.32 (4H, m), 7.18-7.23 (6H, m), 3.31 (1H, br. s), 2.57 (2H, t, *J* = 6.6 Hz), 1.58 (2H, t, *J* = 6.6 Hz), 1.10 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 197.7, 143.8, 128.5, 128.4, 126.7, 64.4, 43.2, 36.9, 36.7, 28.1. LCMS (HpH): t_R = 1.30 min, $[M+H^+]$ 264.3. HRMS: ($C_{19}H_{22}N$) $[M+H^+]$ requires 264.1752, found $[M+H^+]$ 264.1753 (error 0.4 ppm).

8.2.5 – Mechanistic Discussion

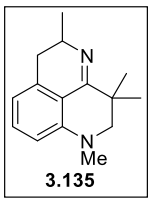
Tandem cyclisation of 3.64



NMR yield: To a vial containing alkene-nitrile-alkene **3.64** (115 mg, 0.51 mmol, 1 eq) and $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq), was added a solution of $PhSiH_3$ (165 mg, 1.53 mmol, 3 eq) in *i*PrOH (2 mL, 0.25 M). The reaction was moderately stirred open to air at 50 ^oC for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 ^oC for 1 h in the microwave. The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. Then internal standard, 1,3,5-trimethoxybenzene (17 mg, 0.10 mmol, 0.2 eq), was added and the mixture dissolved in $CDCl_3$. Analysis by ^1H NMR showed **3.136** in a 18% yield and 22% remaining starting material **3.64**. Tandem cyclised product **3.135** remained in the acidified aqueous layer, addition of sat. $NaHCO_{3(aq)}$ (50 mL) and extraction with EtOAc (3 x 25 mL) gave crude **3.135**. Analysis by ^1H NMR could not quantify the product yield of **3.135**.

Characterisation was made from purified samples obtained by MDAP:

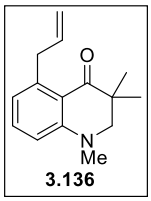
1,3,3,5-Tetramethyl-2,3,5,6-tetrahydro-1*H*-benzo[*de*][1,6]naphthyridine (3.135)



Brown gum. ν_{max} (neat): 2959, 2926, 2867, 2814, 1621, 1593, 1494, 760 cm^{-1}. ^1H NMR (600 MHz, CHLOROFORM-d) δ = 7.18 (1H, t, *J* = 7.9 Hz), 6.53 (1H, d, *J* = 8.4 Hz), 6.45 (1H, d, *J* = 7.3 Hz), 3.66-3.72 (1H, m), 2.97-3.07 (2H, m), 2.96 (3H, s), 2.72 (1H, dd, *J* = 15.8 and 5.5 Hz), 2.39 (1H, dd, *J* = 15.8 and 9.9 Hz), 1.27 (3H, d, *J* = 7.0 Hz), 1.18 (3H, s), 1.15 (3H, s). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 166.3, 146.4, 137.8, 131.5, 115.9, 111.7, 110.1, 63.6, 51.3, 39.2, 36.8, 33.4, 24.2, 23.5, 21.3. LCMS (HpH): t_R = 1.17 min, $[M+H^+]$ 229.1.

HRMS: ($C_{15}H_{21}N_2$) [M+H$^+$] requires 229.1705, found 229.1704 [M+H$^+$] (error -0.4 ppm).

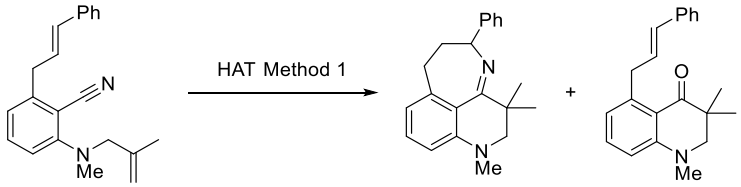
5-Allyl-1,3,3-trimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.136)



3.136

Brown gum. ν_{max} (neat): 2927, 1666, 1593, 1131 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.25-7.29 (1H, m), 6.57-6.60 (2H, m), 6.05 (1H, ddt, *J* = 16.9, 10.2 and 6.4 Hz), 4.95-5.02 (2H, m), 3.80 (2H, d, *J* = 6.4 Hz), 3.18 (2H, s), 3.02 (3H, s), 1.14 (6H, s). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 200.0, 152.7, 144.7, 138.1, 133.9, 120.0, 116.1, 114.6, 111.3, 63.1, 42.0, 40.0, 39.8, 22.2. LCMS (HpH): t_R = 1.33 min, [M+H$^+$] 230.1. HRMS: ($C_{15}H_{20}NO$) [M+H$^+$] requires 230.1545, found 230.1545 [M+H$^+$] (error 0.0 ppm).

Tandem cyclisation of 3.65

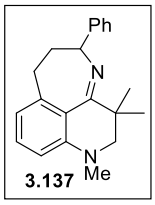


3.65 **3.137**, 14% **3.138**, 10%

NMR yield: To a vial containing alkene-nitrile-alkene **3.65** (146 mg, 0.48 mmol, 1 eq) and Fe(acac)$_3$ (35 mg, 0.10 mmol, 0.2 eq), was added a solution of $PhSiH_3$ (158 mg, 1.46 mmol, 3 eq) in *i*PrOH (2 mL, 0.25 M). The reaction was moderately stirred open to air at 50 ^{o}C for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 ^{o}C for 1 h in the microwave. The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. Then internal standard, 1,3,5-trimethoxybenzene (9 mg, 0.05 mmol, 0.1 eq), was added and the mixture dissolved in $CDCl_3$. Analysis by ^{1}H NMR showed **3.138** in a 10% yield. Tandem cyclised product **3.137** remained in the acidified aqueous layer, addition of sat. $NaHCO_{3(aq)}$ (50 mL) and extraction with EtOAc (3 x 25 mL) gave crude **3.65** to which internal standard, 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol, 0.1 eq), was added. Analysis by ^{1}H NMR showed **3.137** in a 14% yield.

Characterisation was made from purified samples obtained by MDAP:

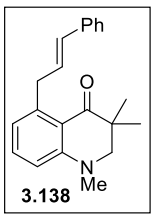
1,3,3-Trimethyl-5-phenyl-1,2,3,5,6,7-hexahydroazepino[2,3,4-*de*]quinoline (3.137)



3.137

Brown gum. ν_{max} (neat): 3060, 2927, 2852, 1619, 1590, 1494, 699 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.57 (2H, d, *J* = 7.3 Hz), 7.31 (2H, t, *J* = 7.6 Hz), 7.16-7.21 (2H, m), 6.55 (2H, t, *J* = 7.7 Hz), 4.23-4.24 (1H, m), 2.95-3.25 (2H, m), 2.94 (3H, s), 2.47-2.62 (3H, m), 2.39-2.44 (1H, m), 1.29 (3H, s), 1.17 (3H, s). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 171.9, 147.0, 146.4, 141.2, 131.4, 128.5, 127.3, 126.5, 116.9, 116.8, 110.0, 64.0, 63.1, 45.3, 38.5, 37.4, 31.4, 24.2, 23.1. LCMS (HpH): t_R = 1.62 min, [M+H^+] 305.1. HRMS: ($C_{21}H_{25}N_2$) [M+H^+] requires 305.2018, found 305.2017 [M+H^+] (error -0.3 ppm).

5-Cinnamyl-1,3,3-trimethyl-2,3-dihydroquinolin-4(1*H*)-one (3.138)

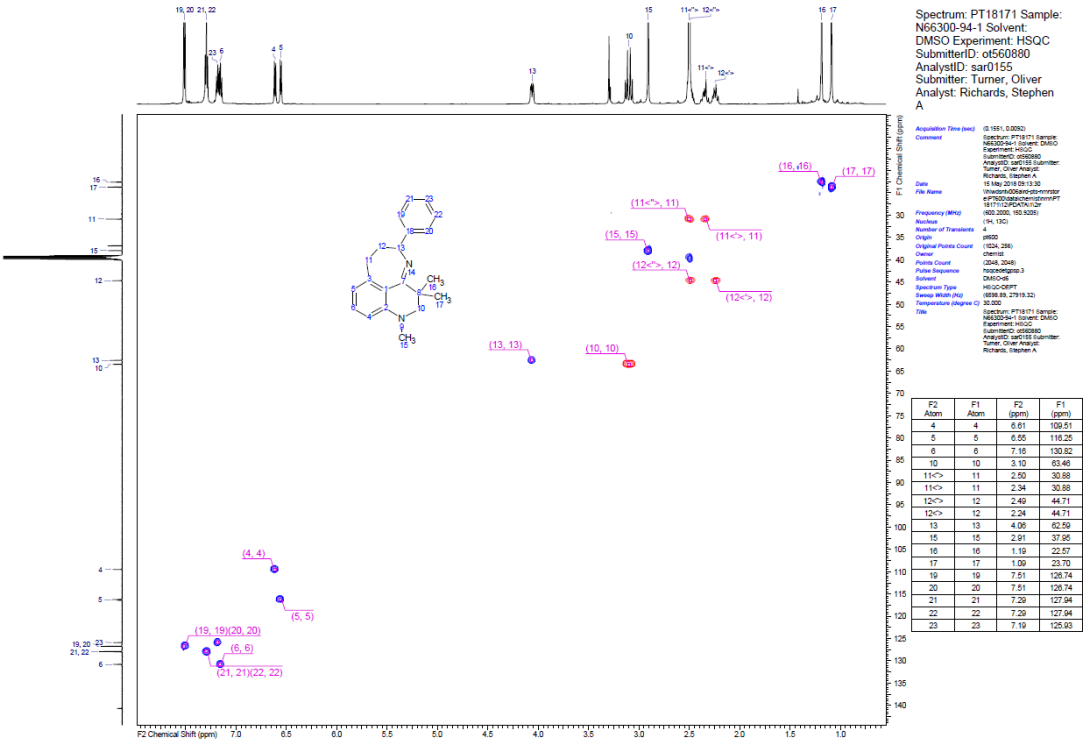


3.138

Brown gum. ν_{max} (neat): 3056, 2928, 1666, 1594, 1265, 733 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.29-7.34 (2H, m), 7.23-7.27 (3H, m), 7.12-7.17 (1H, m), 6.58-6.64 (2H, m), 6.37-6.49 (2H, m), 3.95 (2H, d, *J* = 6.1 Hz), 3.19 (2H, s), 3.02 (3H, s), 1.15 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 200.1, 152.7, 144.8, 138.1, 133.9, 130.2, 128.3, 126.7, 126.1, 120.0, 116.1, 111.4, 63.0, 42.0, 41.0, 40.0, 38.9, 22.2. LCMS (HpH): t_R = 1.52 min, [M+H^+] 306.1. HRMS: ($C_{21}H_{24}NO$) [M+H^+] requires 306.1858, found 306.1847 [M+H^+] (error -0.3 ppm).

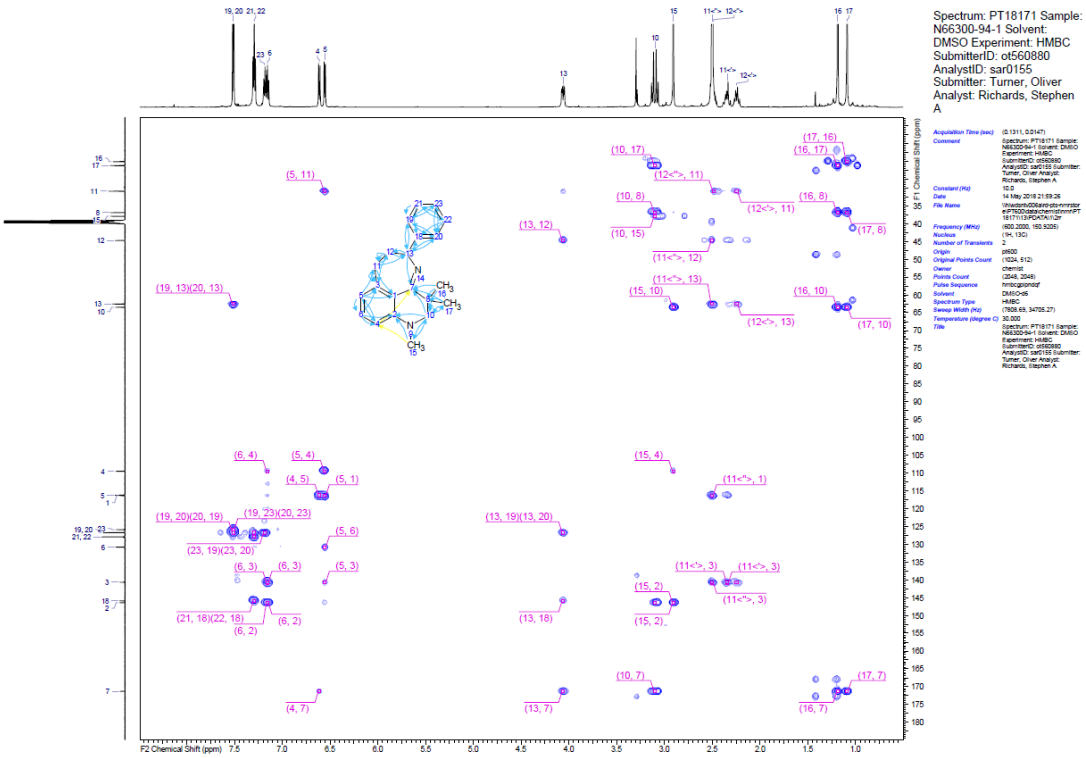
2D NMR spectra to confirm the structure of **3.137** are shown below:

HSQC Spectrum of **3.137** (600 MHz, DMSO-d_6)

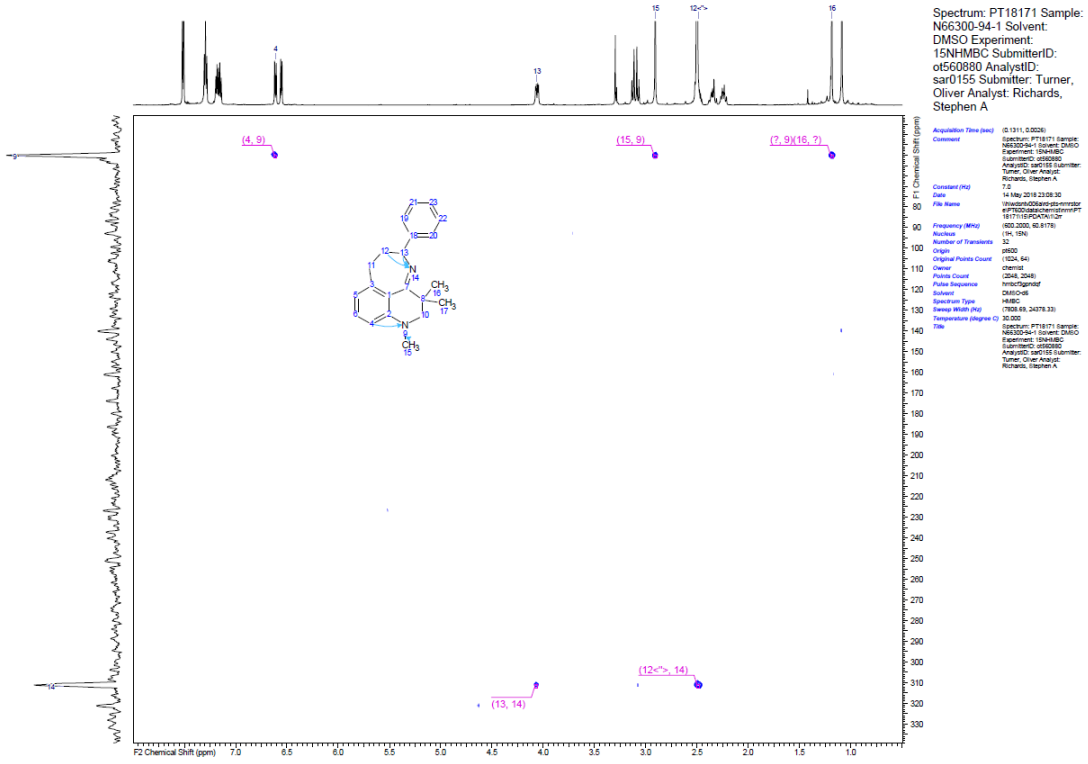


F2 Atom	F1 Atom	F2 (ppm)	F1 (ppm)
4	4	6.61	109.51
5	5	6.55	116.25
6	6	7.16	130.82
10	10	3.10	63.46
11<'>	11	2.50	30.88
11<>	11	2.34	30.88
12<'>	12	2.49	44.71
12<>	12	2.24	44.71
13	13	4.06	62.59
15	15	2.91	37.86
16	16	1.19	22.57
17	17	1.09	23.70
19	19	7.51	126.74
20	20	7.51	126.74
21	21	7.29	127.94
22	22	7.29	127.94
23	23	7.19	125.93

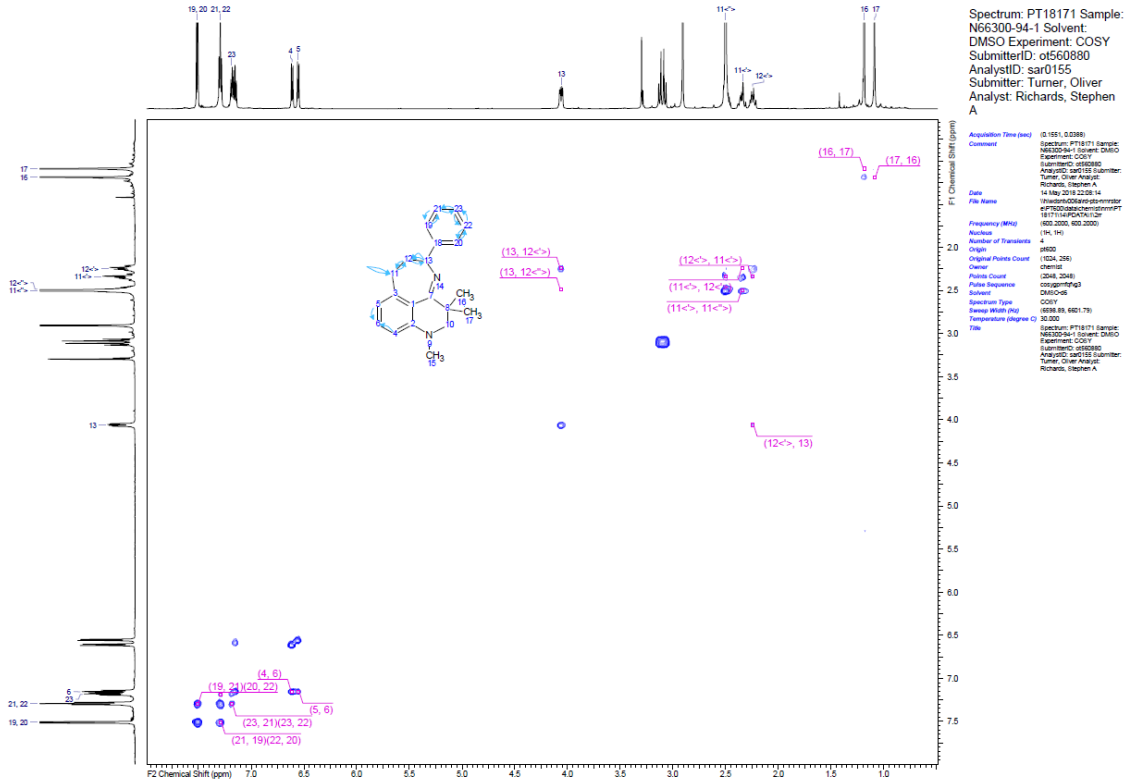
HMBC Spectrum of **3.137** (600 MHz, DMSO-d_6)



^{15}N-HMBC Spectrum of **3.137** (600 MHz, DMSO-d_6)



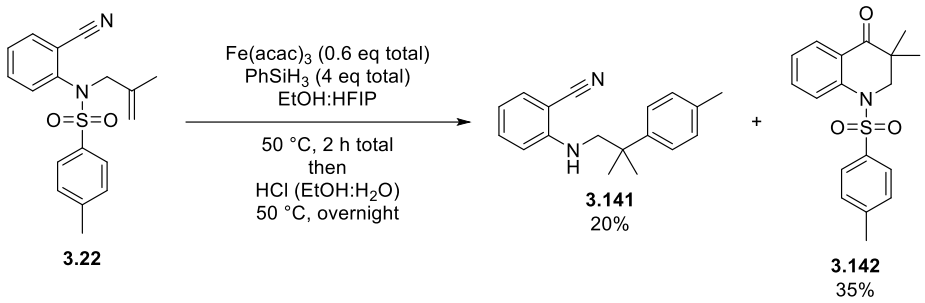
COSY Spectrum of **3.137** (600 MHz, DMSO-d_6)



COSY spectrum (DMSO-d^6) of compound **3.137** showing coupling between protons on C11 and C12 [One proton from each CH_2 coincides with peak of residual partially deuterated DMSO], consistent with the seven-membered ring of **3.137**.

8.2.6 – Intriguing Observations

HAT Reaction of *N*-(2-cyanophenyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (3.22)



To a solution of **3.22** (102 mg, 0.31 mmol, 1 eq) and $Fe(acac)_3$ (58 mg, 0.17 mmol, 0.5 eq) in HFIP (0.75 mL) and EtOH (0.75 mL), $PhSiH_3$ (115 μL, 0.93 mmol, 3 eq) was added. The reaction was stirred at 50 ^oC for 1 h. Then further $Fe(acac)_3$ (11 mg, 0.03 mmol, 0.1 eq) and $PhSiH_3$ (38 μL, 0.45 mmol, 1 eq) was added, and the reaction stirred at 50 ^oC for a further 1 h. The reaction was stopped and concentrated *in vacuo*. Then $HCl_{(aq)}$ (2M, 2 mL) and HCl (EtOH, 1.25 M, 0.66 mL) were added and the reaction stirred at 50 ^oC overnight. The reaction was allowed to cool to RT, water added (15 mL) and the aqueous layer extracted with EtOAc (3 x 15 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude brown oil was purified by automated column chromatography on silica gel (0-10% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford:

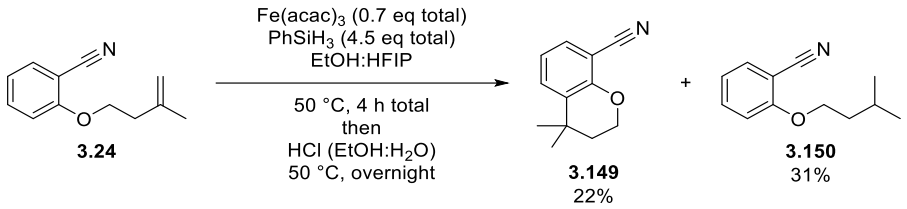
3.141 as a colourless oil (17 mg, 0.06 mmol, 20%);

ν_{max} (neat): 3078, 2860, 1687, 1598, 1451, 1238, 754 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.27-7.34 (4H, m), 7.16-7.18 (2H, m), 6.58-6.62 (2H, m), 4.33 (1H, br.s), 3.28 (2H, d, *J* = 5.6 Hz), 2.33 (3H, s), 1.43 (6H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.6, 142.7, 136.1, 134.1, 132.7, 129.4, 125.8, 117.6, 116.3, 110.8, 95.8, 55.3, 38.5, 26.9, 20.9. LCMS (Formic): t_R = 1.45 min, $[M+H^+]$ = 265.1. HRMS: ($C_{18}H_{21}N_2$) $[M+H^+]$ requires 265.1705, found 265.1703 $[M+H^+]$ (error -0.8 ppm).

3.142 as an orange solid (35 mg, 0.11 mmol, 35%);

M.pt.: 104-106 ^{o}C. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.01 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.80-7.82 (2H, m), 7.63 (1H, d, *J* = 7.8 Hz), 7.39-7.43 (1H, m), 7.33 (2H, d, *J* = 7.8 Hz), 7.07-7.11 (1H, m), 3.96 (2H, s), 2.42 (3H, s), 1.26 (6H, s). LCMS (Formic): t_R = 1.28 min, [M+H^{+}] = 330.0.

HAT Reaction of 2-((3-methylbut-3-en-1-yl)oxy)benzonitrile (3.24)



To a solution of **3.24** (170 mg, 0.91 mmol, 1 eq) and Fe(acac)$_3$ (155 mg, 0.44 mmol, 0.5 eq) in HFIP (1.5 mL) and EtOH (1.5 mL), $PhSiH_3$ (336 μL, 2.72 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 3 h. Then further Fe(acac)$_3$ (80 mg, 0.23 mmol, 0.2 eq) and $PhSiH_3$ (168 μL, 1.36 mmol, 1.5 eq) was added, and the reaction stirred at 50 ^{o}C for a further 1 h. The reaction was stopped and concentrated *in vacuo*. Then HCl $_{(aq)}$ (2M, 5mL) and HCl (EtOH, 1.25 M, 2 mL) were added and the reaction stirred at 50 ^{o}C overnight. The reaction was allowed to cool to RT, water added (25 mL) and the aqueous layer extracted with EtOAc (3 x 15 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude brown oil was purified by automated column chromatography on silica gel (0-10% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford:

3.149 as a yellow gum (37 mg, 0.20 mmol, 22%);

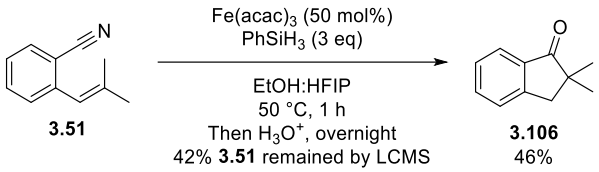
ν_{max} (neat): 2962, 2228, 1590, 1443, 1133, 744 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.46 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.35 (1H, dd, *J* = 7.6 and 1.7 Hz), 6.90 (1H, t, *J* = 7.8 Hz), 4.32-4.35 (2H, m), 1.86-1.88 (2H, m), 1.34 (6H, s). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 155.9, 132.9, 131.5, 131.3, 120.3, 116.9, 101.0, 64.0,

36.7, 30.64, 30.59. LCMS (Formic): t_R = 1.15 min, [M+/-H^+] = not found. HRMS: ($C_{12}H_{13}NO$) [M+H^+] requires 188.1075, found [M+H^+] 188.1078 (error 1.6 ppm).

3.150 as a colourless oil (53 mg, 0.28 mmol, 31%);

ν_{max} (neat): 2957, 2871, 2227, 1598, 1132, 1108 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.47-7.54 (2H, m), 6.94-6.99 (2H, m), 4.09 (2H, t, *J* = 6.6 Hz), 1.90 (1H, spt, *J* = 6.6 Hz), 1.74 (2H, q, *J* = 6.6 Hz), 0.98 (6H, d, *J* = 6.6 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 160.9, 134.2, 133.8, 120.5, 116.5, 112.2, 102.1, 67.5, 37.6, 25.0, 22.5. LCMS (HpH): t_R = 1.26 min, [M+/-H^+] = not found. HRMS: ($C_{12}H_{15}NO$) [M+H^+] requires 190.1232, found [M+H^+] 190.1234 (error 1.1 ppm).

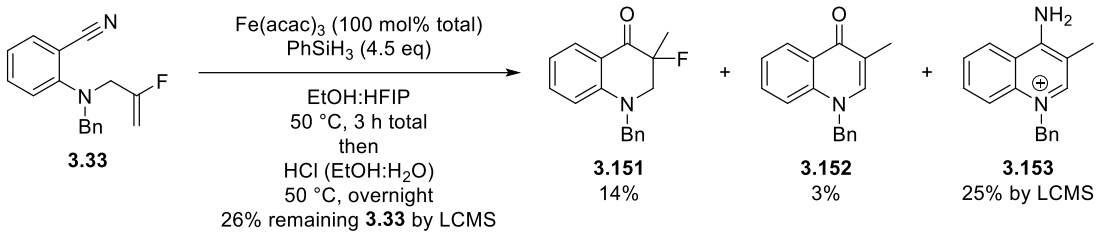
HAT Reaction of 2-(2-methylprop-1-en-1-yl)benzonitrile (3.51)



To a solution of **3.51** (50 mg, 0.32 mmol, 1 eq) and $Fe(acac)_3$ (56 mg, 0.16 mmol, 50 mol%) in HFIP (0.75 mL) and EtOH (0.75 mL), $PhSiH_3$ (117 μL, 0.95 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 1 h, then the reaction stopped and concentrated *in vacuo*. Then $HCl_{(aq)}$ (2M, 0.33 mL) and HCl (EtOH, 1.25 M, 0.66 mL) were added and the reaction stirred at 50 ^{o}C until full hydrolysis of the imine was observed (overnight). The reaction was allowed to cool to RT, water added (10 mL) and the aqueous layer extracted with EtOAc (3 x 10 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude brown oil was purified by automated column chromatography on silica gel (0-10 EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **3.106** as a colourless oil (23 mg, 0.15 mmol, 46%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.76 (1H, dd, *J* = 7.6 and 0.5 Hz), 7.59 (1H, td, *J* = 7.4 and 1.3 Hz), 7.41-7.44 (1H, m), 7.35-7.39 (1H, m), 3.00 (2H, s), 1.24 (6H, s). LCMS (Formic): t_R = 1.04 min, [M+H^+] = 161.0.

HAT Reaction of 2-(benzyl(2-fluoroallyl)amino)benzonitrile (3.33)



To a solution of **3.33** (76 mg, 0.29 mmol, 1 eq) and $Fe(acac)_3$ (78 mg, 0.22 mmol, 77 mol%) in HFIP (0.75 mL) and EtOH (0.75 mL), $PhSiH_3$ (160 μL, 1.22 mmol, 4.5 eq) was added. The reaction was stirred at 50 ^oC for 2 h. Further $Fe(acac)_3$ (23 mg, 0.07 mmol, 23 mol%) was added and the reaction stirred at 50 ^oC for a further 1 h. The reaction was stopped and concentrated *in vacuo*. Then $HCl_{(aq)}$ (2M, 0.66 mL) and HCl (EtOH, 1.25 M, 2.0 mL) were added and the reaction stirred at 50 ^oC overnight. The reaction was allowed to cool to RT, water (10 mL) added and the aqueous layer extracted with EtOAc (3 x 10 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude brown oil was purified by automated column chromatography on silica gel (0-10% EtOAc:cyclohexane). Desired fractions were combined, re-purified by MDAP (HpH) and the desired fractions dried *in vacuo* to afford a yellow solid as a mixture of **3.151** (11 mg, 0.04 mmol, 14%) and impurity **3.152** (2 mg, 8 µmol, 3%).

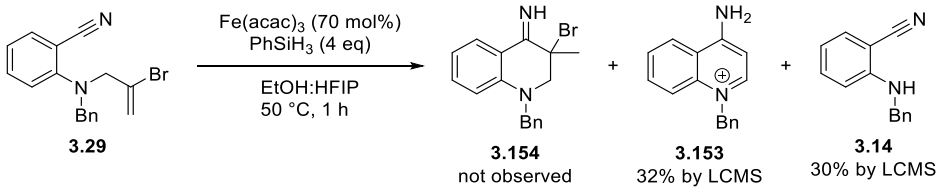
3.151: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.97 (1H, dd, *J* = 8.0 and 1.6 Hz), 7.26-7.38 (6H, m), 6.79 (1H, ddd, *J* = 8.0, 7.1 and 0.9 Hz), 6.74 (1 H, d, *J* = 8.6 Hz), 4.55-4.69 (2H, m), 3.78 (1H, dd, *J* = 13.2 and 9.8 Hz), 3.50 (1H, dd, *J* =18.2 and 13.1 Hz), 1.58 (3H, d, *J* = 21.0 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = complex due to impurity. LCMS (HpH): t_R = 1.22 min, $[M+H^+]$ = 270.0. HRMS: ($C_{17}H_{17}FNO$) $[M+H^+]$ requires 270.1294, found 270.1295 $[M+H^+]$ (error 0.4 ppm).

A sample of the aqueous layer was dried *in vacuo* and purified by MDAP (HpH) for characterisation of **3.153** (counterion unknown):

^{1}H NMR (600 MHz, CHLOROFORM-d) δ = 8.84 (1H, d, *J* = 8.1 Hz), 7.98 (1H, s), 7.65-7.7.68 (1H, m), 7.54-7.57 (2H, m), 7.30-7.35 (3H, m), 7.09-7.10 (2H, m), 5.61 (2H, s),

2.33 (3H, s). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 158.1, 143.5, 137.8, 133.9, 133.7, 129.4, 128.8, 126.5, 126.4, 126.2, 117.3, 116.8, 111.1, 57.6, 15.0. LCMS (HpH): t_R = 0.86 min, [M+] = 249.1.

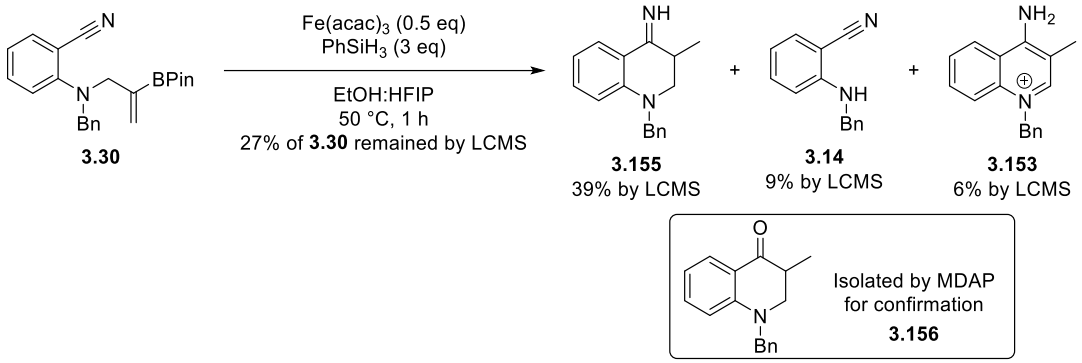
HAT Reaction of 2-(benzyl(2-bromoallyl)amino)benzonitrile (3.29)



To a solution of **3.29** (32 mg, 0.10 mmol, 1 eq) and $Fe(acac)_3$ (24 mg, 0.07 mmol, 70 mol%) in HFIP (0.5 mL) and EtOH (0.5 mL), $PhSiH_3$ (50 μL, 0.41 mmol, 4 eq) was added. The reaction was stirred at 50 ^{o}C for 1 h. Reaction analysed by LCMS and then abandoned.

LCMS (HpH): t_R = 0.59 min, [M^+] 249.1 (**3.153**); t_R = 1.19 min, [M+H^+] 209.1 (**3.14**).

HAT reaction of 2-(benzyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)amino)benzonitrile (3.30)



To a solution of **3.30** (19 mg, 0.05 mmol, 1 eq) and $Fe(acac)_3$ (9 mg, 0.03 mmol, 51 mol%) in HFIP (0.25 mL) and EtOH (0.25 mL), $PhSiH_3$ (19 μL, 0.15 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 1 h and then analysed by LCMS.

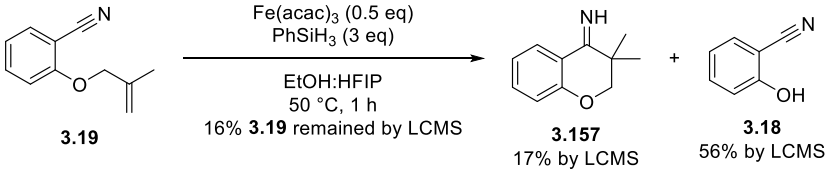
LCMS (Formic): t_R = 0.60 min, [M^+] 249.1 (**3.153**); t_R = 0.65 min, [M+H^+] 251.1 (**3.155**); t_R = 1.20 min, [M+H^+] 209.1 (**3.14**).

A sample of the reaction mixture was purified by MDAP (formic) for characterisation of **3.156**:

^{1}H NMR (600 MHz, CHLOROFORM-d) δ = 7.94 (1H, dd, *J* = 7.7 and 1.8 Hz), 7.34-7.36 (2H, m), 7.27-7.32 (4H, m), 6.72-6.74 (1H, m), 6.70 (1H, d, *J* = 8.8 Hz), 4.53-4.61 (2H, m), 3.52 (1H, dd, *J* = 12.1 and 5.5 Hz), 3.35 (1H, t, *J* = 11.9 Hz), 2.75-2.81 (1H, m), 1.21 (3H, d, *J* = 7.0 Hz). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 196.2, 151.4, 137.4, 135.2, 128.8, 128.5, 127.4, 126.8, 119.2, 117.0, 113.2, 56.0, 55.2, 40.9, 12.6. LCMS (Formic): t_R = 1.25 min, [M+H] = 252.1.

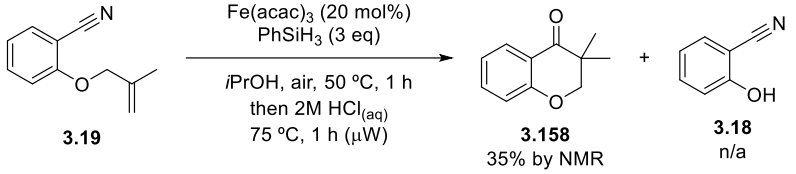
8.2.7 – Challenging Substrates

HAT Reaction of 2-((2-methylallyl)oxy)benzonitrile (3.19)



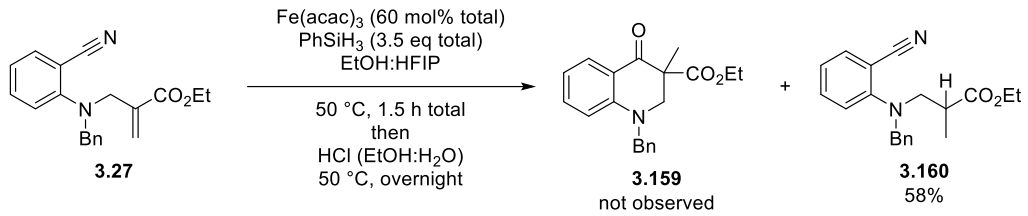
To a solution of **3.19** (52 mg, 0.30 mmol, 1 eq) and $Fe(acac)_3$ (53 mg, 0.15 mmol, 50 mol%) in HFIP (0.75 mL) and EtOH (0.75 mL), $PhSiH_3$ (110 μL, 0.90 mmol, 3 eq) was added. The reaction was stirred at 50 °C for 1 h, analysed by LCMS and abandoned.

LCMS (HpH): t_R = 0.38 min, $[M\text{-}H^+]$ 118.2 (**3.18**); t_R = 0.92 min, $[M+H^+]$ 176.1 (**3.157**).



NMR yield: To a vial containing **3.19** (85 mg, 0.49 mmol, 1 eq) and $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq), was added a solution of $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq) in *i*PrOH (2 mL, 0.25 M). The reaction was stirred open to air at 50 °C for 1 h. Then 2M $HCl_{(aq)}$ (2 mL) was added and the reaction stirred at 75 °C for 1 h in the microwave. The reaction was cooled to RT, water (50 mL) added and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organics were passed through a hydrophobic frit and concentrated *in vacuo*. Then internal standard, 1,3,5-trimethoxybenzene (24 mg, 0.14 mmol, 0.3 eq), added and the reaction mixture diluted in $CDCl_3$. Analysis by ^1H NMR showed **3.158** in a 35% yield.

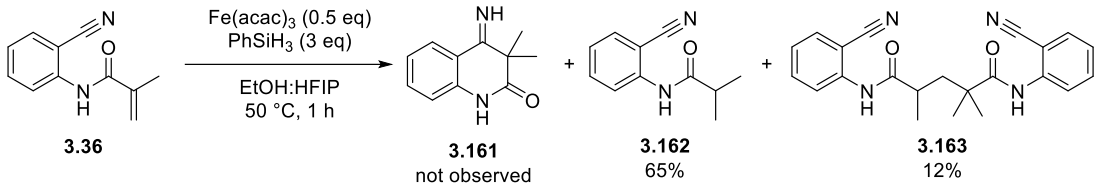
HAT Reaction of ethyl 2-((benzyl(2-cyanophenyl)amino)methyl)acrylate (3.27)



To a solution of **3.27** (106 mg, 0.33 mmol, 1 eq) and $Fe(acac)_3$ (58 mg, 0.17 mmol, 50 mol%) in HFIP (1 mL) and EtOH (1 mL), $PhSiH_3$ (122 μL, 0.99 mmol, 3 eq) was added. The reaction was stirred at 50 ^oC for 1 h. Then further $Fe(acac)_3$ (12 mg, 0.03 mmol, 10 mol%) and $PhSiH_3$ (20 μL, 0.17 mmol, 0.5 eq) was added, and the reaction stirred at 50 ^oC for a further 0.5 h. The reaction was stopped and $HCl_{(aq)}$ (2M, 1.0 mL) and HCl (EtOH, 1.25 M, 1.0 mL) were added and the reaction stirred at 50 ^oC overnight. The reaction was allowed to cool to RT, water added (25 mL) and the aqueous layer extracted with EtOAc (3 x 15 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude brown oil was purified by automated column chromatography on silica gel (0-20% TBME:cyclohexane). Desired fractions were combined and re-purified by MDAP (HpH) and the desired fractions dried *in vacuo* to afford **3.160** as a brown gum (62 mg, 0.19 mmol, 58%).

ν_{max} (neat): 2978, 2937, 2219, 1728, 1595, 1488, 1445, 1183, 758 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.56 (1H, dd, *J* = 7.8 and 1.7 Hz), 7.40 (1H, ddd, *J* = 8.7, 7.2, and 1.7 Hz), 7.22-7.31 (5H, m), 6.95-7.01 (2H, m), 4.45-4.55 (2H, m), 4.00-4.06 (2H, m), 3.57 (1H, dd, *J* = 13.9 and 8.6 Hz), 3.28 (1H, dd, *J* = 13.9 and 6.1 Hz), 2.71-2.79 (1H, m), 1.18 (3H, t, *J* = 7.1 Hz), 1.11 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 175.2, 153.5, 137.1, 134.8, 133.2, 128.5, 128.3, 127.5, 121.6, 121.4, 118.8, 106.3, 60.6, 58.7, 54.4, 38.4, 15.2, 14.1. LCMS (HpH): t_R = 1.31 min, $[M+H^+]$ = 323.3. HRMS: ($C_{20}H_{23}N_2O_2$) $[M+H^+]$ requires 323.1760, found $[M+H^+]$ 323.1759 (error -0.3 ppm).

HAT Reaction of *N*-(2-cyanophenyl)methacrylamide (3.36)

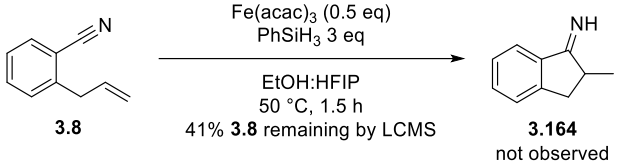


To a solution of **3.36** (93 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (88 mg, 0.25 mmol, 0.5 eq) in HFIP (1 mL) and EtOH (1 mL), $PhSiH_3$ (185 μL, 1.50 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 1 h. The reaction was cooled to RT, concentrated *in vacuo* and purified by automated column chromatography on silica gel (0-50% EtOAc:cyclohexane). Desired fractions were combined and dried *in vacuo* to yield **3.162** as a white solid (61 mg, 0.32 mmol, 65%) and **3.163** as an off-white solid (22 mg, 0.06 mmol, 12%).

3.162: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.43 (1H, d, *J* = 8.3 Hz), 7.66 (1H, br.s), 7.56-7.61 (2H, m), 7.14-7.18 (1H, m), 2.63 (1H, sept, *J* = 6.9 Hz), 1.30 (6H, d, *J* = 6.9 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 175.4, 140.7, 134.2, 132.1, 124.0, 121.2, 116.4, 101.8, 36.9, 19.4. LCMS (HpH): t_R = 0.75 min, [M-H$^+$] = 187.2.

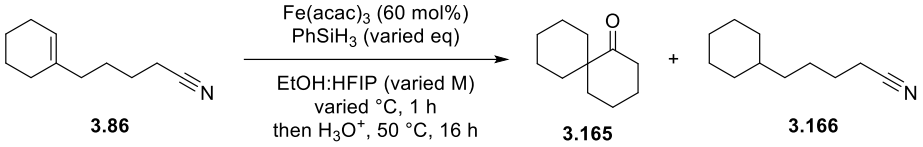
3.163: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.38 (1H, br.s), 8.35 (1H, d, *J* = 8.3 Hz), 8.23 (1H, d, *J* = 8.3 Hz), 7.99 (1H, br.s), 7.48-7.57 (4H, m), 7.11-7.18 (2H, m), 2.60-2.69 (1H, m), 2.42 (1H, dd, *J* = 14.4 and 7.3 Hz), 1.63-1.64 (1H, m), 1.44 (3H, s), 1.40 (3H, s), 1.31 (3H, d, *J* = 6.9 Hz) . ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 176.2, 175.2, 140.7, 140.3, 134.2, 133.8, 132.4, 132.0, 124.4, 124.0, 121.9, 116.51, 116.45, 102.9, 102.8, 45.0, 43.8, 39.1, 26.5, 25.9, 19.9. LCMS (HpH): t_R = 0.97 min, [M+H$^+$] = 375.2.

HAT Reaction of 2-allylbenzonitrile (3.8)



To a solution of **3.8** (74 mg, 0.51 mmol, 1 eq) and $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) in HFIP (1 mL) and EtOH (1 mL), $PhSiH_3$ (187 μL, 1.52 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 1.5 h, analysed by LCMS and abandoned as **3.164** was not observed. LCMS complex, no identifiable side-products.

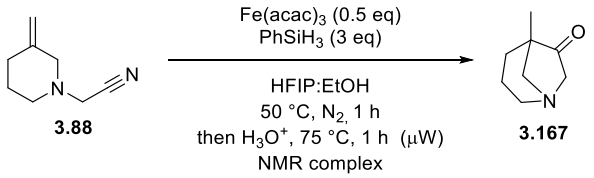
HAT Reaction of 5-(cyclohex-1-en-1-yl)pentanenitrile (3.86)



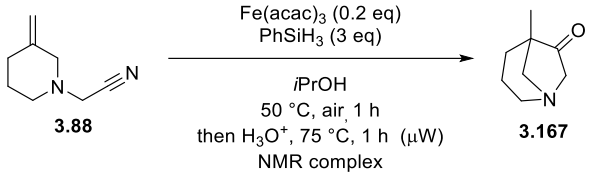
To a vial was added **3.86** (41 mg, 0.25 mmol, 1 eq) and $Fe(acac)_3$ (53 mg, 0.15 mmol, 60 mol%), dissolved in EtOH and HFIP (varied ratios and concentration). Then $PhSiH_3$ added (varied equivalents). The reaction was sealed and stirred at temperature (varied) for 1 h. Then 0.5 mL (HCl, EtOH, 1.25M) and 0.5 mL (HCl, H_2O, 2M) added and the reaction stirred at 50 ^{o}C overnight (16 h). Then water (25 mL) added and the aqueous layer extracted EtOAc (3 x15 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.*

The ratio of **3.165**:**3.166** of the crude reaction mixture was then determined ^{1}H NMR by comparison of triplets (α-C=O *vs* α-C≡N) (δ = 2.38 *vs*. δ = 2.32). Results shown in Table 6, p.57.

HAT Reaction of 2-(3-methylenepiperidin-1-yl)acetonitrile (3.88)

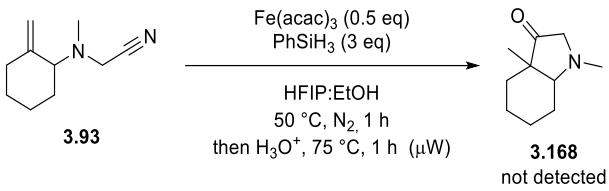


The title reaction was carried out according to general method 2 using alkene-nitrile **3.88** (67 mg, 0.49 mmol, 1 eq), $Fe(acac)_3$ (85 mg, 0.24 mmol, 0.5 eq) and $PhSiH_3$ (163 mg, 1.51 mmol, 3 eq). The crude reaction mixture was analysed by ^1H NMR and the reaction abandoned due to complexity.

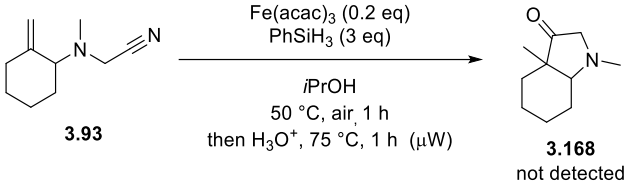


The title reaction was carried out according to general method 1 using alkene-nitrile **3.88** (69 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (163 mg, 1.50 mmol, 3 eq). The crude reaction mixture was analysed by ^1H NMR and the reaction abandoned due to complexity.

HAT Reaction of 2-(methyl(2-methylenecyclohexyl)amino)acetonitrile (3.93)

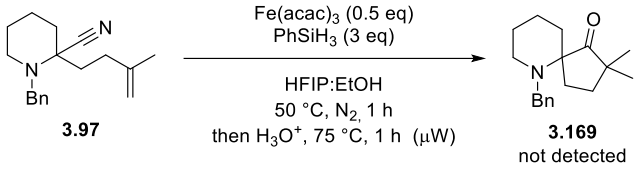


The title reaction was carried out according to general method 2 using alkene-nitrile **3.93** (84 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (167 mg, 1.54 mmol, 3 eq). The crude reaction mixture was analysed by ^1H NMR and the reaction abandoned as **3.168** was not observed.

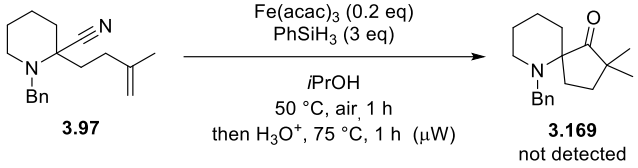


The title reaction was carried out according to general method 1 using alkene-nitrile **3.93** (83 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (168 mg, 1.55 mmol, 3 eq). The crude reaction mixture was analysed by ^1H NMR and the reaction abandoned as **3.168** was not observed.

HAT Reaction of 1-benzyl-2-(3-methylbut-3-en-1-yl)piperidine-2-carbonitrile (3.97)

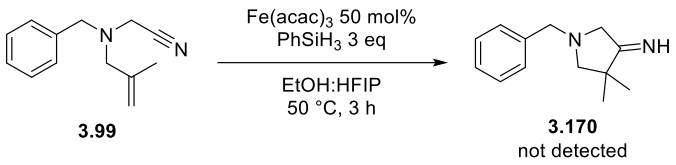


The title reaction was carried out according to general method 2 using alkene-nitrile **3.97** (136 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (89 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (166 mg, 1.53 mmol, 3 eq). The crude reaction mixture was analysed by mass spec (direct injection) and the reaction abandoned as **3.169** was not observed, decyanation was the major species.



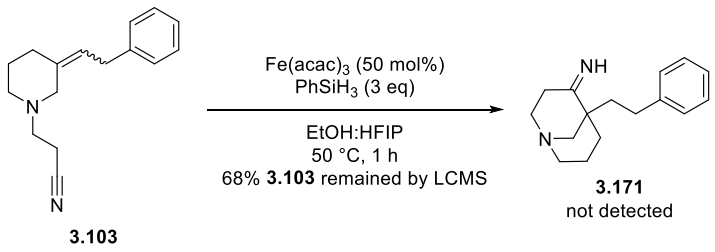
The title reaction was carried out according to general method 1 using alkene-nitrile **3.97** (132 mg, 0.49 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (162 mg, 1.50 mmol, 3 eq). The crude reaction mixture was analysed by ^1H NMR and the reaction abandoned as **3.169** was not observed.

HAT Reaction of 2-(benzyl(2-methylallyl)amino)acetonitrile (3.99)



To a solution of **3.99** (80 mg, 0.40 mmol, 1 eq) and $Fe(acac)_3$ (70 mg, 0.20 mmol, 0.5 eq) in HFIP (0.75 mL) and EtOH (0.75 mL), $PhSiH_3$ (147 μL, 1.12 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 3 h, analysed by LCMS and abandoned as **3.170** was not observed. LCMS was complex, no identifiable side-products and **3.99** consumed.

HAT Reaction of 3-(3-(2-phenylethylidene)piperidin-1-yl)propanenitrile (3.103)

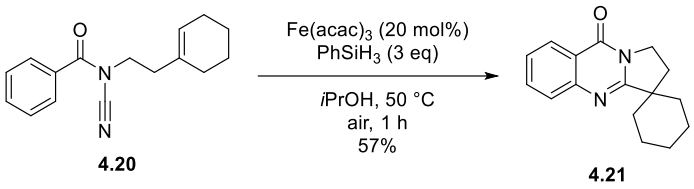


To a solution of **3.103** (35 mg, 0.15mmol, 1 eq) and $Fe(acac)_3$ (27 mg, 0.08 mmol, 0.5 eq) in HFIP (0.3 mL) and EtOH (0.3 mL), $PhSiH_3$ (54 μL, 0.44 mmol, 3 eq) was added. The reaction was stirred at 50 ^{o}C for 1 h, analysed by LCMS and abandoned as **3.171** was not observed. LCMS complex, no identifiable side-products and 68% **3.103** remaining.

8.3 – Synthetic Procedures for Section 4

8.3.1 – Preliminary Investigations

Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)benzamide (4.20)

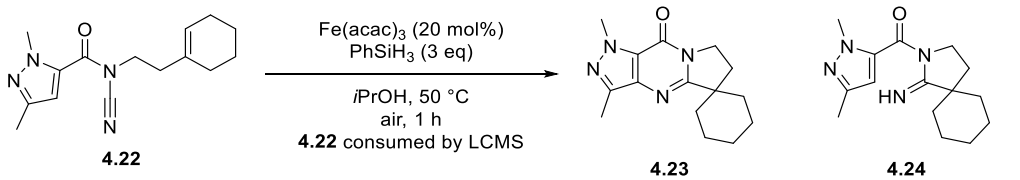


4.20 **4.21**

To a vial was added **4.20** (129 mg, 0.51 mmol, 1 eq) and $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq), to this was added a solution of $PhSiH_3$ (165 mg, 1.52 mmol, 3 eq) in *i*PrOH (2 mL). The reaction was then stirred open to air, at 50 °C, for 1 h. The reaction was cooled to RT and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-50% TBME:cyclohexane) to afford **4.21** as a colourless gum (73 mg, 0.29 mmol, 57%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.27 (1H, d, *J* = 7.8 Hz), 7.70 (2H, d, *J* = 3.4 Hz), 7.38-7.44 (1H, m), 4.08-4.12 (2H, m), 2.16-2.20 (2H, m), 1.89-1.95 (2H, m), 1.81-1.84 (2H, m), 1.72-1.74 (1H, m), 1.64-1.67 (2H, m), 1.39-1.51 (3H, m). LCMS (HpH): t_R = 1.08 min, [M+H$^+$] 255.2.

Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (4.22)



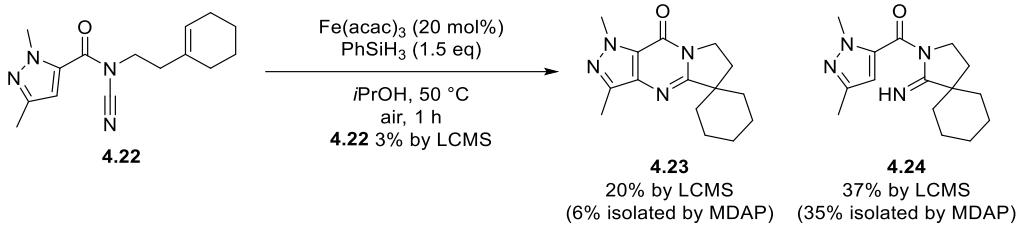
4.22 **4.23** 9% by LCMS (3% isolated by MDAP) **4.24** 46% by LCMS (36% isolated by MDAP)

To a vial was added **4.22** (137 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq), to this was added a solution of $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq) in *i*PrOH (2 mL). The reaction was then stirred open to air, at 50 °C, for 1 h. The reaction was cooled to RT and concentrated *in vacuo*. Purification by MDAP (HpH) yielded **4.24** as

a colourless gum (50 mg, 0.18 mmol, 36%) and **4.23** as a white solid (5 mg, 0.02 mmol, 3%).

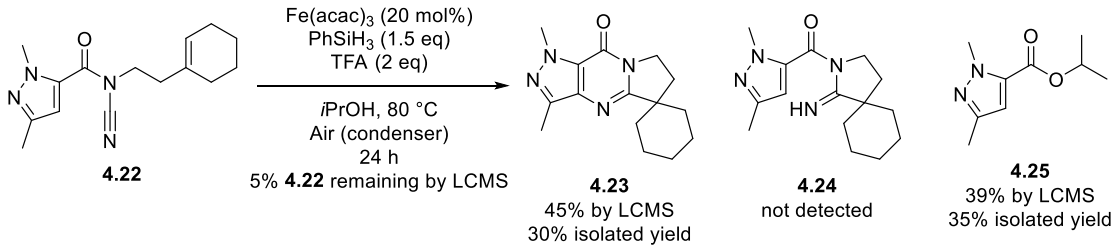
4.23: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.22 (3H, s), 4.02-4.06 (2H, m), 2.48 (3H, s), 2.17-2.20 (2H, m), 1.80-1.92 (4H, m), 1.71-1.72 (1H, m), 1.60-1.63 (2H, m), 1.41-1.43 (3H, m). LCMS (HpH): t_R = 1.04 min, [M+H$^+$] 273.2.

4.24: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 6.57-6.60 (1H, m), 6.33 (1H, s), 4.09 (3H, s), 3.56-3.61 (2H, m), 2.24 (3H, m), 2.00-2.03 (2H, m), 1.84-1.87 (2H, m), 1.73-1.77 (3H, m), 1.57-1.68 (2H, m), 1.15-1.35 (3H, m). LCMS (HpH): t_R = 0.92 min, [M+H$^+$] 275.2.



To a vial was added **4.22** (137 mg, 0.50 mmol, 1 eq) and Fe(acac)$_3$ (37 mg, 0.10 mmol, 0.2 eq), to this was added a solution of $PhSiH_3$ (81 mg, 0.75 mmol, 1.5 eq) in *i*PrOH (2 mL). The reaction was then stirred open to air, at 50 ^{o}C, for 1 h. The reaction was cooled to RT and concentrated *in vacuo*. Purification by MDAP (HpH) yielded **4.24** as a brown oil (49 mg, 0.18 mmol, 35%) and **4.23** as a white solid (8 mg, 0.03 mmol, 6%).

4.23 and **4.24**: data consistent with above



To a solution of **4.22** in *i*PrOH (1 mL) was added TFA (77 µL, 2 eq) and stirred at RT for 5 mins. Then the solution was transferred to an RBF containing Fe(acac)$_3$ (36 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (83 mg, 0.77 mmol, 1.5 eq) along with further *i*PrOH (1 mL).

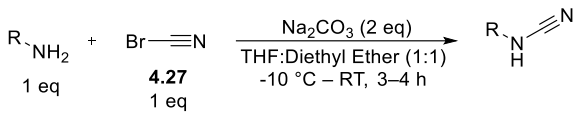
The reaction stirred at 80 ^{o}C with a condenser (attached with a compressed air bubbler) for 24 h. The reaction stopped, cooled to RT and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel (0-50% EtOAc:cyclohexane) to afford **4.23** as a white solid (40 mg, 0.15 mmol, 30%) and **4.25** as a colourless oil (31 mg, 0.17 mmol, 34%).

4.23: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.21 (3H, s), 4.02-4.06 (2H, m), 2.47 (3H, s), 2.17-2.20 (2H, m), 1.77-1.92 (4H, m), 1.69-1.72 (1H, m), 1.60-1.63 (2H, m), 1.38-1.49 (3H, m). LCMS (HpH): t_R = 1.04 min, [M+H$^+$] 273.2. ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 162.8, 153.5, 141.3, 139.7, 124.9, 46.7, 42.6, 38.1, 34.2, 31.3, 25.4, 22.4, 10.7. HRMS: ($C_{15}H_{21}N_4O$) [M+H$^+$] requires 273.1715, found [M+H$^+$] 273.1720 (error 1.8 ppm).

4.25: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 6.59 (1H, s), 5.19 (1H, sept, *J* = 6.2 Hz), 4.10 (3H, s), 2.25 (3H, s), 1.34 (6H, d, *J* = 5.9 Hz). LCMS (HpH): t_R = 1.00 min, [M+H$^+$] 183.2. ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 159.5, 146.8, 133.4, 110.3, 68.5, 39.1, 21.9, 13.2.

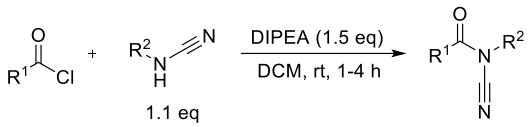
8.3.2 – Synthesis of Substrates

General Method 1



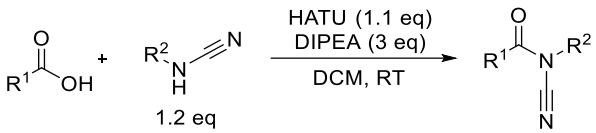
To a cooled (-10 ^{o}C) solution of cyanogen bromide (**4.27**) (1 eq) in diethyl ether (1M) was added sodium carbonate (2 eq). To this stirred suspension was added a solution of *amine* (1 eq) in THF (1M) slowly. The reaction mixture allowed to warm to RT and stirred for 3−4 h. The solids were removed via filtration (sinter funnel), washed with EtOAc and the organics dried *in vacuo* to afford the desired *cyanamides* which were used crude in the next step.

General Method 2



Acid chloride (5.0 mmol, 1 eq) in DCM (10 mL, 0.5M) was cooled over ice, *cyanamide* (5.5 mmol, 1.1 eq) and DIPEA (7.5 mmol, 1.5 eq) was then added. The reaction stirred at RT until completion (usually 1 h), then water added (50 mL) and extracted with DCM (3 x 15 mL). The organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel to afford the desired *N*-cyanamide alkenes.

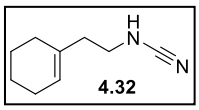
General Method 3



A mixture of *cyanamide* (6.0 mmol, 1.2 eq), *carboxylic acid* (5.0 mmol, 1 eq) and HATU (2.09 g, 5.5 mmol, 1.1 eq) in DCM (0.5M) was added DIPEA (2.6 mL, 3 eq). The reaction stirred at RT until completion, then water added (250 mL) and extracted with DCM (3

x 75 mL). The organics were passed through a hydrophobic frit and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel to afford the desired *N*-cyanamide alkenes.

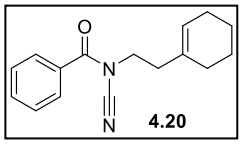
_N_-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (4.32)



The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (8.462 g, 79.89 mmol, 1 eq), sodium carbonate (16.934 g, 159.78 mmol, 2 eq) and 2-(cyclohex-1-en-1-yl)ethan-1-amine (**X**) (10.035 g, 80.14 mmol, 1 eq). Affording **4.32** as a crude yellow oil (10.022 g, 66.71 mmol, 83%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.51-5.53 (1H, m), 3.87 (1H, br.s), 3.15 (2H, td, *J* = 6.9 and 5.4 Hz), 2.22 (2H, t, *J* = 6.9 Hz), 1.99-2.03 (2H, m), 1.89-1.94 (2H, m), 1.53-1.67 (4H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 133.1, 124.9, 116.5, 44.2, 38.0, 27.9, 25.2, 22.7, 22.2.

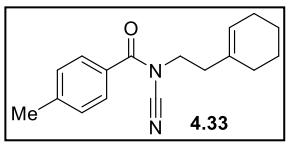
_N_-cyano-_N_-(2-(cyclohex-1-en-1-yl)ethyl)benzamide (4.20)



The title compound was prepared according to general method 2 using benzoyl chloride (700 mg, 4.98 mmol, 1 eq) and **4.32** (835 mg, 5.56 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-15% TBME:cyclohexane) afforded **4.20** as a colourless oil (1.087 g, 4.27 mmol, 86%).

ν_{max} (neat): 2926, 2230, 1701, 1272, 699 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.74-7.76 (2H, m), 7.54-7.59 (1H, m), 7.44-7.48 (2H, m), 5.60 (1H, br. s), 3.84 (2H, t, *J* = 6.8 Hz), 2.40 (2H, t, *J* = 6.8 Hz), 1.99-2.01 (4H, m), 1.62-1.67 (2H, m), 1.53-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.4, 132.9, 132.8, 131.4, 128.6, 128.4, 125.4, 111.1, 45.8, 36.0, 27.9, 25.4, 22.8, 22.2. LCMS (HpH): t_R = 1.32 min, [M+H$^+$] 255.2. HRMS: ($C_{16}H_{19}N_2O$) [M+H$^+$] requires 255.1497, found [M+H$^+$] 255.1506 (error 3.5 ppm).

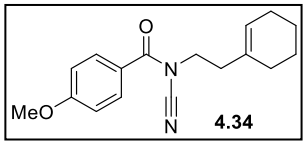
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzamide (4.33)**



The title compound was prepared according to general method 2 using 4-methylbenzoyl chloride (771 mg, 4.99 mmol, 1 eq) and **4.32** (830 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.33** as a colourless oil (1.165 g, 4.34 mmol, 87%).

ν_{max} (neat): 2926, 2230, 1699, 1274, 742 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.67 (2H, d, *J* = 8.1 Hz), 7.27 (2H, d, *J* = 8.1 Hz), 5.60 (1H, br. s), 3.83 (2H, t, *J* = 6.8 Hz), 2.39-2.41 (5H, m), 2.00-2.01 (4H, m), 1.62-1.67 (2H, m), 1.53-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.3, 143.8, 132.8, 129.2, 128.6, 128.5, 125.4, 111.4, 45.8, 36.0, 27.9, 25.4, 22.8, 22.1, 21.7. LCMS (HpH): t_R = 1.39 min, $[M+H^+]$ 269.1. HRMS: ($C_{17}H_{21}N_2O$) $[M+H^+]$ requires 269.1654, found $[M+H^+]$ 269.1664 (error 3.7 ppm).

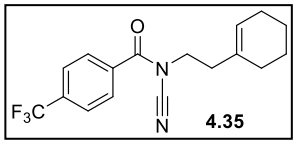
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-methoxybenzamide (4.34)**



The title compound was prepared according to general method 2 using 4-methoxybenzoyl chloride (855 mg, 5.01 mmol, 1 eq) and **4.32** (829 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-40% TBME:cyclohexane) afforded **4.34** as a colourless oil (1.209 g, 4.25 mmol, 85%).

ν_{max} (neat): 2927, 2228, 1694, 1604, 1254 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.77-7.81 (2H, m), 6.93-6.97 (2H, m), 5.59 (1H, br. s), 3.86 (3H, s), 3.82 (2H, t, *J* = 7.0 Hz), 2.40 (2H, t, *J* = 6.8 Hz), 2.00 (4H, br. s), 1.62-1.67 (2H, m), 1.53-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.6, 163.4, 132.9, 130.9, 125.3, 123.4, 113.9, 111.6, 55.5, 45.9, 36.0, 27.9, 25.4, 22.8, 22.2. LCMS (HpH): t_R = 1.33 min, $[M+H^+]$ 285.1. HRMS: ($C_{17}H_{21}N_2O_2$) $[M+H^+]$ requires 285.1603, found $[M+H^+]$ 285.1614 (error 3.9 ppm).

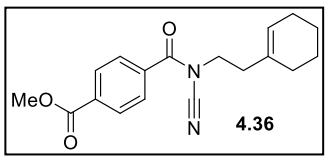
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-(trifluoromethyl)benzamide (4.35)**



The title compound was prepared according to general method 2 using 4-(trifluoromethyl)benzoyl chloride (1.049 g, 5.03 mmol, 1 eq) and **4.32** (829 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.35** as a white solid (1.401 g, 4.35 mmol, 86%).

M.pt.: 55-58 ^{o}C. ν_{max} (neat): 2943, 2857, 2234, 1703, 1282, 1126 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.86 (2H, d, *J* = 8.1 Hz), 7.76 (2H, d, *J* = 8.3 Hz), 5.61 (1H, br. s), 3.88 (2H, t, *J* = 6.7 Hz), 2.42 (2H, t, *J* = 6.8 Hz), 2.00-2.04 (4H, m), 1.63-1.68 (2H, m), 1.55-1.60 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.2, 134.6 (d, *J* = 1.5 Hz), 134.4 (q, *J* = 33.0 Hz), 132.7, 128.9, 125.7-125.8 (m), 123.3 (q, *J* = 272.9 Hz), 110.6, 45.9, 36.0, 27.8, 25.4, 22.7, 22.1. ^{19}F{^{1}H} NMR (376 MHz, CHLOROFORM-d) δ = -63.32. LCMS (Formic): t_R = 1.42 min, [M+H$^+$] 323.1. HRMS: ($C_{17}H_{18}F_3N_2O$) [M+H$^+$] requires 323.1371, found [M+H$^+$] 323.1376 (error 1.5 ppm).

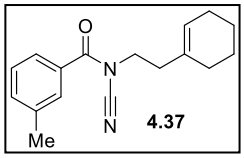
Methyl 4-(cyano(2-(cyclohex-1-en-1-yl)ethyl)carbamoyl)benzoate (4.36)



The title compound was prepared according to general method 2 using methyl 4-(chlorocarbonyl)benzoate (992 mg, 4.99 mmol, 1 eq) and **4.32** (829 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-40% TBME:cyclohexane) afforded **4.36** as a white solid (1.156 g, 3.70 mmol, 74%).

M.pt.: 95-97 ^{o}C. ν_{max} (neat): 2932, 2835, 2237, 1702, 1273, 722 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.13-8.16 (2H, m), 7.79-7.81 (2H, m), 5.61 (1H, br. s), 3.95 (3H, s), 3.87 (3H, t, *J* = 6.8 Hz), 2.42 (2H, t, *J* = 6.8 Hz), 2.00-2.02 (4H, m), 1.62-1.68 (2H, m), 1.54-1.59 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.7, 165.8, 135.1, 133.9, 132.7, 129.8, 128.4, 125.6, 110.6, 52.5, 45.9, 36.0, 27.8, 25.4, 22.7, 22.1. LCMS (HpH): t_R = 1.33 min, [M+H$^+$] 313.1. HRMS: ($C_{18}H_{21}N_2O_3$) [M+H$^+$] requires 313.1552, found [M+H$^+$] 313.1559 (error 2.2 ppm).

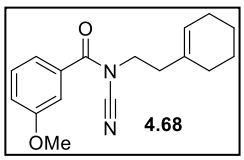
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-3-methylbenzamidemethylbenzamide (4.37)**



The title compound was prepared according to general method 2 using 3-methylbenzoyl chloride (775 mg, 5.02 mmol, 1 eq) and **4.32** (829 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-15% TBME:cyclohexane) afforded **4.37** as a colourless oil (903 mg, 3.36 mmol, 67%).

ν_{max} (neat): 2926, 2835, 2231, 1701, 1278, 733 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.54-7.56 (2H, m), 7.33-7.39 (2H, m), 5.60 (1H, br. s), 3.84 (2H, t, *J* = 7.0 Hz), 2.39-2.42 (5H, m), 1.99-2.02 (4H, m), 1.62-1.68 (2H, m), 1.53-1.60 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.6, 138.6, 133.7, 132.8, 131.3, 129.0, 128.4, 125.5, 125.4, 111.1, 45.8, 36.0, 27.9, 25.4, 22.8, 22.1, 21.3. LCMS (HpH): t_R = 1.39 min, $[M+H^+]$ 269.2. HRMS: ($C_{17}H_{21}N_2O$) $[M+H^+]$ requires 269.1654, found $[M+H^+]$ 269.1664 (error 3.7 ppm).

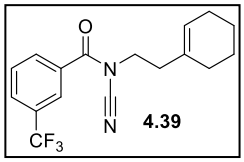
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-3-methoxybenzamide (4.38)**



The title compound was prepared according to general method 2 using 3-methoxybenzoyl chloride (851 mg, 4.99 mmol, 1 eq) and **4.32** (841 mg, 5.60 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.68** as a colourless oil (1.228 g, 4.32 mmol, 87%).

ν_{max} (neat): 2927, 2836, 2231, 1702, 1276, 739 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.40 (2H, m), 7.23-7.24 (1H, m), 7.09-7.12 (1H, m), 5.61 (1H, br. s), 3.83-3.86 (5H, m), 2.41 (2H, t, *J* = 6.9 Hz), 1.99-2.02 (4H, m), 1.62-1.68 (2H, m), 1.54-1.59 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.2, 159.6, 132.8, 132.5, 129.7, 125.5, 120.6, 119.3, 113.4, 111.0, 55.5, 45.9, 36.0, 27.9, 25.4, 22.8, 22.1. LCMS (HpH): t_R = 1.34 min, $[M+H^+]$ 285.1. HRMS: ($C_{17}H_{21}N_2O_2$) $[M+H^+]$ requires 285.1603, found $[M+H^+]$ 285.1600 (error -1.1 ppm).

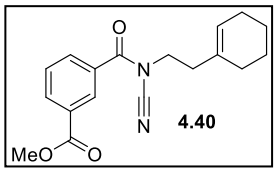
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-3-(trifluoromethyl)benzamide (4.39)**



The title compound was prepared according to general method 2 using 3-(trifluoromethyl)benzoyl chloride (1.048 g, 5.03 mmol, 1 eq) and **4.32** (829 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.39** as a colourless oil (953 mg, 2.96 mmol, 59%).

ν_{max} (neat): 2929, 2838, 2233, 1706, 1334, 1251, 1126 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.01 (1H, s), 7.79 (1H, d, *J* = 7.8 Hz), 7.84 (1H, d, *J* = 7.8 Hz), 7.62 (1H, t, *J* = 7.6 Hz), 5.62 (1H, br. s), 3.87 (2H, t, *J* = 6.8 Hz), 2.42 (2H, t, *J* = 6.7 Hz), 2.00-2.02 (4H, m), 1.62-1.68 (2H, m), 1.54-1.59 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.1, 132.7, 132.2, 131.4 (q, *J* = 32.8 Hz), 131.4, 129.4 (q, *J* = 3.6 Hz), 129.2, 125.6-125.8 (m), 123.3 (q, *J* = 272.4 Hz), 110.6, 45.9, 36.0, 27.8, 25.3, 22.7, 22.1. $^{19}F\{^{1}H\}$ NMR (376 MHz, CHLOROFORM-d) δ = -63.05. LCMS (HpH): t_R = 1.43 min, $[M+H^+]$ 323.2. HRMS: ($C_{17}H_{18}F_3N_2O$) $[M+H^+]$ requires 323.13711, found $[M+H^+]$ 323.1376 (error 1.5 ppm).

Methyl 3-(cyano(2-(cyclohex-1-en-1-yl)ethyl)carbamoyl)benzoatebenzoate (4.40)

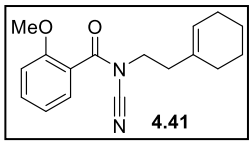


The title compound was prepared according to general method 2 using methyl 3-(chlorocarbonyl)benzoate (993 mg, 5.00 mmol, 1 eq) and **4.32** (837 mg, 5.57 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.40** as a colourless oil (875 mg, 2.80 mmol, 56%).

ν_{max} (neat): 2928, 2863, 2232, 1724, 1705, 1240, 721 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.43 (1H, t, *J* = 1.5 Hz), 8.27 (1H, dt, *J* = 7.8 and 1.3 Hz), 7.94 (1H, dt, *J* = 7.7 and 1.4 Hz), 7.60 (1H, t, *J* = 7.8 Hz), 5.64 (1H, br. s), 3.97 (3H, s), 3.89 (2H, t, *J* = 6.8 Hz), 2.45 (2H, t, *J* = 6.8 Hz), 2.04-2.06 (2H, m), 1.67-1.71 (2H, m), 1.57-1.62 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.6, 165.6, 133.7, 132.7, 132.3, 131.8, 130.8, 129.6, 128.9, 125.7, 110.8, 52.5, 45.9, 36.0, 27.8, 25.3, 22.7, 22.1. LCMS

(Formic): t_R = 1.31 min, [M+H$^+$] 313.1. HRMS: ($C_{18}H_{21}N_2O_3$) [M+H$^+$] requires 313.1552, found [M+H$^+$] 313.1557 (error 1.6 ppm).

_N_-cyano-_N_-(2-(cyclohex-1-en-1-yl)ethyl)-2-methoxybenzamide (4.41)

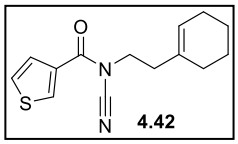


4.41

The title compound was prepared according to general method 2 using 2-methoxybenzoyl chloride (866 mg, 5.07 mmol, 1 eq) and **4.32** (836 mg, 5.56 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.41** as a colourless oil (1.278 g, 4.49 mmol, 89%).

NMR (400 MHz, CHLOROFORM-d) δ = 7.44-7.48 (1H, m), 7.34 (1H, dd, *J* = 7.6 and 1.7 Hz), 7.01 (1H, td, *J* = 7.5 and 1.0 Hz), 6.97 (1H, d, *J* = 8.3 Hz), 5.57-5.60 (1H, m), 3.89 (3H, s), 3.81 (2H, t, *J* = 7.0 Hz), 2.38 (2H, t, *J* = 7.0 Hz), 2.00-2.04 (4H, m), 1.62-1.68 (2H, m), 1.54-1.60 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.0, 156.7, 133.2, 132.8, 129.1, 125.1, 122.0, 120.8, 111.5, 110.7, 55.8, 45.2, 36.0, 27.9, 25.4, 22.8, 22.2. LCMS (HpH): t_R = 1.31 min, [M+H$^+$] 285.1.

_N_-cyano-_N_-(2-(cyclohex-1-en-1-yl)ethyl)thiophene-3-carboxamidemethoxybenzamide (4.42)

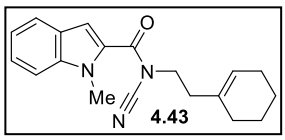


4.42

The title compound was prepared according to general method 2 using thiophene-3-carbonyl chloride (729 mg, 4.97 mmol, 1 eq) and **4.32** (827 mg, 5.51 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-15% TBME:cyclohexane) afforded **4.42** as a colourless oil (1.097 g, 4.22 mmol, 85%).

NMR (400 MHz, CHLOROFORM-d) δ = 8.24 (1H, dd, *J* = 2.9 and 1.5 Hz), 7.57 (1H, dd, *J* = 5.4 and 1.5 Hz), 7.36 (1H, dd, *J* = 5.4 and 2.9 Hz), 5.55-5.59 (1H, m), 3.83 (2H, t, *J* = 7.1 Hz), 2.39 (2H, t, *J* = 7.1 Hz), 1.98-2.01 (4H, m), 1.60-1.67 (2H, m), 1.52-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 162.0, 132.8, 132.6, 128.1, 126.3, 125.4, 111.5, 46.1, 36.0, 27.9, 25.3, 22.8, 22.1. LCMS (HpH): t_R = 1.31 min, [M+H$^+$] 261.5.

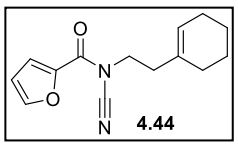
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-1-methyl-1H-indole-2-carboxamide (4.43)**



The title compound was prepared according to general method 2 using 1-methyl-1H-indole-2-carbonyl chloride (979 mg, 5.05 mmol, 1 eq) and **4.32** (833 mg, 5.55 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-15% TBME:cyclohexane) afforded **4.43** as a white solid (1.2647 g, 2.80 mmol, 82%).

M.pt.: 79-81 ^{o}C. ν_{max} (neat): 2958, 2922, 2232, 1700, 1229, 737 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.69 (1H, d, *J* = 8.1 Hz), 7.49 (1H, s), 7.35-7.40 (2H, m), 7.16 (1H, ddd, *J* = 8.0, 5.8, and 2.1 Hz), 5.61 (br. s), 3.92 (3H, s), 3.86 (2H, t, *J* = 6.8 Hz), 2.42 (2H, t, *J* = 6.8 Hz), 2.00-2.01 (4H, m), 1.62-1.68 (2H, m), 1.54-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 160.8, 139.7, 132.8, 126.9, 126.0, 125.52, 125.46, 123.1, 121.1, 111.4, 110.6, 110.2, 45.8, 36.1, 31.7, 27.9, 25.4, 22.8, 22.2. LCMS (HpH): t_R = 1.46 min, [M+H$^+$] 308.1. HRMS: ($C_{19}H_{22}N_3O$) [M+H$^+$] requires 308.1763, found [M+H$^+$] 308.762 (error -0.3 ppm).

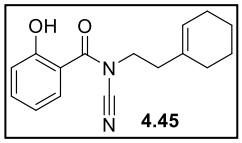
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)furan-2-carboxamide (4.44)**



The title compound was prepared according to general method 2 using furan-2-carbonyl chloride (659 mg, 5.04 mmol, 1 eq) and **4.32** (846 mg, 5.63 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.44** as a colourless oil (1.075 g, 4.40 mmol, 87%).

NMR (400 MHz, CHLOROFORM-d) δ = 7.66-7.67 (1H, m), 7.52-7.54 (1H, m), 6.58 (1H, dd, *J* = 3.7 and 1.7 Hz), 5.53-5.57 (1H, m), 3.84 (2H, t, *J* = 7.1 Hz), 2.38 (2H, t, *J* = 7.1 Hz), 1.94-2.00 (4H, m), 1.60-1.67 (2H, m), 1.51-1.57 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 156.3, 147.0, 144.0, 132.6, 125.4, 120.1, 112.2, 110.6, 46.3, 35.9, 28.0, 25.3, 22.7, 22.1. LCMS (HpH): t_R = 1.25 min, [M+H$^+$] 245.4.

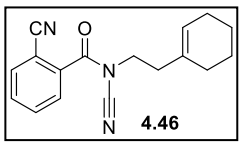
***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-hydroxybenzamide (4.45)**



The title compound was prepared according to general method 3 using 2-hydroxybenzoic acid (696 mg, 5.04 mmol, 1 eq) and **4.32**(909 mg, 6.05 mmol, 1.2 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.45** as an off-white solid (383 mg, 1.42 mmol, 28%).

M.pt.: 67-69 ^{o}C. NMR (400 MHz, CHLOROFORM-d) δ = 8.01 (1H, dd, *J* = 7.8 and 2.0 Hz), 7.56-7.60 (1H, m), 7.22-7.26 (1H, m), 7.08 (1H, d, *J* = 8.3 Hz), 6.31 (1H, br. s), 5.44-5.47 (1H, m), 4.18 (2H, t, *J* = 7.8 Hz), 2.36 (2H, t, *J* = 7.3 Hz), 2.05-2.09 (2H, m) 1.90-1.94 (2H, m), 1.59-1.65 (2H, m), 1.50-1.56 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 159.3, 152.8, 150.5, 135.2, 134.7, 128.0, 124.2, 123.3, 115.3, 114.4, 41.8, 34.9, 28.4, 25.3, 22.9, 22.3. LCMS (HpH): t_R = 1.30 min, [M+H$^+$] 271.1.

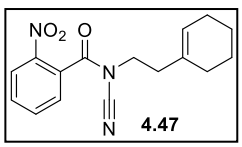
***N*,2-dicyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)benzamide (4.46)**



The title compound was prepared according to general method 3 using 2-cyanobenzoic acid (734 mg, 4.99 mmol, 1 eq) and **4.32** (912 mg, 6.07 mmol, 1.2 eq). Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.46** as a white solid (442.5 mg, 1.58 mmol, 32%).

M.pt.: 72-74 ^{o}C. NMR (400 MHz, CHLOROFORM-d) δ = 7.82 (1H, d, *J* = 7.3 Hz), 7.65-7.72 (3H, m), 5.62-5.65 (1H, m), 3.90 (2H, t, *J* = 6.9 Hz), 2.45 (2H, t, *J* = 6.9 Hz), 1.98-2.05 (4H, m), 1.64-1.69 (2H, m), 1.54-1.59 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.7, 135.0, 134.1, 132.6, 132.3, 128.4, 125.8, 115.9, 111.7, 109.8, 45.8, 35.9, 27.8, 25.3, 22.7, 22.1. LCMS (HpH): t_R = 1.25 min, [M+H$^+$] 280.1.

***N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-nitrobenzamide (4.47)**

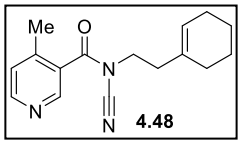


The title compound was prepared according to general method 3 using 2-nitrobenzoic acid (835 mg, 4.99 mmol, 1 eq) and **4.32** (907 mg, 6.04 mmol, 1.2 eq). Purification by automated column

chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.47** as a yellow solid (1.313 g, 4.39 mmol, 88%).

M.pt.: 56-58 ^{o}C. NMR (400 MHz, CHLOROFORM-d) δ = 8.27 (1H, dd, *J* = 8.3 and 1.0 Hz), 7.80 (1H, td, *J* = 7.5 and 1.2 Hz), 7.71 (1H, td, *J* = 8.1 and 1.5 Hz), 7.50 (1H, dd, *J* = 7.6 and 1.2 Hz), 5.63-5.66 (1H, m), 3.89 (2H, t, *J* = 7.1 Hz), 2.45 (2H, t, *J* = 7.1 Hz), 2.00-2.07 (4H, m), 1.65-1.70 (2H, m), 1.56-1.61 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.4, 145.4, 134.7, 132.6, 131.9, 129.3, 128.5, 125.4, 125.0, 109.8, 45.1, 35.7, 27.9, 25.3, 22.7, 22.1. LCMS (HpH): t_R = 1.30 min, [M+H$^+$] 300.1.

_N_-cyano-_N_-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylnicotinamide (4.48)

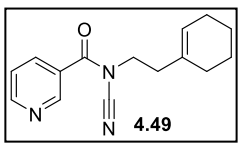


4.48

The title compound was prepared according to general method 3 using 4-methylnicotinic acid (3.143 g, 22.92 mmol, 1 eq) and **4.32** (3.909 g, 26.0 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-50% EtOAc:cyclohexane, 1% NEt_3) and then further purification by automated reverse phase column chromatography on C18 silica gel (20-75% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate) afforded **4.48** as an amber oil (1.900 g, 7.05 mmol, 31%).

ν_{max} (neat): 2926, 2836, 2233, 1708, 1274 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.61 (1H, s), 8.59 (1H, d, *J* = 5.1 Hz), 7.22 (1H, d, *J* = 5.1 Hz), 5.63 (1H, br. s), 3.88 (2H, t, *J* = 6.6 Hz), 2.41-2.45 (5H, m), 2.00-2.06 (4H, m), 1.64-1.69 (2H, m), 1.54-1.60 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.3, 152.0, 147.6, 145.6, 132.6, 129.0, 125.9, 125.6, 109.9, 45.0, 36.1, 27.7, 25.3, 22.7, 22.1, 18.9. LCMS (HpH): t_R = 1.17 min, [M+H$^+$] 270.2. HRMS: ($C_{16}H_{20}N_3O$) [M+H$^+$] requires 270.1606, found [M+H$^+$] 270.1608. (error 0.7 ppm).

_N_-cyano-_N_-(2-(cyclohex-1-en-1-yl)ethyl)nicotinamide (4.49)



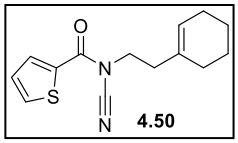
4.49

The title compound was prepared according to general method 3 using nicotinic acid (495 mg, 4.02 mmol, 1 eq) and **4.32** (645 mg, 4.29 mmol, 1.1 eq). Purification by automated column

chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.49** as a yellow oil (720 mg, 2.82 mmol, 70%).

ν_{max} (neat): 2926, 2232, 1703, 1280, 722 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.99 (1H, dd, *J* = 2.2 and 0.7 Hz), 8.81 (1H, dd, *J* = 4.9 and 1.7 Hz), 8.07 (dt, *J* = 8.1 Hz), 7.43 (1H, ddd, *J* = 8.1, 4.9 and 0.9 Hz), 5.61 (1H, br. s/), 3.87 (2H, t, *J* = 6.8 Hz), 2.42 (2H, t, *J* = 6.8 Hz), 1.99-2.03 (4H, m), 1.53-1.68 (4H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.4, 153.4, 149.4, 135.7, 132.7, 127.6, 125.7, 123.1, 110.6, 45.9, 36.0, 27.8, 25.3, 22.7, 22.1. LCMS (HpH): t_R = 1.11 min, $[M+H^+]$ 256.2. HRMS: ($C_{15}H_{18}N_3O$) $[M+H^+]$ requires 256.1450, found $[M+H^+]$ 256.1456 (error 2.3 ppm).

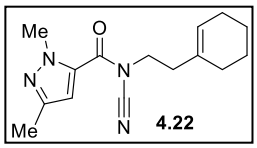
N-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (4.50)



The title compound was prepared according to general method 3 using thiophene-2-carboxylic acid (3.197 g, 24.95 mmol, 1 eq) and **4.32** (4.173 g, 27.78 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-15% TBME:cyclohexane) afforded **4.50** as a yellow oil (5.215 g, 20.03 mmol, 80%).

NMR (400 MHz, CHLOROFORM-d) δ = 8.08 (1H, dd, *J* = 3.9 and 1.0 Hz), 7.68 (1H, dd, *J* = 4.9 and 1.0 Hz), 7.13 (1H, dd, *J* = 4.9 and 3.9 Hz), 5.54-5.57 (1H, m), 3.84 (2H, t, *J* = 7.1 Hz), 2.39 (2H, t, *J* = 6.9 Hz), 1.96-2.00 (4H, m), 1.61-1.66 (2H , m), 1.51-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 160.3, 134.1, 134.0, 133.3, 132.7, 128.0, 125.4, 111.3, 46.7, 36.0, 27.9, 25.3, 22.8, 22.1. LCMS (Formic): t_R = 1.28 min, $[M+H^+]$ 261.1.

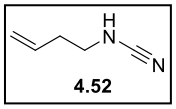
N-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (4.22)



The title compound was prepared according to general method 3 using 1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid (4.200 g, 30.0 mmol, 1 eq) and **4.32** (5.066 g, 33.7 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% EtOAc:cyclohexane) afforded **4.22** as a viscous yellow oil (6.756 g, 24.81 mmol, 83%).

ν_{max} (neat): 2927, 2232, 1694, 1438, 1244, 745 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 6.88 (1H, s), 5.56 (1H, br. s), 4.02 (3H, s), 3.82 (2H, t, *J* = 6.9 Hz), 2.37 (2H, t, *J* = 6.8 Hz), 2.29 (3H, s), 1.98-2.00 (4H, s), 1.61-1.67 (2H, m), 1.52-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 158.8, 147.0, 132.6, 131.5, 125.5, 110.6, 110.3, 45.9, 39.3, 35.9, 27.9, 25.3, 22.7, 22.1, 132.2. LCMS (HpH): t_R = 1.24 min, $[M+H^+]$ 273.2. HRMS: ($C_{15}H_{21}N_4O$) $[M+H^+]$ requires 273.1715, found $[M+H^+]$ 273.1718 (error 1.1 ppm).

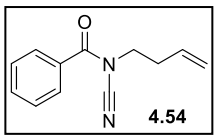
_N_-(but-3-en-1-yl)cyanamide (4.52)



The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (1.075 g, 10.15 mmol, 1 eq), sodium carbonate (2.124 g, 20.04 mmol, 2 eq) and but-3-en-1-amine (**4.51**) (718 mg, 10.09 mmol, 1 eq). Affording **4.52** as a crude yellow oil (890 mg, 9.26 mmol, 92%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.70-5.80 (1H, m), 5.13-5.20 (2H, m), 4.13 (1H, br. s), 3.12-3.17 (2H, m), 2.36 (2H, qt, *J* = 6.8 and 1.3 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 133.6, 118.4, 116.4, 45.3, 33.9.

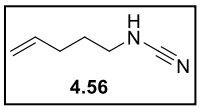
_N_-(but-3-en-1-yl)-_N_-cyanobenzamide (4.54)



The title compound was prepared according to general method 2 using benzoyl chloride (712 mg, 5.07 mmol, 1 eq) and **4.52** (536 mg, 5.58 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.54** as a colourless oil (907 mg, 4.53 mmol, 89%).

ν_{max} (neat): 3079, 2980, 2231, 1701, 1271, 699 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.77-7.79 (2H, m), 7.57-7.61 (1H, m), 7.46-7.50 (2H, m), 5.83 (1H, ddt, *J* = 17.1, 10.1 and 6.9 Hz), 5.25 (1H, dq, J = 17.1 and 1.5 Hz), 5.19 (1H, dd, *J* = 10.3 and 1.2 Hz), 3.85 (2H, t, *J* = 7.0 Hz), 2.54-2.60 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.4, 133.1, 133.0, 131.1, 128.6, 128.5, 118.8, 111.0, 46.8, 32.0. LCMS (Formic): t_R = 1.05 min, $[M+H^+]$ 201.1. HRMS: ($C_{12}H_{13}N_2O$) $[M+H^+]$ requires 201.1028, found $[M+H^+]$ 201.1021 (error -3.5 ppm).

***N*-(pent-4-en-1-yl)cyanamide (4.56)**

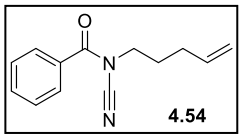


4.56

The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (1.263 g, 11.92 mmol, 1 eq), sodium carbonate (2.504 g, 23.62 mmol, 2 eq) and pent-4-en-1-amine (**4.51**) (1.056 g, 12.40 mmol, 1 eq). Affording **4.56** as a crude yellow oil (830 mg, 7.54 mmol, 61%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.78 (1H, ddt, *J* = 17.1, 10.2 and 6.7 Hz), 5.00-5.09 (2H, m), 4.71 (1H, br. s), 3.03-3.10 (2H, m), 2.12-2.17 (2H, m), 1.71 (2H, quin, *J* = 7.2 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 137.0, 115.7, 116.3, 45.3, 30.3, 28.7.

***N*-cyano-N-(pent-4-en-1-yl)benzamide (4.54)**

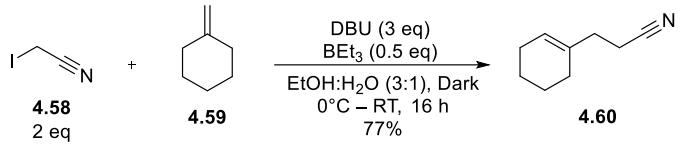


4.54

The title compound was prepared according to general method 2 using benzoyl chloride (705 mg, 5.02 mmol, 1 eq) and **4.56** (614 mg, 5.57 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) and then further purification by MDAP (TFA, method C) afforded **4.54** as a colourless oil (493 mg, 2.30 mmol, 46%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.78-7.81 (2H, m), 7.58 (1H, tt, *J* = 7.3 and 1.0 Hz), 7.46-7.49 (2H, m), 5.82 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz), 5.03-5.13 (2H, m), 3.77 (2H, t, *J* = 7.3 Hz), 2.17-2.23 (2H, m), 1.92 (2H, quin, *J* = 7.3 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.4, 136.5, 133.1, 131.2, 128.6, 116.2, 111.1, 47.3, 30.4, 26.7. LCMS (HpH): t_R = 1.14 min, [M+H$^+$] 215.2.

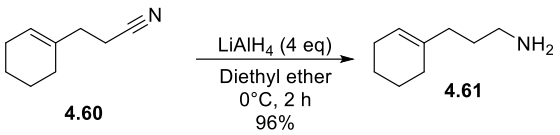
3-(cyclohex-1-en-1-yl)propanenitrile[131] (4.60)



To a solution of 2-iodoacetonitrile (**4.58**) (8.381 g, 50.20 mmol, 2 eq) and methylenecyclohexane (**4.59**) (2.413 g, 25.09 mmol, 1 eq) in EtOH:H_2O (3:1, 25 mL), in the dark open to air, was added a solution of triethyl borane (6.3 mL, 2M, diethyl ether, 0.5 eq) via syringe-pump over 2 h. After the addition was complete the reaction was stirred for 1 h at RT and then DBU (11.4 mL, 3 eq) was added over ice and the reaction mixture stirred overnight at RT (16 h). The reaction was quenched by addition of sat. $NH_4Cl_{(aq)}$ (75 ml) and the aqueous layer extracted with diethyl ether (75 mL x 2). The combined organics then washed with water (50 ml), passed through a hydrophobic frit and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-5% diethyl ether:cyclohexane) afforded **4.60** as a colourless oil (2.610 g, 19.30 mmol, 77%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.52-5.55 (1H, m), 2.43 (2H, t, *J* = 7.9 Hz), 2.27 (2H, t, *J* = 7.4 Hz), 1.99-2.05 (2H, m), 1.91-1.94 (2H, m), 1.61-1.67 (2H, m), 1.53-1.60 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 134.0, 123.8, 119.7, 33.4, 27.9, 25.1, 22.7, 22.1, 16.0.

3-(cyclohex-1-en-1-yl)propan-1-amine (4.61)

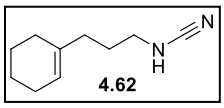


To a solution of $LiAlH_4$ (77 mL, 1M, diethyl ether, 4 eq) over ice was added a solution of **4.60** (2.589 g, 19.14 mmol, 1 eq) in diethyl ether (20 mL) slowly. The reaction mixture stirred for 2 h over ice, followed by dropwise addition of 10% $NaOH_{(aq)}$ (10 mL) until gas evolution had ceased. The resulting suspension was filtered, washed

with diethyl ether and the organics dried *in vacuo* to afford **4.61** as a colourless oil (2.566 g, 18.42 mmol, 96%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.39-5.41 (1H, m), 2.67 (2H, t, *J* = 6.9 Hz), 1.90-2.00 (6H, m), 1.50-1.64 (6H, m), 1.16 (2H, br. s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 137.4, 121.0, 42.1, 35.3, 31.8, 28.3, 25.2, 23.0, 22.6.

_N_-(4-(cyclohex-1-en-1-yl)butyl)cyanamide (4.62)

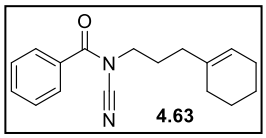


4.62

The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (1.078 g, 10.18 mmol, 1 eq), sodium carbonate (2.124 g, 20.04 mmol, 2 eq) and **4.62** (1.405 g, 10.09 mmol, 1 eq). Affording **4.62** as a crude yellow oil (1.433 g, 8.04 mmol, 80%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.42-5.44 (1H, m), 4.17 (1H, br. s), 3.05 (2H, td, *J* = 7.0 and 5.6 Hz), 1.96-2.02 (4H, m), 1.89-1.92 (2H, m), 1.70 (2H, quin, *J* = 6.9 Hz), 1.59-1.65 (2H, m), 1.51-1.68 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 136.1, 122.1, 116.7, 45.8, 34.6, 28.1, 27.4, 25.2, 22.9, 22.4.

_N_-cyano-_N_-(3-(cyclohex-1-en-1-yl)propyl)benzamide (4.63)

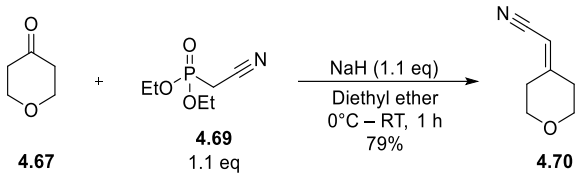


4.63

The title compound was prepared according to general method 2 using benzoyl chloride (706 mg, 5.02 mmol, 1 eq) and **4.62** (906 mg, 5.52 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane) afforded **4.63** as a colourless oil (1.067 g, 3.97 mmol, 79%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.79 (2H, dd, *J* = 8.8 and 1.0 Hz), 7.56-7.60 (1H, m), 7.47 (2H, t, *J* = 8.3 Hz), 5.46-5.49 (1H, m), 3.73 (2H, t, *J* = 7.8 Hz), 2.07 (2H, t, *J* = 7.8 Hz), 1.90-2.00 (6H, m), 1.60-1.66 (2H, m), 1.52-1.58 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.4, 135.6, 133.0, 131.2, 128.58, 128.55, 122.5, 111.2, 47.6, 34.6, 28.1, 25.4, 25.2, 22.9, 22.4. LCMS (Formic): t_R = 1.39 min, [M+H$^+$] 269.2.

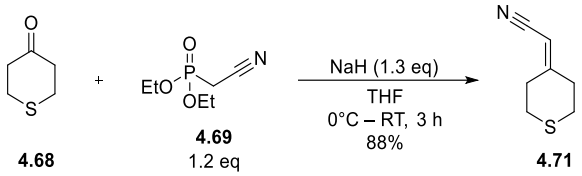
2-(Tetrahydro-4*H*-pyran-4-ylidene)acetonitrile[132] (4.70)



To a suspension of NaH (60% dispersion in mineral oil) (626 mg, 15.66 mmol, 1.1 eq) in diethyl ether (40 mL), over ice, was added diethyl (cyanomethyl)phosphonate (**4.69**) (2.792 g, 15.76 mmol, 1.1 eq) slowly. The reaction mixture was stirred for 5 min and then a solution of tetrahydro-4*H*-pyran-4-one (**4.67**) (1.426 g, 14.24 mmol, 1 eq) in diethyl ether (40 mL) was added slowly. The reaction allowed to warm to RT and stirred for 1 h. Water (100 mL) was added and the aqueous layer extracted with EtOAc (50 mL x 3). The organics were combined via a hydrophobic frit and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-30% EtOAc:cyclohexane) afforded **4.70** as a white solid (1.383 g, 11.23 mmol, 79%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.16-5.17 (1H, m), 3.76 (4H, dt, *J* = 12.8 and 5.6 Hz), 2.61-2.64 (2H, m), 2.38-2.41 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 162.7, 116.2, 93.7, 68.3, 68.1, 36.0, 33.7.

2-(Tetrahydro-4*H*-thiopyran-4-ylidene)acetonitrile[135] (4.71)

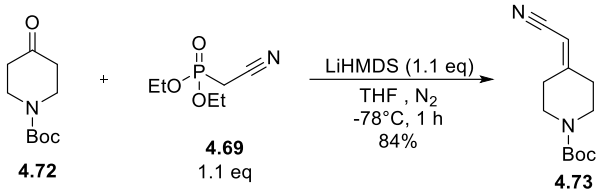


To a solution of diethyl (cyanomethyl)phosphonate (**4.69**) (3.206 g, 18.10 mmol, 1.2 eq) in THF (20 mL), over ice, was added NaH (60% dispersion in mineral oil) (804 mg, 20.10 mmol, 1.3 eq) in one portion. The reaction mixture was stirred for 5 min and then a solution of tetrahydro-4*H*-thiopyran-4-one (**4.68**) (1.744 g, 15.01 mmol, 1 eq) in THF (5 mL) was added slowly. The reaction allowed to warm to RT and stirred for 3 h. Water (100 mL) was added and the aqueous layer extracted with DCM (50 mL x 3).

The organics were combined via a hydrophobic frit and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-15% EtOAc:cyclohexane) afforded **4.71** as a white solid (1.837 g, 13.19 mmol, 88%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.15-5.16 (1H, m), 2.84-2.87 (2H, m), 2.73-2.79 (4H, m), 2.58-2.61 (2H, m).

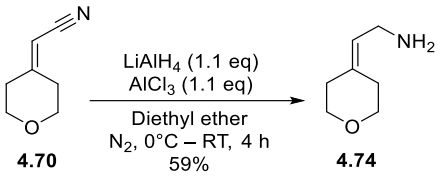
***Tert*-butyl 4-(cyanomethylene)piperidine-1-carboxylate[136] (4.73)**



A solution of diethyl (cyanomethyl)phosphonate (**4.69**) (2.924 g, 16.51 mmol, 1.1 eq) was cooled under N_2 over dry ice/acetone. A solution of LiHMDS (16.6 mL, 1M, THF, 1.1 eq) was then added and the reaction mixture stirred for 5 min. A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (**4.72**) (3.007 g, 15.09 mmol, 1 eq) in THF (6 mL) was added slowly and the reaction stirred for 1 h. Sat. $NH_4Cl_{(aq)}$ (20 mL) was then added, followed by water (100 mL) and the aqueous layer extracted with EtOAc (50 mL x 3). The organics were combined via a hydrophobic frit and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-50% EtOAc:cyclohexane) afforded **4.73** as a white solid (2.806 g, 12.62 mmol, 84%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.18-5.20 (1H, m), 3.51 (4H, dt, *J* = 11.7 and 5.9 Hz), 2.56 (2H, t, *J* = 5.6 Hz), 2.33 (2H, t, *J* = 5.4 Hz), 1.48 (9H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 163.5, 154.4, 116.2, 94.4, 80.3, 44.4, 35.0, 32.6, 28.4.

2-(Tetrahydro-4*H*-pyran-4-ylidene)ethan-1-amine (4.74)

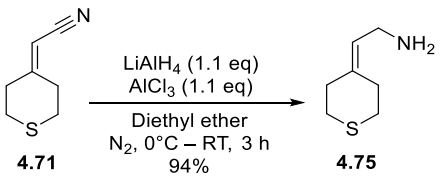


4.70 **4.74**

To a solution of $AlCl_3$ (1.632 g, 12.24 mmol, 1.1 eq) in diethyl ether (15 mL), over ice, was added a solution of $LiAlH_4$ (12.2 mL, 1M, diethyl ether, 1.1 eq) under N_2. After stirring for 5 mins, a solution of **4.70** (1.360 g, 11.04 mmol, 1 eq) in diethyl ether (10 mL) was added slowly. The reaction mixture was allowed to warm to RT and stirred for 4 h. Water (5 mL) was added dropwise, over ice, followed by $NaOH_{(aq)}$ (150 mL, 2M) and the aqueous layer extracted with diethyl ether (75 mL x 2). The organics were combined via a hydrophobic frit and dried *in vacuo* to afford **4.74** as a crude yellow oil (835 mg, 6.57 mmol, 59%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.32 (1H, tt, *J* = 7.0 and 1.2 Hz), 3.67 (4H, dt, *J* = 11.4 and 5.6 Hz), 3.29 (2H, d, *J* = 6.9 Hz), 2.28-2.32 (2H, m), 2.20-2.23 (2H, m).

2-(Tetrahydro-4*H*-thiopyran-4-ylidene)ethan-1-amine (4.75)

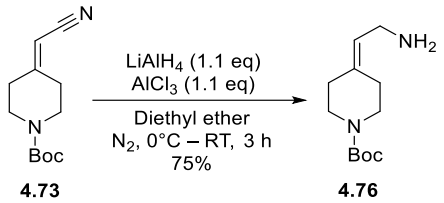


4.71 **4.75**

To a solution of $AlCl_3$ (1.973 g, 14.80 mmol, 1.1 eq) in diethyl ether (20 mL), over ice, was added a solution of $LiAlH_4$ (14.5 mL, 1M, diethyl ether, 1.1 eq) under N_2. After stirring for 5 mins, a solution of **4.71** (1.832 g, 13.16 mmol, 1 eq) in diethyl ether (15 mL) was added slowly. The reaction mixture was allowed to warm to RT and stirred for 3 h. Water (10 mL) was added dropwise, over ice, followed by $NaOH_{(aq)}$ (150 mL, 2M) and the aqueous layer extracted with diethyl ether (75 mL x 2). The organics were combined via a hydrophobic frit and dried *in vacuo* to afford **4.75** as a crude yellow oil (1.767 g, 12.33 mmol, 94%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.31 (1H, t, *J* = 6.9 Hz), 3.28 (2H, d, *J* = 6.9 Hz), 2.62-2.68 (4H, m), 2.50-2.53 (2H, m), 2.42-2.45 (2H, m).

Tert-butyl 4-(2-aminoethylidene)piperidine-1-carboxylate (4.76)

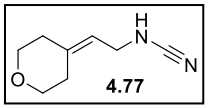


4.73 **4.76**

To a solution of $AlCl_3$ (1.856 g, 14.00 mmol, 1.1 eq) in diethyl ether (20 mL), over ice, was added a solution of $LiAlH_4$ (14.0 mL, 1M, diethyl ether, 1.1 eq) under N_2. After stirring for 5 mins, a solution of **4.73** (2.797 g, 12.58 mmol, 1 eq) in diethyl ether (15 mL) was added slowly. The reaction mixture was allowed to warm to RT and stirred for 3 h. Water (10 mL) was added dropwise, over ice, followed by $NaOH_{(aq)}$ (150 mL, 2M) and the aqueous layer extracted with diethyl ether (75 mL x 2). The organics were combined via a hydrophobic frit and dried *in vacuo* to afford **4.76** as a crude yellow oil (2.136 g, 9.44 mmol, 75%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.34 (1H, t, *J* = 6.9 Hz), 3.38-3.43 (4H, m), 3.28 (2H, d, *J* = 6.9 Hz), 2.21-2.23 (2H, m), 2.13-2.16 (2H, m), 1.47 (9H, s).

***N*-(2-(tetrahydro-4*H*-pyran-4-ylidene)ethyl)cyanamide (4.77)**

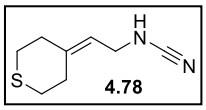


4.77

The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (670 mg, 6.32 mmol, 1 eq), sodium carbonate (1.036 g, 9.78 mmol, 1.5 eq) and **4.74** (827 mg, 6.50 mmol, 1 eq). Affording **4.77** as a crude brown oil (837 mg, 5.50 mmol, 85%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.35 (1H, t, *J* = 7.1 Hz), 3.67-3.73 (6H, m), 2.31-2.34 (2H, m), 2.26-2.29 (2H, m).

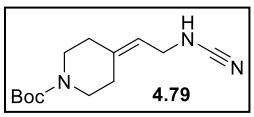
***N*-(2-(tetrahydro-4H-thiopyran-4-ylidene)ethyl)cyanamide (4.78)**



The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (1.302 g, 12.29 mmol, 1 eq), sodium carbonate (2.594 g, 24.47 mmol, 2 eq) and **4.75** (1.758 g, 12.27 mmol, 1 eq). Affording **4.78** as a crude off-white solid (1.505 g, 8.94 mmol, 73%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.34 (1H, t, *J* = 7.3 Hz), 3.66-3.69 (2H, m), 2.67-2.71 (4H, m), 2.53-2.56 (2H, m), 2.48-2.51 (2H, m).

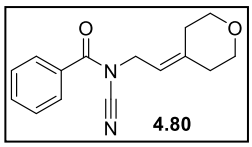
***Tert*-butyl 4-(2-cyanamidoethylidene)piperidine-1-carboxylate (4.79)**



The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (979 mg, 9.24 mmol, 1 eq), sodium carbonate (1.996 g, 18.83 mmol, 2 eq) and **4.76** (2.112 g, 9.33 mmol, 1 eq). Affording **4.79** as a crude brown oil (1.211 g, 4.82 mmol, 52%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.38 (1H, t, *J* = 7.3 Hz), 3.67-3.70 (2H, m), 3.44 (4H, t, *J* = 5.4 Hz), 2.24-2.27 (2H, m), 2.19-2.22 (2H, m), 1.47 (9H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 154.7, 142.7, 117.7, 115.8, 79.8, 60.4, 42.6, 35.8, 28.4.

***N*-cyano-*N*-(2-(tetrahydro-4*H*-pyran-4-ylidene)ethyl)benzamide (4.80)**

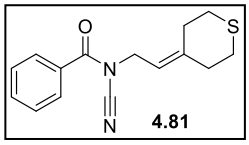


The title compound was prepared according to general method 2 using benzoyl chloride (642 mg, 4.57 mmol, 1 eq) and crude **4.77** (830 mg, 5.45 mmol, 1.2 eq). Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.80** as a white solid (676 mg, 2.64 mmol, 58%).

M.pt.: 67-69 ^{o}C. ν_{max} (neat): 2963, 2851, 2226, 1697, 1686, 1307, 1097, 709 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.80-7.83 (2H, m), 7.58-7.62 (2H, m), 7.47-7.51 (2H, m), 5.46 (1H, t, *J* = 7.8 Hz), 4.36 (2H, d, *J* = 7.8 Hz), 3.74 (4H, t, *J* = 5.6 Hz), 2.42-2.45 (2H, m), 2.33 (2H, t, *J* = 5.4 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.2, 144.5, 135.2, 131.0, 128.6, 114.1, 111.0, 69.2, 68.7, 44.1, 37.0, 30.1. LCMS (HpH): t_R

= 1.02 min, [M+/-H$^+$] not found. HRMS: ($C_{15}H_{17}N_2O_2$) [M+H$^+$] requires 257.1290, found [M+H$^+$] 257.1293 (error 1.2 ppm).

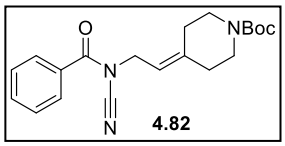
_N_-cyano-_N_-(2-(tetrahydro-4_H_-thiopyran-4-ylidene)ethyl)benzamide (4.81)



The title compound was prepared according to general method 2 using benzoyl chloride (1.123 g, 7.99 mmol, 1 eq) and crude **4.78** (1.500 g, 8.91 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.81** as an off-white solid (1.679 g, 6.17 mmol, 77%).

M.pt.: 58-60 ^{o}C. ν_{max} (neat): 2906, 2228, 1689, 1302, 707 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.79-7.83 (2H, m), 7.58-7.63 (1H, m), 7.47-7.52 (2H, m), 5.46 (1H, t, *J* = 7.8 Hz), 4.35 (2H, d, *J* = 7.3 Hz), 2.72-2.75 (4H, m), 2.65-2.68 (2H, m), 2.54-2.57 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.2, 146.4, 133.2, 131.0, 128.6, 115.5, 111.0, 43.9, 38.9, 31.0, 30.9, 30.4. LCMS (HpH): t_R = 1.19 min, [M+/-H$^+$] not found. HRMS: ($C_{15}H_{17}N_2OS$) [M+H$^+$] requires 273.1062, [M+H$^+$] not found.

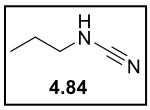
_N_-cyano-_N_-(2-(tetrahydro-4_H_-thiopyran-4-ylidene)ethyl)benzamide (4.82)



The title compound was prepared according to general method 2 using benzoyl chloride (570 mg, 4.06 mmol, 1 eq) and crude **4.79** (1.200 g, 4.77 mmol, 1.2 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.82** as an off-white solid (611 mg, 1.718 mmol, 42%).

M.pt.: 117-119 ^{o}C. ν_{max} (neat): 2974, 2854, 2229, 1709, 1675 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.80-7.83 (2H, m), 7.58-7.62 (1H, m), 7.47-7.51 (2H, m), 5.49 (1H, t, *J* = 7.8 Hz), 4.63 (2H, *J* = 7.8 Hz), 3.48 (4H, q, *J* = 5.9 Hz), 2.37 (2H, t, *J* = 5.6 Hz), 2.26 (2H, t, *J* = 5.9 Hz), 1.47 (9H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.2, 154.6, 145.2, 133.2, 131.0, 128.63, 128.61, 114.8, 110.9, 79.7, 44.2, 36.0, 28.8, 28.4. LCMS (HpH): t_R = 1.28 min, [M(-Boc)+H$^+$] 256.4. HRMS: ($C_{15}H_{18}N_3O$) [M(-Boc)+H$^+$] requires 256.1450, found [M(-Boc)+H$^+$] 256.1456 (error 2.3 ppm).

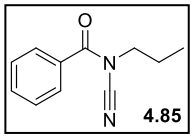
***N*-propylcyanamide (4.84)**



The title compound was prepared according to general method 1 using cyanogen bromide (**4.27**) (2.124 g, 20.05 mmol, 1 eq), sodium carbonate (4.236 g, 39.97 mmol, 2 eq) and 2 propan-1-amine (**4.83**) (1.188 g, 20.09 mmol, 1 eq). Affording **4.84** as a crude colourless oil (1.624 g, 19.30 mmol, 96%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 4.54 (1H, br. s), 3.03 (2H, td, *J* = 7.1 and 5.4 Hz), 1.63 (2H, sext, *J* = 7.2 Hz), 0.97 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 117.0, 47.7, 23.0, 10.8.

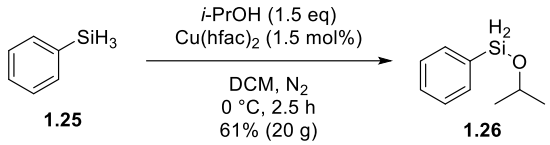
***N*-cyano-*N*-propylbenzamide (4.85)**



The title compound was prepared according to general method 2 using benzoyl chloride (2.112 g, 15.03 mmol, 1 eq) and crude **4.84** (1.395 g, 16.58 mmol, 1.1 eq). Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.85** as a colourless oil (2.429 g, 12.90 mmol, 88%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.79-7.81 (2H, m), 7.58 (1H, tt, *J* = 7.3 and 1.5 Hz), 7.47-7.50 (2H, m), 3.73 (2H, t, *J* = 7.3 Hz), 1.84 (2H, sext, *J* = 7.3 Hz), 1.05 (3H, t, *J* = 7.3 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.5, 133.0, 131.2, 128.6, 111.2, 49.4, 21.0, 10.8. LCMS (HpH): t_R = 1.03 min, [M+H$^+$] 189.2.

8.3.3 – Synthesis of isopropoxy(phenyl)silane[50]



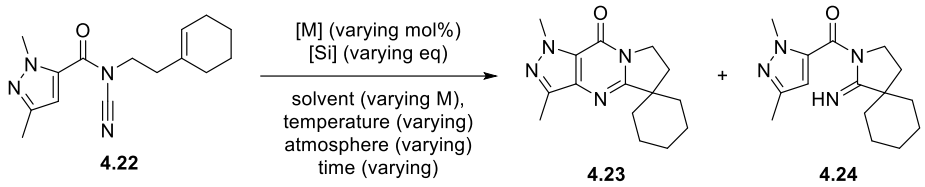
$Cu(hfac)_2$ was dried overnight (vacuum oven), a colour change from green to dark blue was observed. A 1 L round bottom flask was charged with $Cu(hfac)_2$ (1.446 g, 3.03 mmol, 1.5 mol%) and the flask then set under a N_2 atmosphere. Dry DCM (70 mL) and dry isopropanol (23 mL, 300 mmol, 1.5 eq) was added, and the solution cooled over ice. Phenylsilane (24.7 mL, 200 mmol, 1 eq) was then added in a single portion and the reaction stirred for 2.5 h over ice. Cyclohexane (150 mL) was added and the resulting suspension filtered through celite, washed with further cyclohexane and the resulting organics collected. The volatiles were removed *in vacuo* and purification via distillation (2.8 mbar, 55 ^{o}C) afforded **1.26** (20.440 g, 123 mmol, 61%) as colourless liquid (stored under N_2).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.64-7.67 (2H, m), 7.37- 7.46 (3H, m), 5.03 (2H, s), 4.08 (1H, sept, *J* = 6.1 Hz), 1.22 (6H, d, *J* = 6.1 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 134.6, 130.4, 128.1, 68.1, 25.0.

8.3.4 – Reaction Optimisation

To a vial was added *N*-cyanamide alkene **4.22** (136 mg, 0.50 mmol, 1 eq), *metal-source* (varying eq), *additive* (on occasion) and *silane-source* (varying eq) in *solvent* (varying). The reaction stirred at *temperature* (varying), under *atmosphere* (varying), for *time* (varying) and analysed by LCMS.

Table 17. Optimisation for the conversion of **4.22** to **4.23**, reactions on a 0.5 mmol scale.



Entry	[M] (mol %)	[Si] (eq)	Solvent (M)	T (°C)	Additive	Atmosphere	Time (h)	LCMS (%UV) 4.22	4.23	4.24
1	$Fe(acac)_3$ (20)	$PhSiH_2(OiPr)$ (1.5)	THF (0.25)	50	-	Open (air)	1	16	14	37
2	"	"	"	60	-	"	1	23	12	36
3	"	"	"	70	-	Air (condenser)	1	50	7	17
4	"	"	EtOAc (0.25)	50	-	Open (air)	1 2	31 32	29 28	12 13
5	"	"	"	"	TFA (2 eq)	"	2	71	3	0
6	"	"	*n*-Hexane (0.25)	"	-	"	2	52	16	15
7	"	"	MeCN (0.25)	"	-	"	2	27	18	47
8	"	$PhSiH_2(OiPr)$ (1.0)	EtOAc (0.25)	"	-	"	2	44	31	12
9	"	$PhSiH_2(OiPr)$ (1.5)	EtOAc (0.25)	"	TBHP (3 eq)	Sealed (air)	2 68	50 47	20 23	2 2
10[a]	"	"	EtOAc (0.25)	"	-	O_2	2 68	36 30	37 52	2 2
11	"	$PhSiH_2(OiPr)$ (3.0)	"	"	-	"	2 19	18 16	36 33	12 15

12	"	$PhSiH_2(OiPr)$ (1.5)	"	60	-	"	2	28	26	12
13	"	"	"	70	-	"	2	28	23	21
14	"	"	"	25	-	"	40	27	17	2
15	"	"	DCM (0.25)	"	-	"	40	60	10	1
16[b]	"	$PhSiH_2(OiPr)$ (3.0*)	EtOAc (0.25)	50	-	"	18	9	43	18
17	$Fe(acac)_3$ (50)	$PhSiH_2(OiPr)$ (1.5)	"	"	-	"	23	32	39	10
18	$Fe(acac)_3$ (100)	"	"	"	-	"	23	22	32	11
19	$Fe(acac)_3$ (5)	"	"	"	-	"	19	38	43	3
20	$Fe(acac)_3$ (20)	"	"	"	TBPB (5 eq)	N_2	66	22	8	3
21	"	"	"	"	DTBP (5 eq)	"	66	0	21	31
22	"	"	EtOAc (0.25),	"	TBHP (5 eq)	"	66	38	27	1
23	"	"	"	"	TBHP (3 eq) Na_2HPO_4 (1 eq)	"	23	36	15	2
24	"	$PhSiH_3$ (1.0)	*i*PrOH (0.25)	"	-	O_2	1	2	28	21
25	"	$PhSiH_2(OiPr)$ (1.5)	EtOAc (0.125)	"	-	"	2	46	23	2
26	"	"	EtOAc (0.05)	"	-	"	2	51	12	0
27	"	"	EtOAc (0.5)	"	-	"	23	32	49	7
28	"	$PhSiH_3$ (1.2)	*i*PrOH (0.25)	"	TFA (1 eq)	"	19	21	42	0
29	"	$PhSiH_3$ (1.5)	*i*PrOH:H_2O (4:1) (0.25)	"	$K_2S_2O_8$ (3 eq)	N_2	6	78	0	0
30	"	$PhSiH_2(OiPr)$ (1.5)^	EtOAc (0.25)	"	-	O_2	4	37	26	2

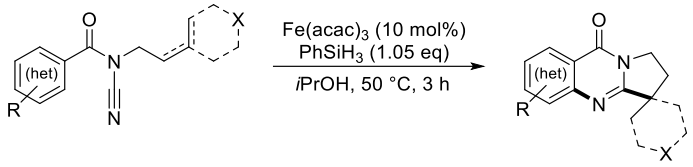
31	"	$PhSiH_2(OiPr)$ (2.0)^^	"	"	-	"	6	31	13	21
32	$Mn(acac)_3$ (20)	$PhSiH_2(OiPr)$ (1.5)	"	"	-	"	1	45	4	8
33	$Mn(dpm)_3$ (20)	"	"	"	-	"	1	17	13	25
34	$Fe(acac)_3$ (20)	$PhSiH_2(O^tBu)$ (1.5)	"	"	-	"	24	45	25	3

[a]37% isolated yield of **4.23**. [b]42% isolated yield of **4.23**. *2 x 1.5 eq, 2nd addition made after 1 h.

^Syringe pump addition over 1 h. ^^Syringe pump addition over 2 h.

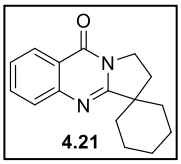
8.3.5 – Substrate Scope

General Method 4



To a vial was added *N-cyanamide alkene* (0.5 mmol, 1 eq) and $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq), to this was added a solution of $PhSiH_3$ (57 mg, 0.53 mmol, 1.05 eq) in *i*PrOH (2 mL, 0.25 M). The reaction was then stirred open to air, at 50 °C, for up to 3 h. Once complete, the reaction was cooled to RT and concentrated *in vacuo*. The crude reaction mixture was purified by automated column chromatography on silica gel to afford the desired quinazolinones.

1',2'-Dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.21)



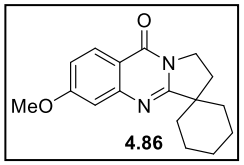
The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.20** (127 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.1 eq). The reaction was stopped after 2 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.21** as a colourless gum (92 mg, 0.36 mmol, 72%).

ν_{max} (neat): 2930, 2853, 1668, 1608, 769 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.25-8.27 (1H, m), 7.68-7.69 (2H, m), 7.37-7.43 (1H, m), 4.09 (2H, t, *J* = 7.6 Hz), 2.17 (2H, t, *J* = 6.9 Hz), 1.89-1.96 (2H, m), 1.80-1.84 (2H, m), 1.71-1.74 (1H, m), 1.64-1.67 (2H, m), 1.39-1.50 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 164.9, 161.1, 149.7, 133.8, 127.1, 126.2, 125.9, 120.9, 47.6, 43.3. 34.0, 30.4, 25.3, 22.4. LCMS (HpH): t_R = 1.10 min, $[M+H^+]$ 255.2. HRMS: ($C_{16}H_{19}N_2O$) $[M+H^+]$ requires 255.1497, found $[M+H^+]$ 255.1503 (error 2.4 ppm).

Scale-up: The title compound was prepared according to a scaled version of general method 4 using *N*-cyanamide alkene **4.20** (1.279 g, 5.03 mmol, 1 eq), $Fe(acac)_3$ (179

mg, 0.51 mmol, 0.1 eq) and $PhSiH_3$ (572 mg, 5.29 mmol, 1.05 eq). The reaction was stopped after 3 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.21** as a colourless gum which crystallised slowly to give a white solid (835 mg, 3.28 mmol, 65%). M.pt.: 74-77 ^{o}C.

6'-Methoxy-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.86)

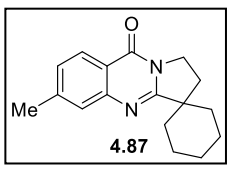


4.86

The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.34** (142 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (17 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (57 mg, 0.52 mmol, 1.05 eq). The reaction was stopped after 1 h. Purification by automated column chromatography on silica gel (0-65% TBME:cyclohexane) afforded **4.86** as a white solid (105 mg, 0.37 mmol, 74%).

M.pt.: 169-171 ^{o}C. ν_{max} (neat): 2971, 2921, 2851, 1669, 1613 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.18 (1H, d, *J* = 8.8 Hz), 7.11 (1H, d, *J* = 2.4 Hz), 7.01 (1H, dd, *J* = 8.8 and 2.4 Hz), 4.10 (2H, t, *J* = 7.1 Hz), 3.93 (3H, s), 2.19 (2H, t, *J* = 6.6 Hz), 1.89-1.95 (2H, m), 1.80-1.86 (2H, m), 1.75-1.77 (1H, m), 1.66-1.69 (2H, m), 1.41-1.52 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.7, 164.4, 160.8, 152.0, 127.7, 116.2, 114.5, 107.8, 55.6, 47.8, 43.3, 34.0, 30.4, 25.3, 22.4. LCMS (HpH): t_R = 1.11 min, [M+H$^+$] 285.1. HRMS: ($C_{17}H_{21}N_2O_2$) [M+H$^+$] requires 285.1603, found [M+H$^+$] 285.1614 (error 3.9 ppm).

6'-Methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.87)

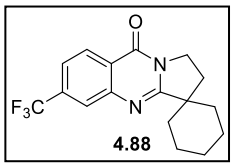


4.87

The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.33** (135 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.1 eq). The reaction was stopped after 2 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.87** as a white solid (100 mg, 0.37 mmol, 74%).

M.pt.: 110-114 °C. ν_{max} (neat): 2925, 2854, 1673, 1609, 787 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.15 (1H, d, *J* = 8.1 Hz), 7.50 (1H, br. s), 7.23 (1H, dd, *J* = 8.1 and 1.2 Hz), 4.08 (2H, t, *J* = 6.6 Hz), 2.47 (3H, s), 2.16 (2H, t, *J* = 7.1 Hz), 1.88-1.94 (2H, m), 1.80-1.84 (2H, m), 1.71-1.74 (1H, m), 1.63-1.66 (2H, m), 1.39-1.50 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.0, 161.1, 149.8, 144.7, 127.5, 126.9, 126.1, 118.5, 47.6, 43.2, 34.0, 30.5, 25.3, 22.4, 21.8. LCMS (HpH): t_R = 1.18 min, $[M+H^+]$ 269.2. HRMS: ($C_{17}H_{21}N_2O$) $[M+H^+]$ requires 269.1654, found $[M+H^+]$ 269.1663 (error 3.3 ppm).

6'-(Trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-]quinazolin]-9'-one (4.88)

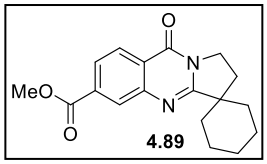


4.88

The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.35** (160 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (17 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.1 eq). The reaction was stopped after 3 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.88** as a white solid (105 mg, 0.33 mmol, 66%).

M.pt.: 125-128 °C. ν_{max} (neat): 2934, 2856, 1659, 1116 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.38 (1H, d, *J* = 8.1 Hz), 8.01 (1H, s), 7.62 (1H, dd, *J* = 8.4 and 1.5 Hz), 4.12 (2H, t, *J* = 7.4 Hz), 2.21 (2H, t, *J* = 7.1 Hz), 1.84-1.95 (4H, m), 1.75-1.76 (1H, m), 1.65-1.68 (2H, m), 1.41-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.5, 160.3, 149.6, 135.4 (q, *J* = 33.0 Hz), 127.4, 124.7-124.9 (m), 123.2, 122.2, 121.9 (q, *J* = 3.2 Hz), 47.8, 43.6, 34.0, 30.5, 25.3, 22.3. $^{19}F\{^{1}H\}$ NMR (376 MHz, CHLOROFORM-d) δ = -63.16. LCMS (HpH): t_R = 1.34 min, $[M+H^+]$ 323.0. HRMS: ($C_{17}H_{18}F_3N_2O$) $[M+H^+]$ requires 323.1371, found $[M+H^+]$ 323.1382 (error 3.4 ppm).

Methyl 9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazoline]-6'-carboxylate (4.89)

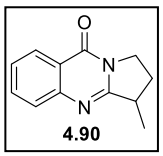


The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.36** (156 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.1 eq). The reaction was stopped after 3 h*. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.89** as a white solid (104 mg, 0.33 mmol, 67%).

*reaction mixture not homogeneous as product precipitated out of solution.

M.pt.: 204-208 ^{o}C. ν_{max} (neat): 2926, 2857, 1719, 1659, 1436, 757 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.40 (1H, d, *J* = 1.2 Hz), 8.32 (1H, d, *J* = 8.4 Hz), 8.02 (1H, dd, *J* = 8.4 and 1.5 Hz), 4.11 (2H, t, *J* = 7.1 Hz), 3.97 (3H, s), 2.20 (2H, t, *J* = 7.1 Hz), 1.90-1.96 (2H, m), 1.84-1.87 (2H, m), 1.72-1.75 (1H, m), 1.65-1.68 (2H, m), 1.41-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.3, 165.8, 160.6, 149.6, 135.0, 129.2, 126.6, 126.0, 124.0, 52.5, 47.7, 43.5, 34.1, 30.6, 25.3, 22.4. LCMS (HpH): t_R = 1.17 min, [M+H$^+$] 313.0. HRMS: ($C_{18}H_{21}N_2O_3$) [M+H$^+$] requires 313.1552, found [M+H$^+$] 313.1563 (error 3.5 ppm).

3-Methyl-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1*H*)-one (4.90)

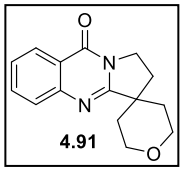


The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.54** (101 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.1 eq). The reaction was stopped after 2 h. Purification by automated column chromatography on silica gel (0-100% TBME:cyclohexane) afforded **4.90** as a white solid (64 mg, 0.32 mmol, 63%).

M.pt.: 133-135 ^{o}C. ν_{max} (neat): 2964, 2928, 1663, 1608, 783, 696 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.27-8.30 (1H, m), 7.67-7.74 (2H, m), 7.47 (1H, ddd, *J* = 8.0, 6.4 and 1.7 Hz), 4.27 (1H, ddd, *J* = 12.3, 8.5 and 3.9 Hz), 4.00 (1H, dt, *J* = 12.2 and 8.1 Hz), 3.27-3.36 (1H, m), 2.49 (1H, dtd, *J* = 12.5, 8.2 and 3.9 Hz), 1.87 (1H, dq, *J* =

12.8 and 8.5 Hz), 1.48 (3H, d, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 162.3, 160.1, 149.4, 134.0, 127.0, 126.4, 126.1, 120.7, 44.5, 38.8, 28.6, 17.2. LCMS (HpH): t_R = 0.75 min, [M+H$^+$] 201.1. HRMS: ($C_{12}H_{13}N_2O$) [M+H$^+$] requires 201.1028, found [M+H$^+$] 201.1036 (error 4.0 ppm).

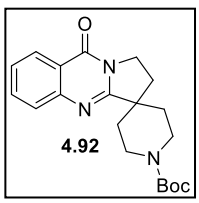
1',2,2',3,5,6-Hexahydro-9'*H*-spiro[pyran-4,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.91)



The title compound was prepared according to general method 2 using *N*-cyanamide alkene **4.80** (131 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (19 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.06 eq). The reaction was stopped after 2 h. Purification by automated column chromatography on silica gel (0-100% EtOAc:cyclohexane) afforded **4.91** as a white solid (92 mg, 0.36 mmol, 71%).

M.pt.: 142-144 ^{o}C. ν_{max} (neat): 2951, 2855, 1652, 1622, 775 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.13 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.77-7.81 (1H, m), 7.67-7.69 (1H, m), 7.47-7.51 (1H, m), 4.05-4.08 (2H, m), 3.93 (2H, dt, *J* = 11.7 and 4.4 Hz), 3.55 (2H, td, *J* = 11.7 and 2.5 Hz), 2.25-2.28 (2H, m), 2.00 (2H, ddd, *J* = 13.7, 11.3 and 4.4 Hz), 1.63 (2H, dd, *J* = 13.5 and 1.7 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 164.5, 160.4, 149.6, 134.5, 127.5, 126.5, 126.1, 121.1, 63.9, 45.3, 43.6, 34.1, 30.1. LCMS (Method A): t_R = 0.75 min, [M+H$^+$] 257.3. HRMS: ($C_{15}H_{17}N_2O_2$) [M+H$^+$] requires 257.1290, found [M+H$^+$] 257.1295 (error 1.9 ppm).

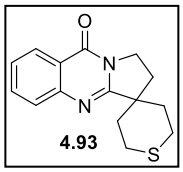
***Tert*-butyl 9'-oxo-1',2'-dihydro-9'*H*-spiro[piperidine-4,3'-pyrrolo[2,1-*b*]quinazoline]-1-carboxylate (4.92)**



The title compound was prepared according to general method 2 using *N*-cyanamide alkene **4.82** (178 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (57 mg, 0.53 mmol, 1.06 eq). The reaction was stopped after 2 h. Purification by automated column chromatography on silica gel (0-100% TBME:cyclohexane) afforded **4.92** as a white solid (129 mg, 0.36 mmol, 72%).

M.pt.: 167-170 °C. ν_{max} (neat): 2975, 2859, 1614, 1664, 773 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM -d) δ = 8.24 (1H, dd, *J* = 7.8 and 1.0 Hz), 7.63-7.71 (2H, m), 7.40 (1H, ddd, *J* = 8.1, 6.6 and 1.5 Hz), 4.10-4.14 (4H, m), 3.09-3.14 (2H, m), 2.17-2.21 (2H, m), 2.04-2.11 (2H, m), 1.60-1.64 (2H, m), 1.46 (9H, s). ^{13}C NMR (101 MHz, CHLOROFORM -d) δ = 163.1, 160.9, 154.6, 149.4, 134.0, 127.3, 121.0, 79.7, 45.7, 43.1, 33.7, 30.8, 28.5. LCMS (HpH): t_R = 1.11 min, [M+H$^+$] 356.4. HRMS: ($C_{20}H_{26}N_3O_3$) [M+H$^+$] requires 356.1974, found [M+H$^+$] 356.1975 (error 0.3 ppm).

1,2,2',3',5',6'-Hexahydro-9*H*-spiro[pyrrolo[2,1-*b*]quinazoline-3,4'-thiopyran]-9-one (4.93)

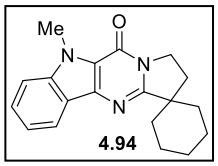


4.93

The title compound was prepared according to general method 2 using *N*-cyanamide alkene **4.81** (137 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.06 eq). The reaction was stopped after 2 h. Purification by automated column chromatography on silica gel (0-100% TBME:cyclohexane) afforded **4.93** as a white solid (74 mg, 0.27 mmol, 54%).

M.pt.: 139-141 °C. ν_{max} (neat): 2959, 2903, 1678, 1610, 773 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM -d) δ = 8.26 (1H, d, *J* = 8.3 Hz), 7.70-7.72 (2H, m), 7.43 (1H, ddd, *J* = 8.1, 4.9 and 3.2 Hz), 4.09-4.13 (2H, m), 2.92-2.95 (2H, m), 2.74 (2H, ddd, *J* = 13.7, 10.8 and 2.9 Hz), 2.31 (1H, ddd, *J* = 13.7, 10.5 and 3.2 Hz), 2.14-2.18 (2H, m), 1.93 (2H, ddd, *J* = 13.7, 6.1 and 2.7 Hz). ^{13}C NMR (101 MHz, CHLOROFORM -d) δ = 163.2, 161.0, 149.4, 134.0, 127.5, 126.3, 121.0, 46.3, 43.0, 34.9, 31.4, 24.2. LCMS (HpH): t_R = 0.95 min, [M+H$^+$] 273.3. HRMS: ($C_{15}H_{17}N_2OS$) [M+H$^+$] requires 273.1062, found [M+H$^+$] 273.1061 (error -0.4 ppm).

6'-Methyl-2',3'-dihydrospiro[cyclohexane-1,1'-pyrrolo[1',2':1,2]pyrimido[5,4-b]indol]-5'(6'*H*)-one (4.94)



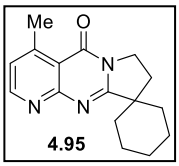
4.94

The title compound was prepared according to general method 4 using *N*-cyanamide alkene **4.43** (154 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (59 mg, 0.54 mmol, 1.08 eq). The reaction was stopped after 3 h. Purification by automated

column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.94** as a yellow solid (64 mg, 0.21 mmol, 42%).

M.pt.: 163-165 °C. ν_{max} (neat): 2929, 2854, 1659, 726 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.19 (1H, d, *J* = 8.1 Hz), 7.50 (1H, ddd, *J* = 8.3, 6.8 and 1.2 Hz), 7.41 (1H, d, *J* = 8.3 Hz), 7.23-7.27 (1H, m), 4.23 (3H, s), 4.15 (2H, t, *J* = 7.1 Hz), 2.22 (2H, *J* = 7.1 Hz), 1.94-2.01 (2H, m), 1.83-1.87 (2H, m), 1.74 (1H, br. s), 1.65-1.68 (2H, m), 1.43-1.49 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 161.7, 155.2, 140.6, 140.2, 127.2, 121.3, 121.1, 120.8, 120.0, 109.7, 47.2, 43.2, 34.4, 31.3, 31.2, 25.5, 22.6. LCMS (HpH): t_R = 1.27 min, [M+H$^+$] 308.1. HRMS: ($C_{19}H_{22}N_3O$) [M+H$^+$] requires 308.1763, found [M+H$^+$] 308.1765 (error 0.6 ppm).

4'-Methyl-7',8'-dihydro-5'*H*-spiro[cyclohexane-1,9'-pyrido[2,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-5'-one (4.95)

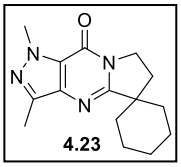


4.95

To *N*-cyanamide alkene **4.48** (134 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (34 mg, 0.10 mmol, 0.2 eq) in EtOAc (2 mL) was added $PhSiH_2(OiPr)$[50] (123 mg, 0.74 mmol, 1.5 eq), in a vial. The vial was sealed and placed under vacuum, then a balloon of oxygen attached. The reaction was stirred at 50 °C for 4 h, then cooled to RT and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-100% TBME:cyclohexane, 1% NEt_3) afforded **4.95** as a yellow gum (59 mg, 0.22 mmol, 44%).

ν_{max} (neat): 2922, 2855, 1665, 1618, 819, 495 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.69 (1H, d, *J* = 4.6 Hz), 7.11 (1H, dd, *J* = 4.8 and 0.6 Hz), 4.07 (2H, t, *J* = 7.1 Hz), 2.88 (3H, s), 2.20 (2H, t, *J* = 7.1 Hz), 2.01-2.08 (2H, m), 1.82-1.86 (2H, m), 1.72-1.74 (1H, m), 1.64-1.67 (2H, m), 1.36-1.49 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 168.0, 161.8, 161.0, 154.1, 152.1, 124.1, 114.9, 48.0, 43.6, 33.8, 30.2, 25.3, 22.4, 22.3. LCMS (HpH): t_R = 0.94 min, [M+H$^+$] 270.2. HRMS: ($C_{16}H_{20}N_3O$) [M+H$^+$] requires 270.1606, found [M+H$^+$] 270.1609 (error 1.1 ppm).

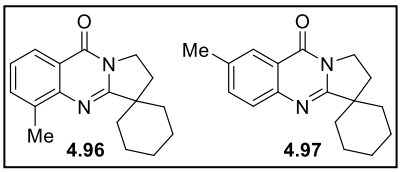
1',3'-Dimethyl-6',7'-dihydrospiro[cyclohexane-1,5'-pyrazolo[4,3-*d*]pyrrolo[1,2-*a*]pyrimidin]-9'(1'*H*)-one (4.23)



To *N*-cyanamide alkene **4.22** (137 mg, 0.50 mmol, 1 eq) and $Fe(acac)_3$ (36 mg, 0.10 mmol, 0.2 eq) in EtOAc (2 mL) was added $PhSiH_2(OiPr)$[50] (129 mg, 0.77 mmol, 1.5 eq), in a vial. The vial was sealed and placed under vacuum, then a balloon of oxygen attached. The reaction was stirred at 50 °C for 1 h, then further $PhSiH_2(OiPr)$[50] (125 mg, 0.75 mmol, 1.5 eq) added and continued overnight (18 h). The reaction then cooled to RT and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-50% EtOAc:cyclohexane) afforded **4.23** as a white solid (57 mg, 0.21 mmol, 42%).

M.pt.: 218-221 °C. ν_{max} (neat): 2924, 2855, 1671 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 4.21 (3H, s), 4.04 (2H, t, *J* = 7.1 Hz), 2.93 (3H, s), 2.18 (2H, t, *J* = 6.9 Hz), 1.80-1.91 (4H, m), 1.71-1.72 (1H, m), 1.60-1.63 (2H, m), 1.41-1.45 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 162.8, 153.5, 141.3, 139.7, 124.9, 46.7, 42.6, 38.1, 34.2, 31.3, 25.4, 22.4, 10.7. LCMS (HpH): t_R = 1.04 min, $[M+H^+]$ 273.2. HRMS: ($C_{15}H_{21}N_4O$) $[M+H^+]$ requires 273.1715, found $[M+H^+]$ 273.120 (error 1.8 ppm).

5'-Methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (4.96) and 7'-methyl-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.97)



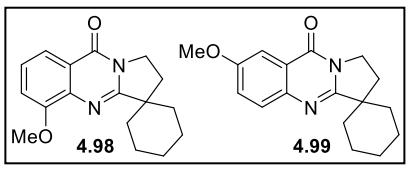
The title compounds were prepared according to general method 4 using *N*-cyanamide alkene **4.37** (135 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (59 mg, 0.54 mmol, 1.1 eq). The reaction was stopped after 3 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.96** (73 mg, 0.27 mmol, 54%) and **4.97** (33 mg, 0.12 mmol, 24%) separately as white solids.

4.96: M.pt.: 151-154 °C. ν_{max} (neat): 2923, 2854, 1655, 1606, 765 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 8.13 (1H, d, *J* = 7.9 Hz), 7.55 (1H, d, *J* = 7.1 Hz), 7.30 (1H,

t, *J* = 7.6 Hz), 4.09 (2H, t, *J* = 7.1 Hz), 2.62 (3H, s), 2.15 (2H, t, *J* = 7.1 Hz), 1.88-1.96 (4H, m), 1.70 (1H, br. s), 1.62-1.1.64 (2H, m), 1.47 (3H, br. s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 163.3. 161.6, 148.3, 135.8, 134.4, 125.4, 123.9, 120.8, 47.4, 43.2, 34.4, 31.3, 25.5, 22.4, 17.5. LCMS (HpH): t_R = 1.39 min, [M+H$^+$] 269.2. HRMS: ($C_{17}H_{21}N_2O$) [M+H$^+$] requires 269.1654, found 269.1665 [M+H$^+$] (error 4.1 ppm).

4.97: M.pt.: 98-102 ^{o}C. ν_{max} (neat): 2925, 2856, 1655, 1624, 828 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.07 (1H, s), 7.60 (1H, d, *J* = 8.4 Hz), 7.52 (1H, dd, *J* = 8.6 and 2.0 Hz), 4.09 (2H, t, *J* = 7.1 Hz), 2.47 (3H, s), 2.17 (2H, t, *J* = 7.1 Hz), 1.88-1.95 (2H, m), 1.81-1.84 (2H, m), 1.73-1.74 (1H, m), 1.64-1.1.67 (2H, m), 1.39-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 164.1, 161.2, 147.7, 136.0, 135.4, 127.0, 125.7, 120.7, 47.6, 43.3, 34.1, 30.5, 25.3, 22.4, 21.2. LCMS (HpH): t_R = 1.18 min, [M+H$^+$] 269.2. HRMS: ($C_{17}H_{21}N_2O$) [M+H$^+$] requires 269.1654, found [M+H$^+$] 269.1655 (error 0.4 ppm).

5'-Methoxy-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-b]quinazolin]-9'-one (4.98) and 7'-methoxy-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.99)



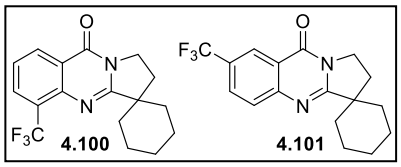
The title compounds were prepared according to general method 4 using *N*-cyanamide alkene **4.38** (141 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (57 mg, 0.52 mmol, 1.05 eq). The reaction was stopped after 3 h. Purification by automated column chromatography on silica gel (0-75% TBME:cyclohexane) afforded **4.98** (60 mg, 0.21 mmol, **43%**) and **4.99** (37 mg, 0.13 mmol, 26%) separately as white solids.

4.98: M.pt.: 184-188 ^{o}C. ν_{max} (neat): 2923, 1672, 1609, 1259, 1071, 760 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.88 (1H, dd, *J* = 8.1 and 1.2 Hz), 7.36 (1H, t, *J* = 8.0 Hz), 7.17 (1H, dd, *J* = 8.0 and 1.1 Hz), 4.10 (2H, t, *J* = 7.1 Hz), 4.01 (3H, s), 2.19 (2H, t, *J* = 7.1 Hz), 1.98-2.05 (2H, m), 1.80-1.83 (2H, m), 1.73-1.74 (1H, m), 1.65-1.1.68 (2H, m), 1.41-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 164.1, 161.1, 154.5, 140.5, 126.1, 122.2, 117.8, 114.3, 56.6, 47.9, 43.4, 33.8, 30.4, 25.2, 22.4. LCMS (HpH):

t_R = 1.04 min, [M+H$^+$] 285.2. HRMS: ($C_{17}H_{21}N_2O_2$) [M+H$^+$] requires 285.1603, found [M+H$^+$] 285.1614 (error 1.1 ppm).

4.99: M.pt.: 113-118 ^oC. ν_{max} (neat): 2924, 2853, 1659, 1618, 1488, 833 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.62-7.65 (2H, m), 7.31 (1H, dd, *J* = 9.0 and 2.9 Hz), 4.10 (2H, t, *J* = 7.6 Hz), 3.91 (3H, s), 2.18 (2H, t, = 7.1 Hz), 1.87-1.94 (2H, m), 1.81-1.84 (2H, m), 1.73-1.75 (1H, m), 1.64-1.1.67 (2H, m), 1.39-1.50 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 162.8, 161.0, 157.8, 144.3, 128.7, 124.1, 121.6, 105.8, 55.8, 47.4, 43.4, 34.1, 30.6, 25.4, 22.5. LCMS (HpH): t_R = 1.13 min, [M+H$^+$] 285.2. HRMS: ($C_{17}H_{21}N_2O_2$) [M+H$^+$] requires 285.1603, found [M+H$^+$] 285.1614 (error 3.9 ppm).

5'-(Trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.100) and 7'-(trifluoromethyl)-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazolin]-9'-one (4.101)



The title compounds were prepared according to general method 4 using *N*-cyanamide alkene **4.39** (162 mg, 0.50 mmol, 1 eq), Fe(acac)$_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.06 eq). The reaction was stopped after 3 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded 107 mg (0.34 mmol, 69%) of a white solid containing a mixture of **4.100** (37 mg, 0.13 mmol, 26%) and **4.101** (60 mg, 0.21 mmol, 43%) (inseparable on silica).

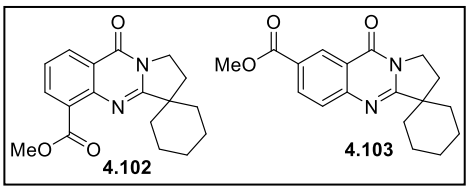
The mixture was purified by TFA MDAP for characterisation:

4.100: M.pt.: 148-154 ^oC. ν_{max} (neat): 2930, 2859, 1664, 1118 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.45 (1H, dd, *J* = 7.9 and 0.9 Hz), 8.01 (1H, dd, *J* = 7.5 and 0.6 Hz), 7.45 (1H, t, *J* = 7.8 Hz), 4.11 (2H, d, *J* = 7.1 Hz), 2.18 (2H, t, *J* = 7.3 Hz), 1.91-1.95 (4H, m), 1.61-1.68 (3H, m), 1.41-1.54 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.5, 160.4, 147.3, 131.5 (q, *J* = 5.1 Hz), 130.4, 126.6 (q, *J* = 30.8 Hz), 124.8, 123.6 (q, *J* = 274.4 Hz), 122.1, 47.6, 43.5, 34.3, 31.5, 25.4, 22.1. ^{19}F{^{1}H} NMR (376 MHz,

CHLOROFORM-d) δ = -60.49. LCMS (HpH): t_R = 1.38 min, [M+H$^+$] 323.2. HRMS: ($C_{17}H_{18}F_3N_2O$) [M+H$^+$] requires 323.13711, found [M+H$^+$] 323.1370 (error -0.3 ppm).

4.101: M.pt.: 200-204 ^oC. ν_{max} (neat): 2939, 2860, 1663, 1115 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.56 (1H, s), 7.9 (1H, dd, *J* = 8.6 and 2.0 Hz), 7.79 (1H, d, *J* = 8.6 Hz), 4.13 (2H, t, *J* = 7.1 Hz), 2.22 (2H, *J* = 7.1 Hz), 1.83-1.95 (4H, m), 1.75-1.77 (1H, m), 1.65-1.68 (2H, m), 1.40-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.2, 160.4, 151.9, 130.1 (q, *J* = 2.9 Hz), 128.2, 128.0 (q, *J* = 33.0 Hz), 123.8 (q, *J* = 271.4 Hz), 124.3 (q, *J* = 3.9 Hz), 120.9, 48.0, 43.6, 34.0, 30.4, 25.3, 22.3. ^{19}F{^{1}H} NMR (376 MHz, CHLOROFORM-d) δ = -62.23 . LCMS (HpH): t_R = 1.31 min, [M+H$^+$] 323.1. HRMS: ($C_{17}H_{18}F_3N_2O$) [M+H$^+$] requires 323.1371, found [M+H$^+$] 323.1371 (error 0.0 ppm).

Methyl 9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazoline]-5'-carboxylate (4.102) and methyl 9'-oxo-1',2'-dihydro-9'*H*-spiro[cyclohexane-1,3'-pyrrolo[2,1-*b*]quinazoline]-7'-carboxylate (4.103)



The title compounds were prepared according to general method 4 using *N*-cyanamide alkene **4.40** (155 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (56 mg, 0.52 mmol, 1.05 eq). The reaction was stopped after 3 h. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded 90 mg (0.29 mmol, 58%) of a white solid containing a mixture of **4.102** (34 mg, 0.11 mmol, **22%**) and **4.103** (56 mg, 0.18 mmol, 36%) (inseparable on silica).

The mixture was purified by TFA MDAP for characterisation:

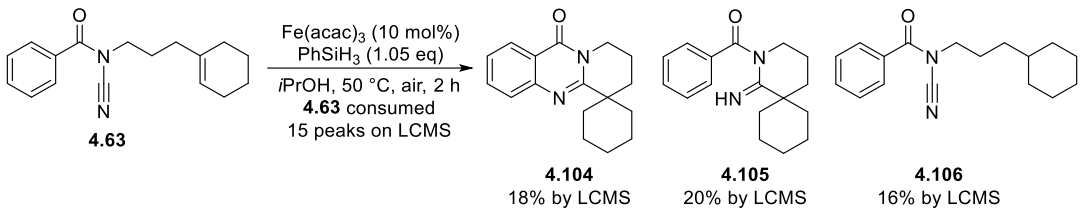
4.102: M.pt.: 120-124 ^oC. ν_{max} (neat): 2927, 2857, 1729, 1675, 1611, 774 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.4 (1H, d, *J* = 7.6 Hz), 8.01 (1H, d, *J* = 7.3 Hz), 7.45 (1H, t, *J* = 7.6 Hz), 4.12 (2H, t, *J* = 7.1 Hz), 4.00 (3H, s), 2.18 (2H, t, *J* = 7.0 Hz), 1.90-1.96 (4H, m), 1.64-1.66 (3H, m), 1.44-1.48 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.9, 165.5, 160.6, 147.1, 134.4, 129.63, 129.60, 125.4, 121.5, 52.4, 47.6, 43.6,

34.2, 31.4, 25.4, 22.1. LCMS (HpH): t_R = 1.13 min, [M+H$^+$] 313.2. HRMS: ($C_{18}H_{21}N_2O_3$) [M+H$^+$] requires 313.1552, found [M+H$^+$] 313.1553 (error 0.3 ppm).

4.103: M.pt.: 106-109 ^oC. ν_{max} (neat): 2928, 2858, 1665, 1609, 1277, 773 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.92 (1H, s), 8.33 (1H, d, *J* = 7.8 Hz), 7.76 (1H, d, *J* = 8.6 Hz), 4.15 (2H, t, *J* = 7.2 Hz), 3.96 (3H, s), 2.24 (2H, t, *J* = 7.2 Hz), 1.93-1.99 (2H, m), 1.84-1.86 (2H, m), 1.68-1.77 (3H, m), 1.40-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.6, 166.0, 160.5, 151.7, 134.5, 128.8, 127.9, 126.8, 120.4, 52.3, 48.4, 43.9, 33.8, 30.3, 25.2, 22.3. LCMS (HpH): t_R = 1.17 min, [M+H$^+$] 313.2. HRMS: ($C_{18}H_{21}N_2O_3$) [M+H$^+$] requires 313.1552, found [M+H$^+$] 313.1547 (error -1.6 ppm).

8.3.6 – Challenging Substrates

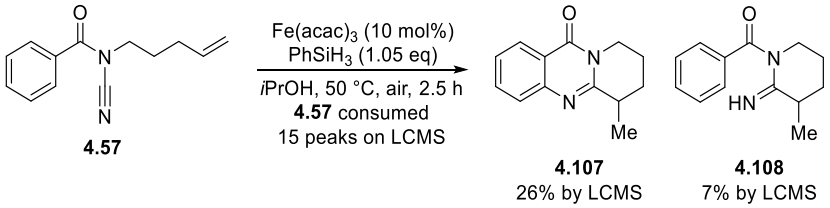
Reaction of *N*-cyano-*N*-(3-(cyclohex-1-en-1-yl)propyl)benzamide (4.63)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.63** (134 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 2 h and then abandoned.

LCMS (HpH): t_R = 1.07 min, $[M+H^+]$ 271.2 (**4.105**); t_R = 1.35 min, $[M+H^+]$ 269.2 (**4.104**); t_R = 1.47 min, $[M+H^+]$ 271.2 (**4.106**).

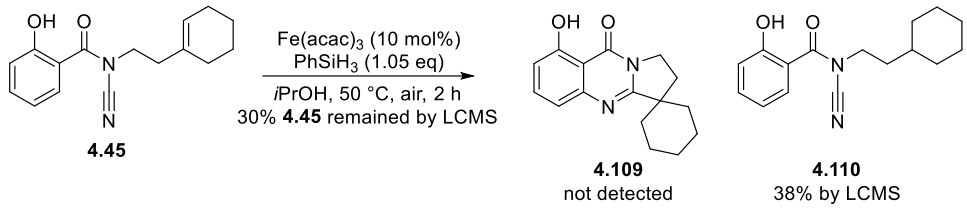
Reaction of *N*-cyano-*N*-(pent-4-en-1-yl)benzamide (4.57)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.57** (107 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (56 mg, 0.52 mmol, 1.05 eq). The reaction was sampled for LCMS analysis after 2.5 h and then abandoned.

LCMS (HpH): t_R = 0.82 min, $[M+H^+]$ 217.2 (**4.108**); t_R = 0.92 min, $[M+H^+]$ 215.2 (**4.107**).

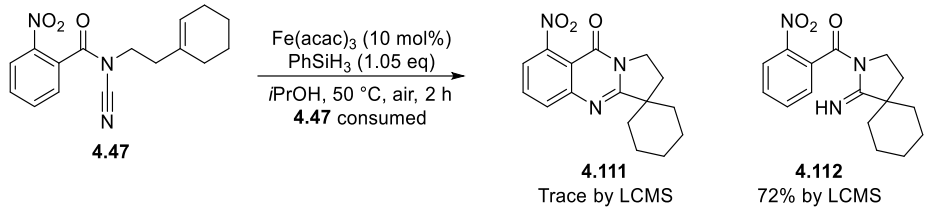
Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-hydroxybenzamide (4.45)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.45** (135 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 2 h and then abandoned.

LCMS (HpH): t_R = 1.37 min, $[M+H^+]$ 273.2 (**4.110**).

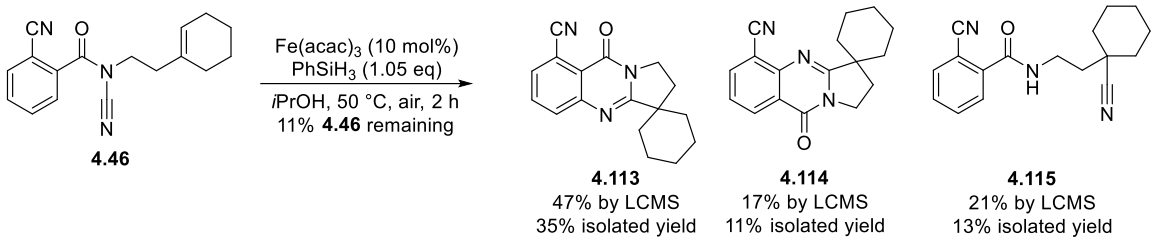
Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-nitrobenzamide (4.47)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.47** (153 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (59 mg, 0.55 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 2 h and then abandoned.

LCMS (HpH): t_R = 1.06 min, $[M+H^+]$ 302.0 (**4.112**); t_R = 1.16 min, $[M+H^+]$ 300.0 (**4.111**).

Reaction of *N*,2-dicyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)benzamide (4.46)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.46** (140 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.08 eq). The reaction was sampled for LCMS analysis after 2 h, cooled to RT and then concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-75% TBME:cyclohexane) afforded **4.113** (48 mg, 0.17 mmol, 35%), **4.114** (16 mg, 0.06 mmol, 11%) and **4.115** (18 mg, 0.07 mmol, 13%) as white solids.

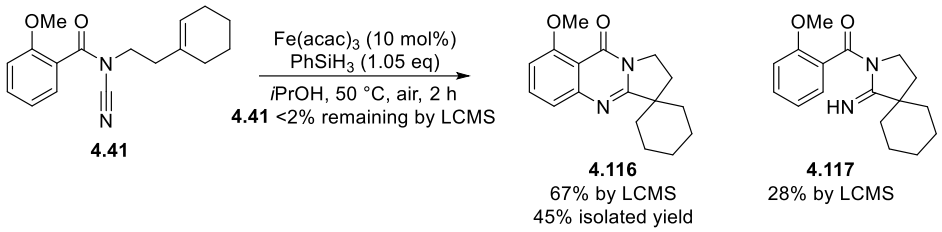
4.113: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.91 (1H, dd, *J* = 8.3 and 2.0 Hz), 7.73-7.80 (2H, m), 4.12-4.16 (2H, m), 2.20-2.23 (2H, m), 1.83-1.94 (4H, m), 1.74-1.77 (1H, m), 1.65-1.67 (2H, m), 1.39-1.51 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 166.7, 158.7, 150.8, 133.4, 133.2, 132.3, 121.2, 117.6, 110.7, 48.0, 43.8, 34.0, 30.4, 25.3, 22.3. LCMS (Formic): t_R = 1.08 min, [M+H$^+$] 280.2.

4.114: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.46 (1H, dd, *J* = 8.1 and 1.5 Hz), 8.03 (1H, dd, *J* = 7.5 and 1.6 Hz), 7.46 (1H, t, *J* = 7.6 Hz), 4.10-4.14 (2H, m), 2.19-2.23 (2H, m), 1.97-2.05 (2H, m), 1.87-1.91 (2H, m), 1.71-1.74 (1H, m), 1.63-1.66 (2H, m), 1.40-1.55 (3H, m). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 167.6, 160.0, 151.0, 138.6, 131.1, 125.4, 121.7, 116.6, 111.2, 48.0, 43.8, 34.1, 30.9, 25.2, 22.2. LCMS (HpH): t_R = 1.16 min, [M+H$^+$] 280.1. HRMS: ($C_{17}H_{18}N_3O$) [M+H$^+$] requires 280.1450, found [M+H$^+$] 280.1452 (error 0.7 ppm).

4.115: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.56 (1H, br. s), 7.84-7.86 (1H, m), 7.73-7.74 (1H, m), 7.62-7.70 (2H, m), 4.03-4.07 (2H, m), 2.09-2.13 (2H, m), 1.98-2.02 (2H, m), 1.72-1.76 (3H, m), 1.59-1.67 (2H, m), 1.31-1.38 (2H, m), 1.15-1.24 (1H, m).

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.8, 133.0, 132.3, 131.0, 123.3, 122.7, 120.8, 37.8, 37.1, 35.5, 34.0, 25.3, 22.8. LCMS (HpH): t_R = 1.05 min, [M+H$^+$] 282.2.

Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-methoxybenzamide (4.41)

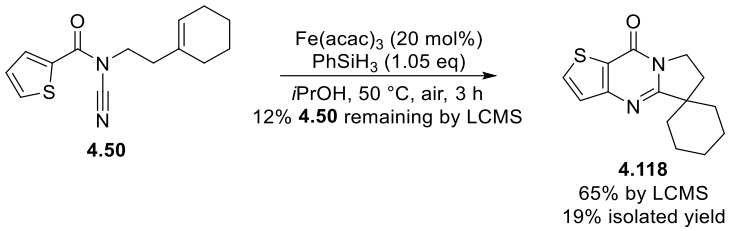


The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.41** (144 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 2 h, cooled to RT and then concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-100% TBME:cyclohexane) afforded **4.116** as a white solid (65 mg, 0.23 mmol, 45%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.58 (1H, t, *J* = 8.1 Hz), 7.26-7.28 (1H, m), 6.83 (1H, d, *J* = 8.3 Hz), 4.03-4.07 (2H, m), 3.98 (3H, s), 2.13-2.16 (2H, m), 1.80-1.93 (4H, m), 1.71-1.74 (1H, m), 1.63-1.66 (2H, m), 1.40-1.47 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.2, 160.3, 159.6, 152.6, 134.1, 119.5, 111.1, 107.1, 56.3, 47.8, 43.4, 33.9, 30.3, 25.3, 22.4. LCMS (HpH): t_R = 1.01 min, [M+H$^+$] 285.2.

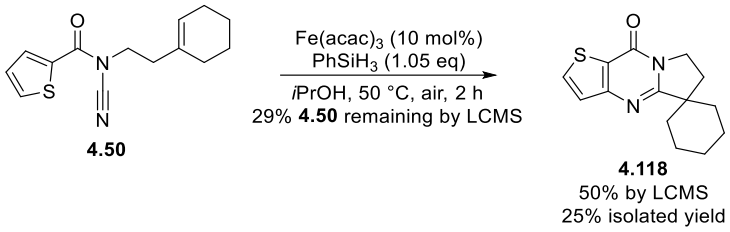
LCMS (HpH): t_R = 1.09 min, [M+H$^+$] 287.2 (**4.117**).

Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)thiophene-2-carboxamide (4.50)

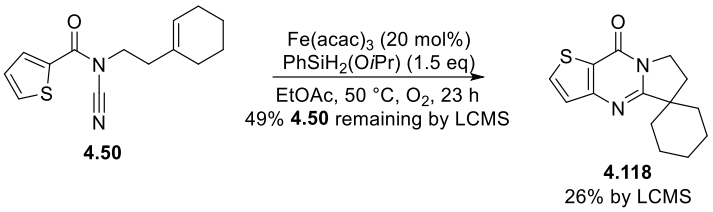


The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.50** (131 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 3 h, cooled to RT and then concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-50% TBME:cyclohexane) afforded **4.118** as a white solid (25 mg, 0.10 mmol, 19%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.74 (1H, d, *J* = 5.4 Hz), 7.32 (1H, d, *J* = 5.4 Hz), 4.11-4.14 (2H, m), 2.21-2.24 (2H, m), 1.80-1.92 (4H, m), 1.73-1.76 (1H, m), 1.65-1.68 (2H, m), 1.41-1.49 (3H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 167.0, 158.8, 157.3, 133.7, 125.0, 121.5, 47.5, 43.4, 34.2, 30.8, 29.7, 25.3, 22.4. LCMS (Formic): t_R = 0.87 min, [M+H$^+$] 261.1.

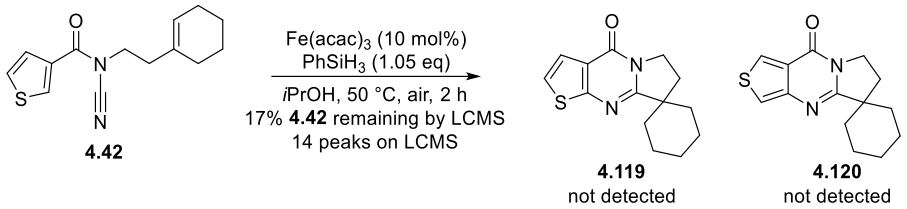


The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.50** (130 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 2 h, cooled to RT and then concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-100% TBME:cyclohexane) afforded **4.118** as a yellow gummy solid (32 mg, 0.12 mmol, 25%) (yield adjusted for 10% impurity with MH+ = 263.3).



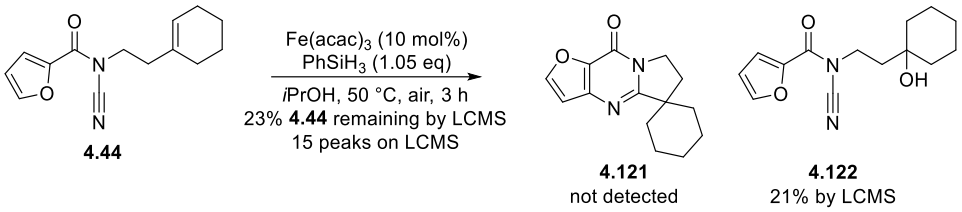
The title reaction was performed according to modified general method 4 using *N*-cyanamide alkene **4.50** (131 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_2(OiPr)$ (127 mg, 0.77 mmol, 1.5 eq) under oxygen. The reaction was sampled for LCMS analysis after 23 h and abandoned.

Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)thiophene-3-carboxamide (4.42)



The title reaction was performed according to general method 4 using **4.42** (129 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (19 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (57 mg, 0.53 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 2 h and abandoned.

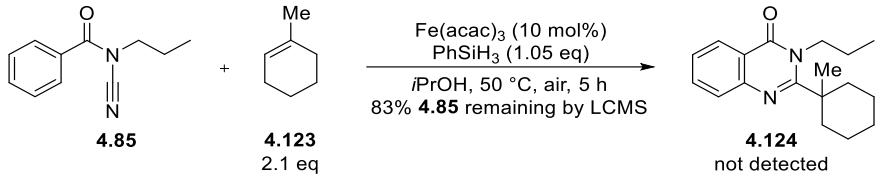
Reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)furan-2-carboxamide (4.44)



The title reaction was performed according to general method 4 using **4.44** (121 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.54 mmol, 1.1 eq). The reaction was sampled for LCMS analysis after 3 h and abandoned.

LCMS (HpH): t_R = 0.87 min, $[M+H^+]$ 261.3 (**4.122**).

Reaction of *N*-cyano-*N*-propylbenzamide (4.85) and 1-methylcyclohex-1-ene (4.123)

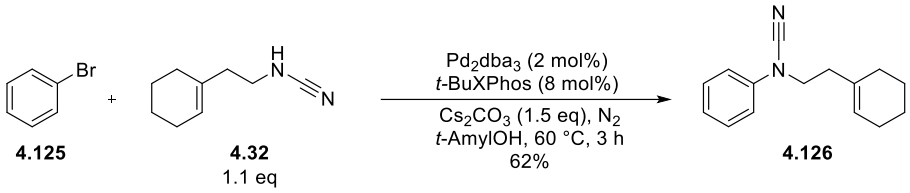


4.85 **4.123** 2.1 eq **4.124** not detected

The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.85** (96 mg, 0.51 mmol, 1 eq), 1-methylcyclohex-1-ene (**4.123**) (105 mg, 1.09 mmol, 2.1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (58 mg, 0.53 mmol, 1.04 eq). The reaction was sampled for LCMS analysis after 5 h and abandoned.

8.3.7 – Removing Amide Moiety

_N_-(2-(cyclohex-1-en-1-yl)ethyl)-_N_-phenylcyanamide (4.126)

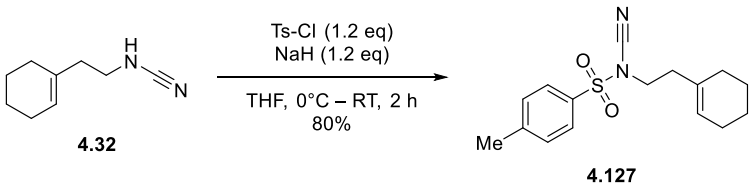


4.125 **4.32** 1.1 eq **4.126**

To a vial was added Pd_2dba_3 (114 mg, 0.13 mmol, 2 mol%), Cs_2CO_3 (2.456 g, 7.54 mmol, 1.5 eq), *t*-BuXPhos (173 mg, 0.41 mmol, 8 mol%), bromobenzene (**4.125**) (813 mg, 5.18 mmol, 1 eq) and *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**) (827 mg, 5.50 mmol, 1.1 eq). The vial was sealed, evacuated and refilled with N_2 (repeated 3 times). Then *t*-amylOH (10 mL) added and the reaction stirred at 60 ^oC for 3 h. The reaction allowed to cool to RT, filtered through celite and washed with DCM. The crude organics were concentrated *in vacuo* and purification by automated column chromatography on silica gel (0-10% TBME:cyclohexane) afforded **4.126** as a yellow oil (726 mg, 3.21 mmol, 62%).

^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.39 (2H, m), 7.06-7.13 (3H, m), 5.49-5.51 (1H, m), 3.66 (2H, t, *J* = 7.4 Hz), 2.41 (2H, t, *J* = 7.4 Hz), 1.96-2.01 (4H, m), 1.60-1.66 (2H, m), 1.52-1.59 (2H, m). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 140.0, 132.8, 129.6, 125.0, 123.4, 116.0, 113.6, 48.2, 35.6, 28.3, 25.3, 22.8, 22.1. LCMS (HpH): t_R = 1.33 min, [$M+H^+$] 227.1.

_N_-cyano-_N_-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide[145] (4.127)



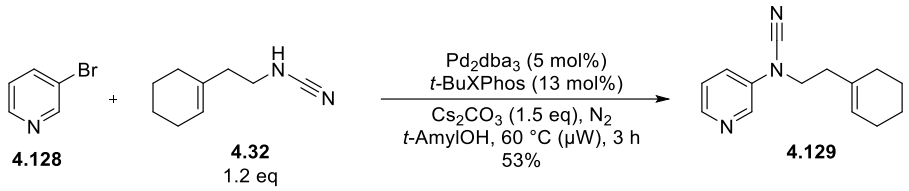
4.32 **4.127**

To a suspension of NaH (60% dispersion in mineral oil) (220 mg, 5.50 mmol, 1.2 eq) in THF (18 mL), over ice, was added a solution of *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**) (671 mg, 4.47 mmol, 1 eq) in THF (5 mL). The reaction was

stirred for 15 min at RT, then cooled again on ice and a solution of tosyl chloride (1.027 g, 5.39 mmol, 1.2 eq) in THF (5 mL) was added. The reaction allowed to warm to RT and stirred for 2 h. The reaction was quenched with the addition of water (25 mL), followed by brine (25 mL) and the aqueous layer extracted with diethyl ether (3 x 25 mL). The organics were combined via a hydrophobic frit and concentrated *in vacuo*. Purification by automated column chromatography on silica gel (0-20% TBME:cyclohexane) afforded **4.127** as a white solid (1.088 g, 3.57 mmol, 80%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.82-7.85 (2H, m), 7.40-7.42 (2H, m), 5.44-5.45 (1H, m), 3.45 (2H, t, *J* = 7.3 Hz), 2.48 (3H, s), 2.25 (2H, t, *J* = 7.3 Hz), 1.94-1.97 (2H, m), 1.84-1.87 (2H, m), 1.56-1.62 (2H, m), 1.49-1.53 (2H, m). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 146.3, 134.0, 131.8, 130.4, 127.8, 125.7, 108.5, 48.7, 36.2, 27.9, 25.2, 22.6, 22.0, 21.8. LCMS (HpH): t_R = 1.36 min, [M+H$^+$] 305.2.

_N_-(2-(cyclohex-1-en-1-yl)ethyl)-_N_-(pyridin-3-yl)cyanamide (4.129)

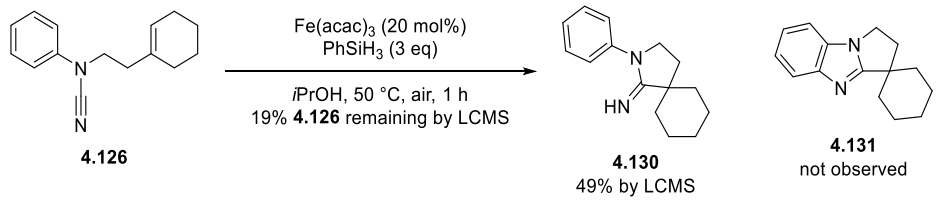


To a vial was added Pd_2dba_3 (302 mg, 0.33 mmol, 5 mol%), Cs_2CO_3 (3.189 g, 9.79 mmol, 1.5 eq), *t*-BuXPhos (364 mg, 0.86 mmol, 13 mol%), 3-bromopyridine (**4.128**) (1.031 g, 3.50 mmol, 1 eq) and *N*-(2-(cyclohex-1-en-1-yl)ethyl)cyanamide (**4.32**) (1.223 g, 8.14 mmol, 1.2 eq). The vial was sealed, evacuated and refilled with N_2 (repeated 3 times). Then *t*-amylOH (13 mL) added and the reaction stirred at 60 ^{o}C in the microwave for 3 h. The reaction allowed to cool to RT, filtered through celite and washed with DCM. The organics were washed with water (50 mL), then brine (50mL) and concentrated *in vacuo.* Purification by automated reverse phase column chromatography on C18 silica gel (20-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate) afforded **4.129** as a yellow oil (785 mg, 3.45 mmol, 53%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.47 (1H, d, *J* = 2.9 Hz), 8.37 (1H, dd, *J* = 4.7 and 1.2 Hz), 7.46 (1H, ddd, *J* = 8.3, 2.9 and 1.5 Hz), 7.31 (1H, dd, *J* = 8.6 and 4.7 Hz),

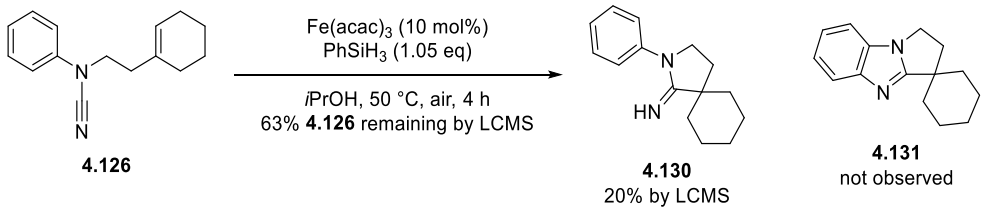
5.50-5.53 (1H, m), 3.71 (2H, t, *J* = 7.3 Hz), 2.43 (2H, t, *J* = 7.1 Hz), 1.97-1.99 (4H, m), 1.61-1.67 (2H, m), 1.52-1.58 (2H, m). LCMS (HpH): t_R = 1.08 min, [M+H$^+$] 228.2.

HAT reaction of *N*-(2-(cyclohex-1-en-1-yl)ethyl)-*N*-phenylcyanamide (4.126)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.126** (113 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (35 mg, 0.10 mmol, 0.2 eq) and $PhSiH_3$ (164 mg, 1.52 mmol, 3 eq). The reaction was sampled for LCMS analysis after 1 h and abandoned.

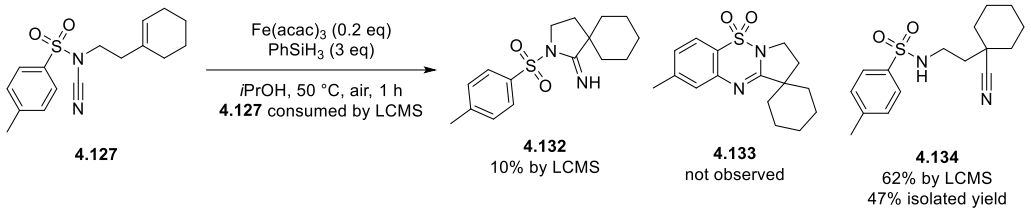
LCMS (HpH): t_R = 1.04 min (broad), [M+H$^+$] 229.2 (**4.130**).



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.126** (113 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (18 mg, 0.05 mmol, 0.1 eq) and $PhSiH_3$ (56 mg, 0.52 mmol, 1.04 eq). The reaction was sampled for LCMS analysis after 4 h and abandoned.

LCMS (HpH): t_R = 0.96 min (broad), [M+H$^+$] 229.3 (**4.130**).

HAT reaction of *N*-cyano-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide (4.127)

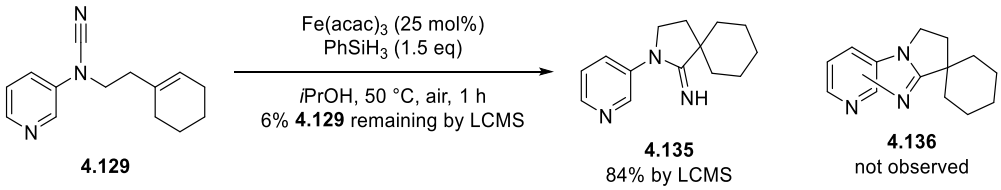


The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.127** (152 mg, 0.50 mmol, 1 eq), $Fe(acac)_3$ (37 mg, 0.11 mmol, 0.2 eq) and $PhSiH_3$ (165 mg, 1.52 mmol, 3 eq). The reaction was sampled for LCMS analysis after 1 h. The reaction was stopped, concentrated *in vacuo* and purified by automated reverse phase column chromatography on C18 silica gel (30-95% acetonitrile:water adjusted to *p*H 10 with ammonium bicarbonate). Further purification by MDAP (HpH) yielded **4.134** (72 mg, 0.24 mmol, 47%) as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.74-7.76 (2H, m), 7.31 (2H, d, *J* = 7.8 Hz), 5.52 (1H, t, *J* = 6.4 Hz), 3.08-3.14 (2H, m), 2.42 (3H, s), 1.86-1.89 (2H, m), 1.73-1.77 (2H, m), 1.68-1.71 (3H, m), 1.49-1.61 (2H, m), 1.10-1.25 (3H, m). ^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 143.6, 136.6, 129.8, 127.1, 122.9, 39.9, 39.1, 37.4, 35.5, 25.1, 22.8, 21.5. LCMS (HpH): t_R = 1.13 min, [M+H$^+$] 305.2.

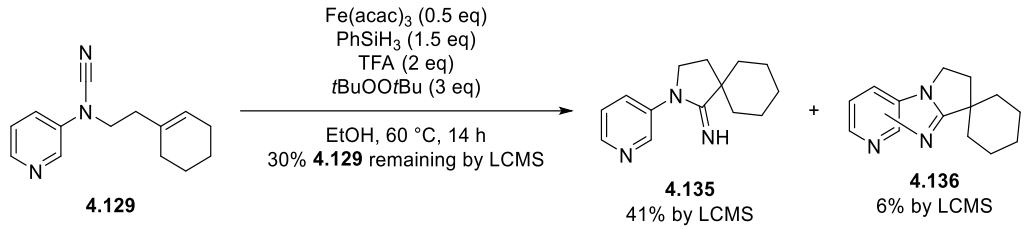
LCMS (HpH): t_R = 1.17 min, [M+H$^+$] 307.2 (**4.132**).

HAT reaction of *N*-(2-(cyclohex-1-en-1-yl)ethyl)-*N*-(pyridin-3-yl)cyanamide (4.129)



The title reaction was performed according to general method 4 using *N*-cyanamide alkene **4.129** (115 mg, 0.51 mmol, 1 eq), $Fe(acac)_3$ (44 mg, 0.13 mmol, 25 mol%) and $PhSiH_3$ (85 mg, 0.78 mmol, 1.5 eq). The reaction was sampled for LCMS analysis after 1 h and abandoned.

LCMS (HpH): t_R = 0.86 min (broad), [M+H$^+$] 230.2 (**4.135**).



4.129

4.135
41% by LCMS

4.136
6% by LCMS

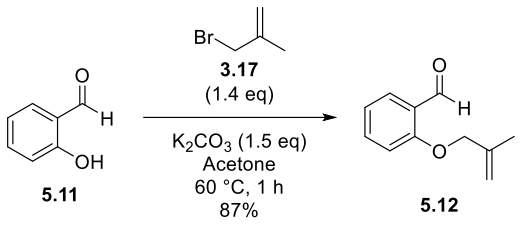
To a solution of **4.129** (96 mg, 0.42 mmol, 1 eq) in EtOH (1 mL) was added TFA (65 µL, 0.85 mmol, 2 eq) and the reaction mixture stirred for 5 mins at RT. Then the solution was transferred (along with 1.5 mL EtOH rinsings) to a vial containing $Fe(acac)_3$ (74 mg, 0.21 mmol, 0.5 eq), *t*BuOO*t*Bu (235 µL, 1.27 mmol, 3 eq) and $PhSiH_3$ (69 mg, 0.64 mmol, 1.5 eq). The reaction vial was sealed, under air, and the reaction stirred at 60 ^oC. The reaction was sampled for LCMS analysis after 14 h and abandoned.

LCMS (HpH): t_R = 0.78 min, [M+H$^+$] 228.2 (**4.136**); t_R = 0.86 min (broad), [M+H$^+$] 230.2 (**4.135**).

8.4 – Synthetic Procedures for Section 5

8.4.1 – Synthesis of Sulfinimine Precursors

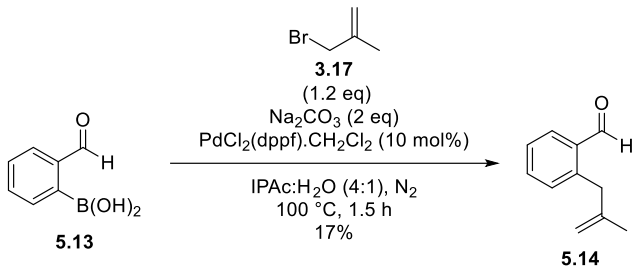
2-((2-Methylallyl)oxy)benzaldehyde[156] (5.12)



To a solution of **5.11** (4.05 g, 33.2 mmol, 1 eq) and K_2CO_3 (6.81 g, 49.3 mmol, 1.5 eq) in acetone (30 mL), **3.17** (4.7 mL, 46.6 mmol, 1.4 eq) was added. The reaction was stirred at 60 ^oC for 1 h. The reaction was allowed to cool to RT, water added (50 mL) and the aqueous layer was extracted with EtOAc (3 x 25mL). The combined organics were washed with brine (50 mL), dried through a hydrophobic frit and evaporated *in vacuo* to afford a light-yellow oil. The crude product was purified by automated column chromatography on silica gel (0-10% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **5.12** as a colourless oil (5.06 g, 28.7 mmol, 87%).

^1H NMR (400 MHz, CHLOROFORM-d) δ = 10.55 (1H, d, *J* = 1.0 Hz), 7.84 (1H, dd, *J* = 7.6 and 1.7 Hz), 7.52 (1H, ddd, *J* = 8.3, 7.3 and 2.0 Hz), 7.00-7.04 (1H, m), 6.97 (1H, d, *J* = 8.8 Hz), 5.12-5.13 (1H, m), 5.03-5.04 (1H, m), 4.55 (2H, s), 1.86 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 189.5, 161.1, 140.0, 135.8, 128.3, 125.1, 120.8, 113.2, 112.9, 72.1, 19.3. LCMS (Formic): t_R = 1.13 min, [M+H$^+$] 177.1. HRMS: ($C_{11}H_{13}O_2$) [M+H$^+$] requires 177.0916, found [M+H$^+$] 177.0909 (error – 4.0 ppm).

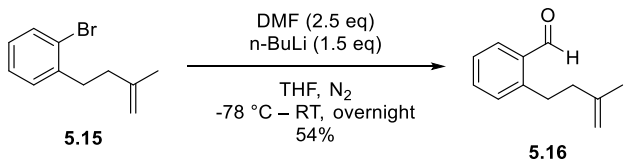
2-(2-Methylallyl)benzaldehyde (5.14)



To a vial, **5.13** (249 mg, 1.66 mmol, 1 eq), **3.17** (270 mg, 2.00 mmol, 1.2 eq), $PdCl_2(dppf).CH_2Cl_2$ (136 mg, 0.17 mmol, 10 mol%) and Na_2CO_3 (353 mg, 3.33 mmol, 2 eq) were added and the vial sealed under N_2. Degassed water (1 mL) and IPAc (4 mL) were added, the reaction stirred at 100 ^oC for 1.5 h and then cooled to RT. Water was added (10 mL) and the aqueous layer extracted with EtOAc (3 x 2 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude reaction material was purified by automated column chromatography on silica gel (0-100% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo,* the crude oil was re-purified by column chromatography on silica gel (0-40% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **5.14** as a colourless oil (45 mg, 0.28 mmol, 17%).

^1H NMR (400 MHz, CHLOROFORM-d) δ = 10.25 (1H, s), 7.87 (1H, dd, *J* = 7.8 and 1.0 Hz), 7.52 (1H, td, *J* = 7.6 and 1.5 Hz), 7.39 (1H, t, *J* = 7.6 Hz), 7.28 (1H, d, *J* = 7.8 Hz), 4.84 (1H, s), 4.46 (1H, s), 3.74 (2H, s), 1.78 (3H, s). LCMS (Formic): t_R = 1.16 min, $[M+H^+]$ not found.

2-(3-Methylbut-3-en-1-yl)benzaldehyde[157] (5.16)



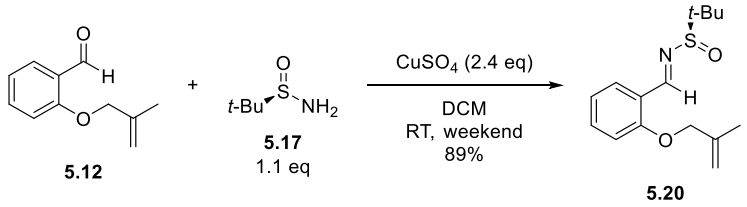
To a flame-dried flask under N_2 was added **X** (953 mg, 4.23 mmol, 1 eq) and THF (4 mL). The flask was cooled to -78 ^oC and n-BuLi (2.5 mL, 6.25 mmol, 1.5 eq) (2.5M, hexanes) was added dropwise under N_2. The resulting solution was stirred for 30 mins

and then dry DMF (0.82 mL, 10.59 mmol, 2.5 eq) added slowly. The reaction was allowed to come to RT slowly and stirred overnight. Then saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the aqueous layer extracted with ether (3 x 10 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (0-15 EtOAc:cyclohexane). Desired fractions were combined and dried *in vacuo* to afford **X** as a colourless oil (401 mg, 2.30 mmol, **54%**).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 10.27 (1H, s), 7.83 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.50 (1H, td, *J* = 7.6 and 1.5 Hz), 7.37 (1H, td, *J* = 7.5 and 1.2 Hz), 7.28 (1H, d, *J* = 7.8 Hz), 4.76-4.77 (1H, m), 4.71-4.72 (1H, m), 3.15-3.19 (2H, m), 2.28-2.32 (2H, m), 1.79 (3H, s). LCMS (Formic): t_R = 1.24 min, [M+H$^+$] 175.0.

8.4.2 – Sulfinimine Synthesis

(R)-2-Methyl-*N*-(2-((2-methylallyl)oxy)benzylidene)propane-2-sulfinamide (5.20)

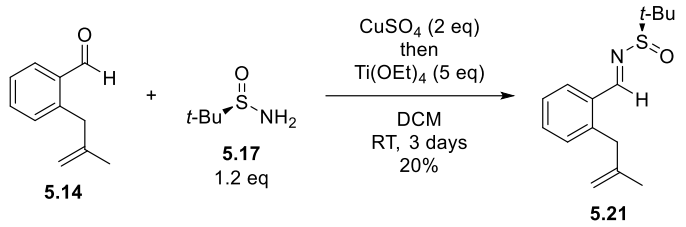


To a flask containing **5.12** (1.036 g, 5.88 mmol, 1 eq), **5.17** (761 mg, 6.28 mmol, 1.1 eq) and $CuSO_4$ (2.224 g, 13.93 mmol, 2.4 eq), DCM (20 mL) was added. The reaction was left to stir over the weekend at RT. Water (50 mL) then added, the organic layer separated and concentrated *in vacuo*. The yellow oil was purified by automated column chromatography on silica gel (0-15% EtOAc:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **5.20** as a colourless oil (1.459 g, 5.22 mmol, 89%).

ν_{max} (neat): 2925, 1593, 1451, 1081, 754 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 9.12 (1H, s), 7.99 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.41-7.45 (1H, m), 7.01 (1H, t, *J* = 7.6 Hz), 6.95 (1H, d, *J* = 8.3 Hz), 5.10 (1H, s), 5.01 (1H, s), 4.53 (2H, s), 1.84 (3H, s), 1.26 (9H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 158.8, 140.2, 133.7, 128.3, 123.2,

120.8, 113.1, 112.8, 72.2, 57.6, 22.6, 19.4. LCMS (HpH): t_R = 1.34 min, [M+H$^+$] 280.2. HRMS: ($C_{15}H_{22}NO_2S$) [M+H$^+$] requires 280.1371, found [M+H$^+$] 280.1369 (error -0.7 ppm).

(R)-2-Methyl-*N*-(2-(2-methylallyl)benzylidene)propane-2-sulfinamide (5.21)

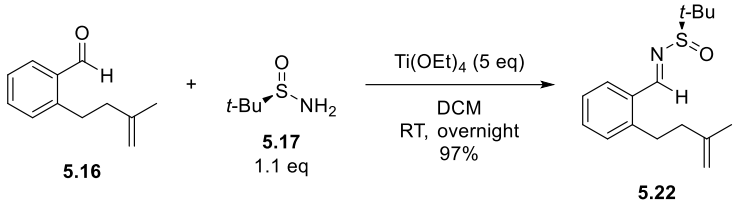


To a stirred solution of **5.14** (45 mg, 0.28 mmol, 1 eq) and **5.17** (41 mg, 0.34 mmol, 1.2 eq) in DCM (1 mL), $CuSO_4$ (90 mg, 0.56 mmol, 2 eq) was added, the reaction was left to stir overnight at RT. Water was added (5 mL) and the aqueous phase extracted with EtOAc (3 x 2 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo* to yield a light-yellow oil. On inspection (^{1}H NMR), it was found the reaction had not gone to completion. The oil was re-taken up in DCM (1 mL) and $CuSO_4$ (90 mg, 0.56 mmol, 2 eq) added, the reaction was left to stir overnight at RT once more. Water was added (5 mL) and the aqueous phase extracted with EtOAc (3 x 2 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo* to yield a light-yellow oil. On inspection (^{1}H NMR), it was found the reaction had not gone to completion once more. The oil was re-taken up in DCM (1 mL) and $Ti(OEt)_4$ (294 μL, 1.40 mmol, 5 eq) was added, the reaction was left to stir overnight at RT. Saturated $NaHCO_{3\,(aq)}$ was added until white Ti salts were seen to precipitate; the slurry was filtered through celite and washed with DCM (10 mL). The organics were dried in *vacuo* and the resulting colourless oil purified by column chromatography on silica gel (0-30% EtOAc:cyclohexane). Desired fractions were combined and dried *in vacuo* to afford **5.21** as a colourless oil (15 mg, 0.06 mmol, 20%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.83 (1H, s), 7.99 (1H, dd, *J* = 7.8 and 1.5 Hz), 7.45 (1H, td, *J* = 7.8 and 1.5 Hz), 7.31-7.35 (1H, m), 7.25-7.27 (1H, m), 4.82-4.83

(1H, m), 4.48-4.49 (1H, m), 3.63 (2H, s), 1.75 (3H, s), 1.25 (9H, s).[13]C NMR (101 MHz, CHLOROFORM-d) δ = 161.4, 144.7, 141.0, 132.6, 132.0, 131.3, 128.9, 126.9, 112.7, 57.6, 40.9, 22.8, 22.6. LCMS (Formic): t_R = 1.35 min, [M+H$^+$] 264.2.

(R)-2-Methyl-*N*-(2-(3-methylbut-3-en-1-yl)benzylidene)propane-2-sulfinamide (5.22)

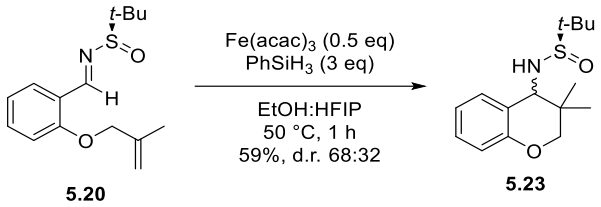


To a stirred solution of **5.16** (99 mg, 0.57 mmol, 1 eq) and **5.17** (77 mg, 0.63 mmol, 1.1 eq) in DCM (3 mL), $Ti(OEt)_4$ (598 μL, 2.85 mmol, 5 eq) was added. The reaction was stirred overnight at RT. Saturated $NaHCO_{3(aq)}$ was added until white Ti salts were seen to precipitate; the slurry was filtered through celite and washed with DCM (10 mL). The organics were dried in *vacuo* to afford **5.17** as a colourless oil (153 mg, 0.55 mmol, 97%).

[1]H NMR (400 MHz, CHLOROFORM-d) δ = 8.87 (1H, s), 7.93 (1H, dd, *J* = 7.6 and 1.2 Hz), 7.41 (1H, td, *J* = 7.8 and 1.5 Hz), 7.26-7.32 (2H, m), 4.75 (1H, br. s), 4.70 (1H, br. s), 3.03-3.17 (2H, m), 2.26-2.31 (2H, m), 1.77 (3H, s), 1.27 (9H, s). LCMS (HpH): t_R = 1.41 min, [M+H$^+$] 278.1.

8.4.3 – HAT Reactions of Chiral Sulfinimines

HAT Reaction of (R)-2-methyl-*N*-(2-((2-methylallyl)oxy)benzylidene)propane-2-sulfinamide (5.20)



To a solution of **5.20** (248 mg, 0.89 mmol, 1 eq) and $Fe(acac)_3$ (152 mg, 0.43 mmol, 0.5 eq) in HFIP (1.5 mL) and EtOH (1.5 mL), $PhSiH_3$ (329 μL, 2.67 mmol, 3 eq) was added. The reaction was heated at 50 ^{o}C for 1 h in a sealed vial (headspace of air). Then water (25 mL) added and the aqueous layer extracted with EtOAc (3 x 15 mL). The organics were combined and washed with citric $acid_{(aq)}$ (1M, 3 x 20 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* A crude ^{1}H NMR was taken at this point to determine d.r. (68:32). The resulting brown oil was then purified by automated column chromatography on silica gel (0-30% EtOAc:cyclohexane). Desired fractions were dried *in vacuo* to afford **5.23** as a mixture of diastereomers (149 mg, 0.53 mmol, 59%).

The diastereomers were separated by MDAP for characterisation:

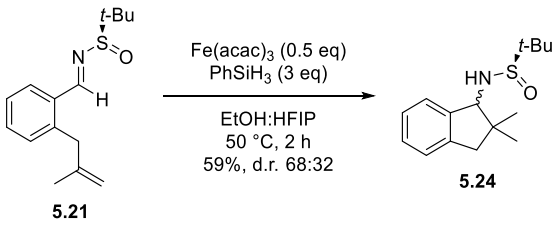
Diastereomer 1 (major, unknown stereochemistry);

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.61 (1H, d, *J* = 7.3 Hz), 7.14-7.18 (1H, m), 6.92-6.96 (1H, m), 6.79 (1H, dd, *J* = 8.3 and 1.0 Hz), 4.18 (1H, d, *J* = 6.9 Hz), 3.77-3.85 (2H, m), 3.29 (1H, d, *J* = 6.9 Hz), 1.28 (9H, s), 0.99 (6H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 154.0, 130.6, 129.1, 123.0, 121.4, 116.4, 73.2, 60.2, 56.6, 33.8, 23.2, 23.1, 19.7. LCMS (HpH): t_R = 1.10 min, [M+H^{+}] 282.1.

Diastereomer 2 (minor, unknown stereochemistry);

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.36 (1H, d, *J* = 7.8 Hz), 7.16-7.20 (1H, m), 6.88-6.92 (1H, m), 6.80-6.82 (1H, m), 3.76-3.91 (2H, m), 3.53 (1H, d, *J* = 7.8 Hz), 2.03 (9H, s), 1.11 (3H, s), 1.05 (3H, s). LCMS (HpH): t_R = 1.05 min, [M+H^{+}] 282.1.

HAT Reaction of (R)-2-methyl-*N*-(2-(2-methylallyl)benzylidene)propane-2-sulfinamide (5.21)



5.21 **5.24**

To a solution of **5.21** (15 mg, 0.06 mmol, 1 eq) and $Fe(acac)_3$ (10 mg, 0.03 mmol, 0.5 eq) in HFIP (0.25 mL) and EtOH (0.25 mL), $PhSiH_3$ (20 μL, 0.17 mmol, 3 eq) was added. The reaction was heated at 50 ^oC for 2 h in a sealed vial (headspace of air). The reaction was allowed to cool to RT and concentrated *in vacuo*. The resulting brown oil was taken up in DMSO:MeOH (1 mL) and filtered to remove insoluble material. The filtrate was purified by MDAP (HpH) and the desired fractions dried *in vacuo* to afford **5.24** as a mixture of diastereomers (10 mg, 0.04 mmol, 67%).

The diastereomers were separated by MDAP for characterisation:

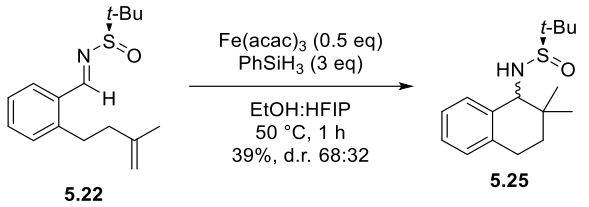
Diastereomer 1 (major, unknown stereochemistry):

^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.63-7.65 (1H, m), 7.20-7.26 (2H, m), 7.16-7.18 (1H, m), 4.47 (1H, d, *J* = 9.3 Hz), 3.34 (1H, d, *J* = 9.8 Hz), 2.69-2.80 (2H, m), 1.32 (9H, s), 1.26 (3H, s), 0.92 (3H, s).^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 143.3, 140.9, 127.8, 126.9, 125.2, 124.7, 71.2, 56.3, 45.45, 45.39, 26.4, 23.0, 22.2. LCMS (HpH): t_R = 1.21 min, $[M+H^+]$ 266.2.

Diastereomer 2 (minor, unknown stereochemistry):

^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.18-7.29 (4H, m), 4.50 (1H, d, *J* = 10.8 Hz), 3.54 (1H, d, *J* = 10.3 Hz), 2.71-2.83 (2H, m), 1.44 (3H, s), 1.34 (9H, s), 0.99 (3H, s).^{13}C NMR (151 MHz, CHLOROFORM-d) δ = 143.6, 141.4, 127.9, 126.4, 125.0, 124.1, 71.4, 56.5, 45.9, 45.2, 26.4, 22.9, 22.3. LCMS (HpH): t_R = 1.18 min, $[M+H^+]$ 266.2.

HAT Reaction of (R)-2-Methyl-*N*-(2-(3-methylbut-3-en-1-yl)benzylidene)propane-2-sulfinamide (5.22)



5.22 **5.25**

To a solution of **5.22** (74 mg, 0.27 mmol, 1 eq) and $Fe(acac)_3$ (48 mg, 0.14 mmol, 0.5 eq) in HFIP (0.75 mL) and EtOH (0.75 mL), $PhSiH_3$ (99 μL, 0.80 mmol) was added. The reaction was heated at 50 ^oC for 1 h in a sealed vial (headspace of air). The reaction was allowed to cool to RT and concentrated *in vacuo*. Then water (25 mL) added and the aqueous layer extracted with EtOAc (3 x 15 mL). The organics were combined and washed with citric $acid_{(aq)}$ (1M, 3 x 10 mL). The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* A crude ^1H NMR was taken at this point to determine d.r. (68:32). The resulting brown oil was then purified by MDAP (HpH) and the desired fractions dried *in vacuo* to afford **5.25** as a mixture of diastereomers (29 mg, 0.11 mmol, 39%).

Diastereomer 1 *(major, stereochemistry unknown)*:

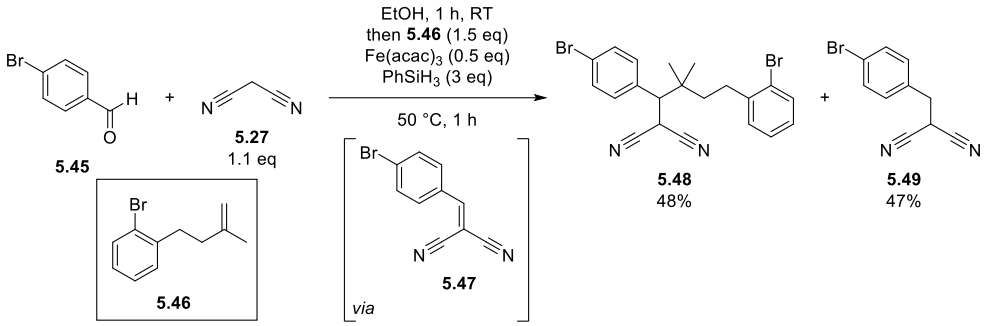
^1H NMR (600 MHz, CHLOROFORM-d) δ = 7.36-7.39 (1H, m), 7.13 -7.21 (2H, m), 7.10 (1H, dd, *J* = 7.1 and 1.2 Hz), 4.06 (1H, d, *J* = 6.9 Hz), 3.49 (1H, d, *J* = 7.3 Hz), 2.72-2.88 (2H, m), 1.75-1.82 (1H, m), 1.56 (1H, dt, *J* = 13.3 and 6.3 Hz), 1.21 (9H, s), 1.06 (3H, s), 1.04 (3H, s).^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 136.6, 136.1, 130.4, 128.9, 127.3, 125.6, 64.0, 56.4, 33.7, 32.4, 26.3, 25.9, 24.9, 22.9. LCMS (HpH): t_R = 1.26 min, $[M+H^+]$ 280.1.

Diastereomer 2 *(minor, stereochemistry unknown)*:

^1H NMR (600 MHz, CHLOROFORM-d) δ = 7.70 (1H, d, *J* = 7.8 Hz), 7.14-7.23 (2H, m), 7.07 (1H, d, *J* = 7.3 Hz), 4.13 (1H, d, *J* = 6.9Hz), 3.25 (1H, d, *J* = 6.9 Hz), 2.71-2.88 (2H, m), 1.72 (1H, dt, *J* = 13.6 and 6.7 Hz), 1.57 (1H, dt, *J* = 13.7 and 6.9 Hz), 1.27 (9H, s), 0.98 (3H, s), 0.95 (3H, s).^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 137.5, 136.2, 130.3, 128.7, 127.1, 126.7, 64.0, 56.5, 34.5, 33.1, 26.7, 26.0, 23.2, 23.1 ppm. LCMS (HpH): t_R = 1.19 min, $[M+H^+]$ 280.1.

8.4.4 – HAT-Mediated Multicomponent Reaction

HAT Reaction of 1-bromo-2-(3-methylbut-3-en-1-yl)benzene (5.46) and 2-(4-bromobenzylidene)malononitrile (5.47)



A solution of **5.45** (94 mg, 0.51 mmol, 1 eq) and **5.27** (36 mg, 0.55 mmol, 1.1 eq) in EtOH (2 mL) was stirred at RT for 1 h. Then **5.46** (172 mg, 0.76 mmol, 1.5 eq), $Fe(acac)_3$ (90 mg, 0.25 mmol, 0.5 eq) and $PhSiH_3$ (188 μL, 1.52 mmol, 3 eq) was added, and the reaction stirred at 50 ^{o}C for 1 h. The reaction was stopped and allowed to cool to RT, then concentrated *in vacuo*. The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude brown oil was purified by automated column chromatography on silica gel (0-30% TBME:cyclohexane). Desired fractions were combined and dried *in vacuo* to afford:

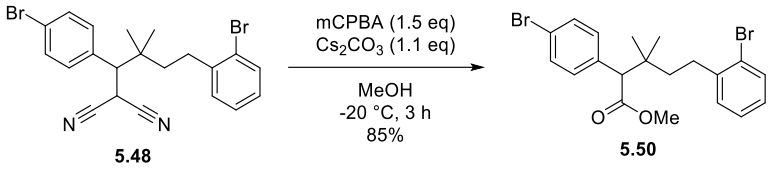
5.48 as a colourless gum (111 mg, 0.24 mmol, 48%);

ν_{max} (neat): 2969, 1591, 1490, 1471, 1078, 1011, 825, 750 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.54-7.56 (2H, m), 7.52 (1H, dd, *J* = 8.1 and 1.2 Hz), 7.32-7.35 (2H, m), 7.21-7.25 (1H, m), 7.13 (1H, dd, *J* = 7.6 and 1.7 Hz), 7.05-7.09 (1H, m), 4.29 (1H, d, *J* = 4.9 Hz), 3.11 (1H, d, *J* = 4.9 Hz), 2.71-2.75 (2H, m), 1.55-1.68 (2H, m), 1.26 (3H, s), 1.12 (3H, s). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 140.7, 134.6, 133.0, 132.1, 131.3, 130.3, 128.1, 127.8, 124.1, 123.1, 113.0, 112.7, 54.9, 41.4, 37.7, 30.9, 25.3, 24.9, 24.8. LCMS (HpH): t_R = 1.53 min, [M-H$^+$] = 459.1.

5.49 as a brown oil (56 mg, 0.24 mmol, 47%);

ν_{max} (neat): 2915, 2258, 1489, 1072, 1012 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.52-7.55 (2H, m), 7.18-7.21 (2H, m), 3.91 (1H, t, *J* = 6.9 Hz), 3.22 (2H, d, *J* = 6.9 Hz). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 132.5, 131.8, 130.8, 123.2, 111.9, 36.1, 24.8. LCMS (HpH): t_R = 1.06 min, $[M\text{-}H^+]$ = 233.0/235.1.

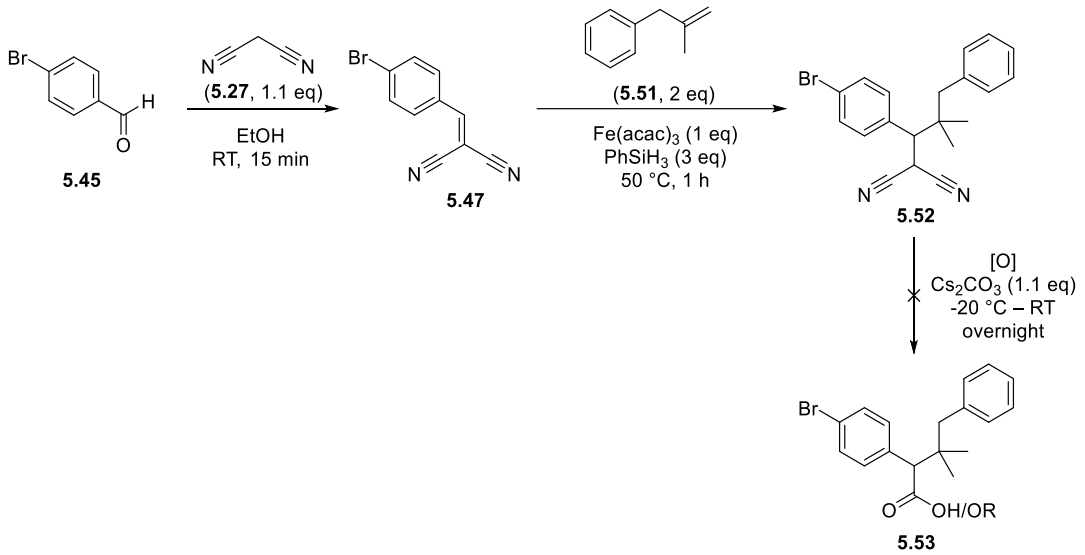
Methyl 5-(2-bromophenyl)-2-(4-bromophenyl)-3,3-dimethylpentanoate (5.50)



To a solution of **5.48** (83 mg, 0.18 mmol, 1 eq) in MeOH (2 mL) at -20 ^{o}C was added Cs_2CO_3 (61 mg, 0.19 mmol, 1.1 eq). The reaction was stirred for 5 min and then *m*CPBA (47 mg, 0.27 mmol, 1.5 eq) added in one portion. The reaction was stirred at -20 ^{o}C for 3 h. The reaction was stopped and allowed to warm to RT slowly. Then saturated $NaHCO_{3\,(aq)}$ (25 mL) added and the aqueous layer extracted with EtOAc (3 x 15 mL). The aqueous layer was quenched with NaClO. The organics were combined, dried through a hydrophobic frit and concentrated *in vacuo.* The crude reaction mixture was purified by automated column chromatography on silica gel (0-100% TBME:cyclohexane). Desired fractions were combined and dried *in vacuo* to afford the desired product **5.50** as a colourless gum (69 mg, 0.15 mmol, 85%).

ν_{max} (neat): 2926, 2853, 1733, 1151, 1011, 748 cm^{-1}. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.50 (1H, dd, *J* = 7.8 and 1.2 Hz), 7.41-7.44 (2H, m), 7.28-7.31 (2H, m), 7.21 (1H, td, *J* = 7.6 and 1.2 Hz), 7.14 (1H, dd, *J* = 7.6 and 2.0 Hz), 7.01-7.05 (1H, m), 3.64 (3H, s), 3.56 (1H s), 2.71-2.76 (2H, m), 1.42-1.68 (2H, m), 1.12 (3H, s), 1.02 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 173.0, 141.9, 134.8, 132.9, 131.8, 131.0, 130.3, 127.6, 124.3, 121.5, 59.7, 51.6, 40.9, 37.3, 31.0, 24.5, 24.1. LCMS (HpH): t_R = 1.67 min, $[M+/\text{-}H^+]$ = not found. HRMS: ($C_{20}H_{23}Br_2O_2$) $[M+H^+]$ requires 453.0065, found 455.0045 (error 0.4 ppm).

Oxidant screen for oxidation of 2-(1-(4-bromophenyl)-2,2-dimethyl-3-phenylpropyl)malononitrile (5.52)



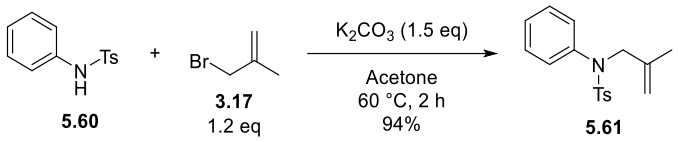
A solution of **5.45** (100 mg, 0.54 mmol, 1 eq) and **5.27** (38 mg, 0.57 mmol, 1.1 eq) in EtOH (2* mL) was stirred at RT for 1 h (the reaction was set up in quadruplicate). Then **5.51** (143 mg, 1.08 mmol, 2 eq), $Fe(acac)_3$ (191 mg, 0.54 mmol, 1 eq), $PhSiH_3$ (200 μL, 1.62 mmol, 3 eq) and on one occasion HFIP (1 mL) was added. The reaction stirred at 50 ^oC for 1 h in a vial sealed under air and analysed by LCMS. The reaction was allowed to cool to RT and then cooled further to -20 ^oC. Addition of Cs_2CO_3 (194 mg, 0.60 mmol, 1.1 eq) (all 4 reactions) and oxidant was then made: *m*CPBA (140 mg, 0.81 mmol, 1.5 eq); TBHP (147 μL, 0.81 mmol, 1.5 eq) (5.5 M in decane); magnesium monoperoxyphthalate (201 mg, 0.41 mmol, 0.75 eq). The reactions were stirred overnight at RT. Further additions of oxidant (same equivalents once more) were made and the reactions stirred at 60 ^oC for 4 h. The remaining reaction with no oxidant added was allowed to stir open to air (following the same reaction times and temperatures, with an additional 1.1 eq of Cs_2CO_3 added at the stage of further oxidant additions). All reactions showed no conversion to the desired oxidised product (intermediate **5.52** remained unreacted), all reactions were abandoned.

*1 mL when using HFIP as a cosolvent for HAT reaction

LCMS (HpH): t_R = 1.43 min, [M-H^+] 365.4/367.4 (**5.52**). Conversions shown in Table 10.

8.4.5 – HAT-Mediated Migration Reaction

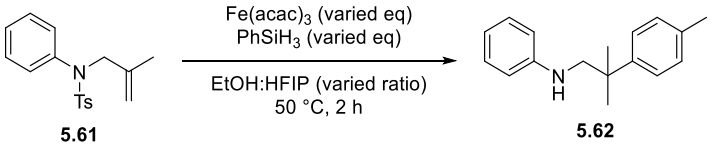
4-Methyl-N-(2-methylallyl)-N-phenylbenzenesulfonamide (5.61)



To a solution of **5.60** (508 mg, 2.05 mmol, 1 eq) in acetone (2 mL), K_2CO_3 (426 mg, 3.08 mmol, 1.5 eq) was added. Then **3.17** (330 mg, 2.44 mmol, 1.2 eq) was added slowly, and the reaction stirred at 60 °C for 2 h. The reaction was allowed to cool to RT, water (25 mL) added and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined organics were dried through a hydrophobic frit and concentrated *in vacuo*. The resulting crude yellow solid was purified by automated column chromatography on silica gel (0-20% TBME:cyclohexane). Desired fractions were combined, and the solvent removed *in vacuo* to afford **5.31** as a white solid (584 mg, 1.94 mmol, 94%).

M.pt.: 115-117 °C. ν_{max} (neat): 3060, 2950, 1345, 1161 cm^{-1}. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.44-7.48 (2H, m), 7.22-7.30 (5H, m), 7.02-7.05 (2H, m), 4.74-4.75 (1H, m), 4.70-4.71 (1H, m), 4.10 (2H, s), 2.42 (3H, s), 1.75 (3H, s).^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 143.4, 139.8, 138.9, 135.3, 129.4, 128.7, 128.6, 127.7, 127.6, 115.0, 56.8, 21.5, 19.9. LCMS (HpH): t_R = 1.30 min, $[M+H^+]$ 302.0.

HAT condition screen for the synthesis of *N*-(2-methyl-2-(*p*-tolyl)propyl)aniline (5.62)



To a solution of **5.61** (25 mg, 0.08 mmol, 1 eq) and $Fe(acac)_3$ (15-30 mg, 0.04-0.08 mmol, 0.5-1 eq) in HFIP (0-0.75 mL) and EtOH (0.25-0.75 mL), $PhSiH_3$ (31-62 μL, 0.26-0.51 mmol, 3-6 eq) was added. The reaction was stirred at 50 °C for 2 h in a vial sealed under air. The reactions were sampled for LCMS and abandoned.

LCMS (HpH): t_R = 1.47 min, $[M+H^+]$ 240.2 (**5.62**). Conversions shown in Table 11.