Exploring New Synthetic Routes Towards Cyanamides

James N. Ayres

This thesis is submitted for the degree of Doctor of Philosophy (PhD) at Cardiff University

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Summary

This thesis describes the development of new routes towards the synthesis of cyanamides. Cyanamides are present in a range of biologically active compounds and are useful functional groups for the synthesis of many interesting compounds such as guanidines, ureas, isoureas and many varieties of heterocycles. A range of methods for the synthesis of cyanamides exist, however the most common technique is utilising cyanogen bromide and amines. The technique is effective and vast arrays of cyanamides can be accessed in one step. However, cyanogen bromide is highly toxic and poses a significant safety risk. In recent times new methods have been developed to avoid cyanogen bromide, however many of these techniques are operationally complex or use other highly toxic compounds.

In this work three new methods for the synthesis of cyanamides have been developed. A new method for cyanamide synthesis using trichloroacetonitrile as a less toxic and safer to handle cyano source has been developed. A range of cyanamides can be formed in an operationally simple one-pot two-step procedure. This technique provides complementary selectivity to cyanogen bromide. It has also been applied to the synthesis of a biologically active PDE4 inhibitor.

The one-pot deoxycyanamidation of alcohols has been developed using *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as a sulfonyl transfer reagent and cyano source accessing a range of tertiary cyanamides. An array of tertiary cyanamides were accessed, including aniline type, which could not be accessed with TCAN. This approach exploits the under-developed desulfonylative (N-S bond cleavage) reactivity pathway of NCTS.

A novel cyanamide and allenamide moiety, *N*-allenyl cyanamides have been synthesised. Utilising the deoxycyanamidation process, propargyl alcohol and a range of sulfonamides could be reacted to access an array of aryl substituted *N*-allenyl cyanamides. In addition, this moiety was investigated as a novel chemical building block accessing a range of otherwise challenging to access bespoke cyanamides by hydroarylation, hydroamination, [4+2] and [2+2] cycloadditions.

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Abbreviations

Ac	Acetate
App.	Apparent
ASAP	Atmospheric solids analysis probe
Ar	Aromatic
AIBN	2,2′-Azobis(2-methylpropionitrile)
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
Br	Broad
Bu	Butyl
C	Celsius
COPD	Chronic obstructive pulmonary disease
COSY	Correlation spectroscopy
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DIB	(Diacetoxyiodo)benzene
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
ESI	Electrospray ionization
Et	Ethyl
Eqn.	Equation
equiv	Equivalents
g	Gram

h	Hours
HMBC	Heteronuclear multi-bond correlation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
*i*pr	Isopropyl
IR	Infrared
kg	Kilogram
KHMDS	Potassium bis(trimethylsilyl)amide
LHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low resolution mass spectrometry
MCPE	Cyclopentyl methyl ether
mg	Milligram
mL	Millilitre
mmol	Millimole
min	Minutes
mol %	Mole percent
mp	Melting point
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NSI	Nanospray ionisation
PDE4	Phosphodiesterase type 4 inhibitor
Ppm	Parts per million
PPY	4-Pyrrolidinopyridine
q	Quartet
R_f	Retardation factor
rt	Room temperature
s	Singlet
Sat.	Saturated
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
S_NAr	Nucleophilic aromatic substitution
T	Time point

TBAB	Tetrabutylammonium bromide
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBME	*tert*-Butyl methyl ether
TCAN	Trichloroacetonitrile
TEAB	Tetraethylammonium bromide
TBAI	Tetrabutylammonium iodide
$TBABF_4$	Tetrabutylammonium tetrafluoroborate
$TBAPF_6$	Tetrabutylammonium hexafluorophosphate
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCN	Trimethylsilylcyanide
Tol	Toluene
TsCl	Tosyl chloride
UV	Ultra-violet

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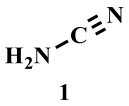
1. Introduction to cyanamides

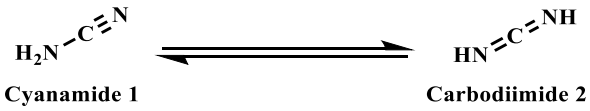
The earliest report of the cyanamide moiety dates back to 1838 from the laboratory of Bineau.[1] Cloez and Cannizzaro subsequently disclosed similar work in 1851 from their laboratory in Paris.[2] In both reports they describe the synthesis of cyanamide **1** by passing a gaseous stream of cyanogen chloride through an ethereal solution of ammonia. After filtration of the resultant ammonium chloride and removal of ether by distillation the remaining residue is perfectly pure cyanamide **1**.



1

Figure 1.1. Cyanamide

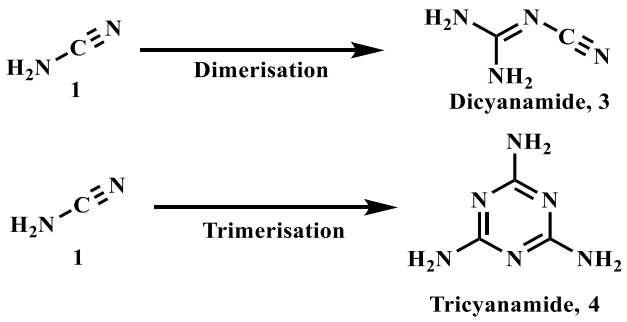
The structure of cyanamide **1** (Figure 1.1) features an sp^3-hybridised nitrogen bonded to a nitrile functionality. Cyanamide itself is a weak acid with a pK_a of 10.3. Cyanamide can exist as one of two tautomeric forms, the cyanamide **1** or carbodiimide **2** (Figure 1.2). However spectroscopic data (IR peak (solid) 2255 cm^{-1}) and its reactivity heavily favour the cyanamide tautomer.[3,4]



Cyanamide 1 **Carbodiimide 2**

Figure 1.2. Tautomerisation of cyanamide

Historically, the isolation of cyanamide has been difficult due to its propensity to dimerise and form dicyanamide **3** (cyanoguanidine) and tricyanamide **4** (melamine) (Scheme 1.1).[5] In fact until the 1960's the only form of cyanamide generally available was calcium cyanamide **5**.[6] A synthesis of calcium cyanamide as a readily available source of cyanamide was developed by Frank and Caro in 1895 - subsequently known as the Frank-Caro process.[7] This process utilised a batch oven reactor filled with ground calcium carbide heated to ~1000 °C. Nitrogen is introduced *via* inlets in the reactor wall. Generally, the reactor runs for several days to yield a solid mass of calcium cyanamide which can then be milled into powder.



Scheme 1.1. Dimerisation and trimerisation of cyanamide

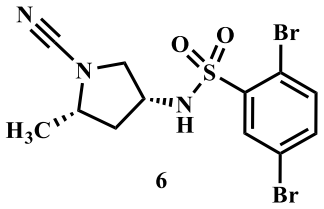
In 1965 the stabilisation of cyanamide was addressed by AlzChem Trostberg GmbH.[8,9] The commercially available 50% solution of cyanamide uses a phosphate buffer and the crystalline form uses a proprietary formic acid ester as stabilisers. In each case the stabiliser works to neutralise alkaline traces (NH_3) which can promote dimerisation and trimerisation. In the case of crystalline cyanamide the formic acid ester absorbs traces of moisture and continuously releases small amounts of formic acid. The chemistry of cyanamide has a rich and diverse history and the cyanamide functional group has proved to be particularly valuable in synthesis and in biologically active molecules as will be described in this chapter.

1.1 Biological importance of the cyanamide moiety

The cyanamide functional group is found in a range of biologically active molecules. Interestingly cyanamide has been found to be a natural product in the *Vicca Villosa* and *Vicca cracca* species of Vetch and in *robinia pseudoacacia*, a deciduous tree, as a plant growth inhibitory compound.[10,11]

Cyanamide has also been implicated in prebiotic chemistry owing to its carbodiimide tautomer. This tautomer is thought to exist readily in space conditions with tautomerism promoted by UV radiation or by water-ice catalysis as detected in interstellar clouds. The carbodiimide tautomer could then assemble amino acids in to peptides.[12,13]

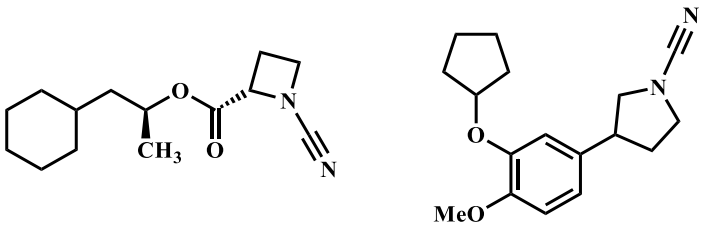
The cyanamide moiety has also been incorporated into a range of more complex molecules such as cathepsin C inhibitor **6** (Figure 1.3).[14] Cathepsin C plays a key role in the activation of a range of degradative enzymes in inflammatory diseases which can cause tissue destruction. Cathepsin C inhibitors are potentially therapeutic compounds for treatment of diseases such as cystic fibrosis or chronic obstructive pulmonary disease (COPD).[15]



6

Figure 1.3. Cathepsin C inhibitor containing a cyanamide moiety

The cyanamide moiety has also been incorporated into a cathepsin K inhibitor **7** (Figure 1.4).[16] The inhibition of cathepsin K can help the treatment of osteoporosis.[17] Compound **8** is a derivative of rolipram a highly researched PDE4 inhibitor (Figure 1.4).[18] PDE4 inhibitors have been researched to find application in the treatment of Alzheimer's disease, spinal cord injuries, cognitive enhancement and respiratory diseases such as COPD and asthma.[19–21]



7 **8**

*Figure 1.4. Cyanamide containing cathepsin K inhibitor **7** and PDE4 inhibitor **8***

Cyanamides are also present in agrochemicals. Once again, the simplest of cyanamides **1** has found application in this field. Dormex® is 1.5% aqueous solution of cyanamide that is typically used as a as a plant growth regulator typically in vineyards and orchards to break bud dormancy.[22] Calcium cyanamide is sold under the trademark PERKLA® as a multipurpose fertiliser.

Thiacloprid **9** is a more complex cyanamide containing agrochemical developed by Bayer Cropscience (Figure 1.5). Thiacloprid is a member of the neonicotinoid class of insecticides. The mechanism of action of this insecticide is via the disruption of the insects nicotinic acetylcholine receptors.[23] Sulfoxaflor **10** is a sulfoximine type insecticide (Figure 1.5). It exhibits excellent efficacy against a broad range of sap-feeding insects, including those resistant to neonicotinoid type insecticides.[24]

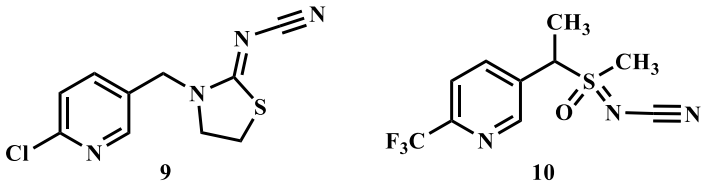
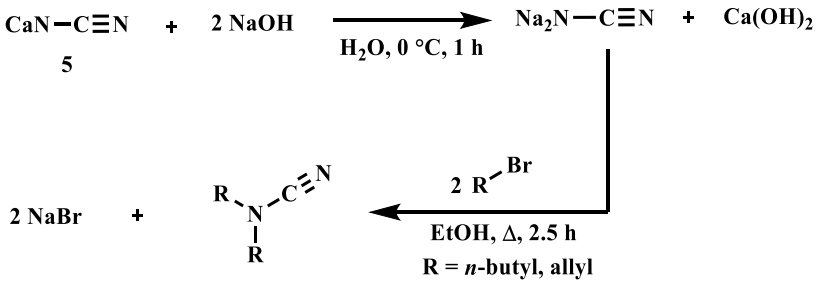


Figure 1.5. Thiacloprid 9 and Sulfoxaflor 10 insecticides

1.2 Synthesis of cyanamides

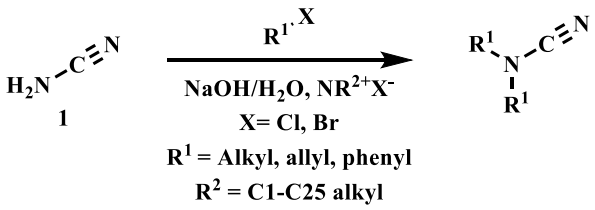
1.2.1 Alkylation of cyanamide

A limited number of strategies for the introduction of the cyanamide moiety have been developed. The simplest technique is the alkylation of cyanamide. However starting with cyanamide generally only yields symmetrical dicyanamides.[25] Vliet treated calcium cyanamide **5** with sodium hydroxide to yield sodium cyanamide. Reaction with an allyl or *n*-butyl bromide yielded disubstituted cyanamides (Scheme 1.2).



Scheme 1.2. Synthesis of disubstituted cyanamides

Cyanamide **1** can also be used to synthesise symmetrical disubstituted cyanamides using phase transfer catalysis. In a US patent from 1980 the reaction of cyanamide with a range of alkyl, allyl and phenyl halides in the presence of quaternary ammonium salts is described (Scheme 1.3).[26]

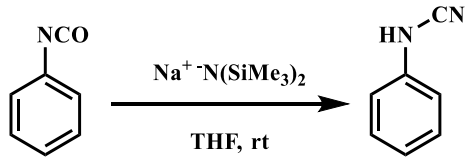


Scheme 1.3. Synthesis of symmetrical disubstituted cyanamides

Despite the simplicity of the starting materials, alkylating cyanamide or calcium cyanamide yields only a very limited scope of symmetrical disubstituted cyanamides. The synthesis of non-symmetrical, or monosubstituted cyanamides is valuable.

1.2.2 Deoxygenation of isocyanates

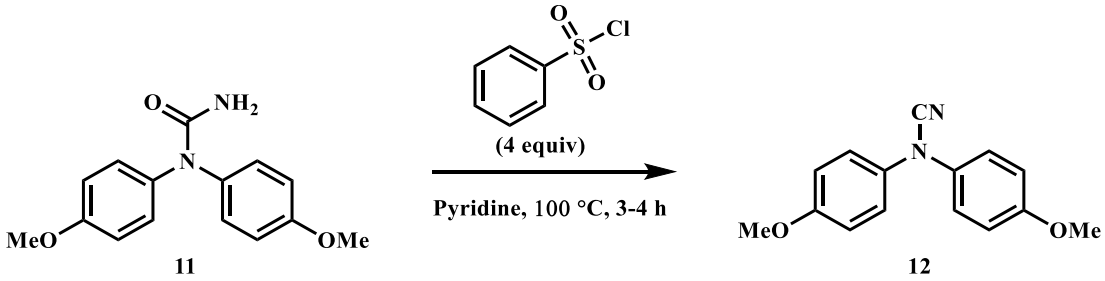
Isocyanates have been converted into cyanamides using sodium bis(trimethylsilyl)amide.[27] Alkyl, acyl and aryl isocyanates can be readily converted into their corresponding cyanamides at room temperature with excellent yields (Scheme 1.4). The use of sodium bis(trimethylsilyl)amide as a deoxygenating agent yields a wide range of cyanamides. However, as sodium bis(trimethylsilyl)amide is a strong base, the substrate must be chosen carefully. In addition to isocyanates, isothiocyanates were found to undergo desulfurisation under the same conditions by the same group in 2008.[28]



Scheme 1.4. The synthesis of cyanamides from isocyanates using a deoxygenation protocol

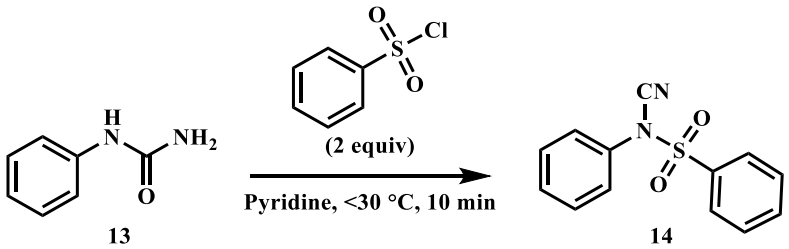
1.2.3 Dehydration of ureas

Ureas can also be converted to cyanamides by dehydration. In work by Robinson *et al.* *N*,*N*-bis(4-methoxyphenyl)urea **11** was converted to *N*,*N*-bis(4-methoxyphenyl)cyanamide in the presence of benzenesulfonyl chloride as a dehydrating agent (Scheme 1.5).[29]



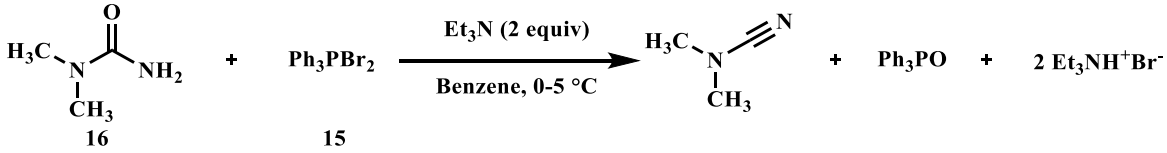
Scheme 1.5. Dehydration of ureas developed by Robinson

The synthesis of sulfonylcyanamides was developed by Kurzer.[30] The reaction of phenyl urea **13** with benzene sulfonyl chloride in pyridine yielded *N*-cyano-*N*-phenylbenzenesulfonamide **14** (Scheme 1.6). The reaction could also be carried out with a range of substituted aromatic ureas and *p*-toluenesulfonyl chloride or *p*-nitrobenzenesulfonyl chloride as dehydrating agents.



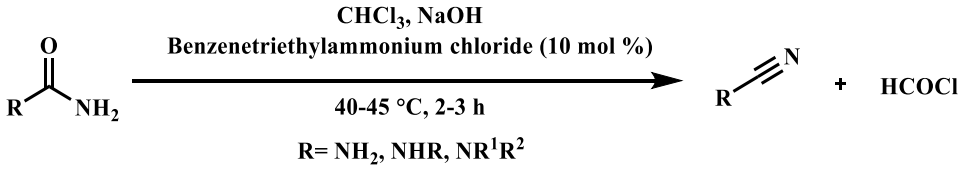
Scheme 1.6. The synthesis of sufonyl cyanamides by dehydration of phenylurea

Bestmann *et al*. reported the use of triphenylphosphine dibromide **15** in the presence of triethylamine to convert *N,N*-dialkylureas **15** into cyanamides (Scheme 1.7).[31] Much like the alkylation of cyanamide, this procedure is limited to the synthesis of dialkyl cyanamides.



Scheme 1.7. The synthesis of dialkylcyanamides from dimethylurea utilising triphenylphosphine dibromide

The dehydration of ureas to form cyanamides has been established with dichlorocarbene (Scheme 1.8).[32] Using chloroform as the solvent the addition of sodium hydroxide affords the dichlorocarbene. A catalytic amount (10 mol %) of benzenetriethylammonium chloride is added as a phase transfer agent. The process readily forms a range of substituted and unsubstituted cyanamides. However due to the highly reactive nature of the dichlorocarbene the presence of some functional groups cannot be tolerated.

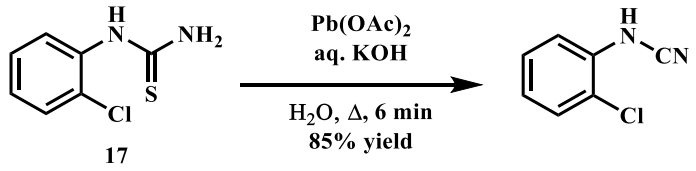


Scheme 1.8. The synthesis of cyanamides with dichlorocarbene

1.2.4 Desulfurisation of thioureas and dithiocarbamates

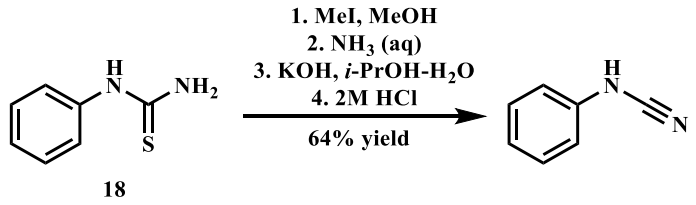
In a similar fashion to deoxygenation of ureas, methods for the desulfurisation of thioureas to form cyanamides have been developed.[33] An example of this technique is from the work of Kurzer utilising lead (II) acetate (Scheme 1.9).[34] *o*-Chlorophenylthiourea **17** is dissolved in water with potassium hydroxide (10 equiv) and heated to 100 °C before a hot saturated solution of lead (II) acetate is added rapidly. The

solution is heated for a further 6 minutes whilst large quantities of lead sulfide are precipitated. An alternative to this highly hazardous chemistry is however desirable.[35]



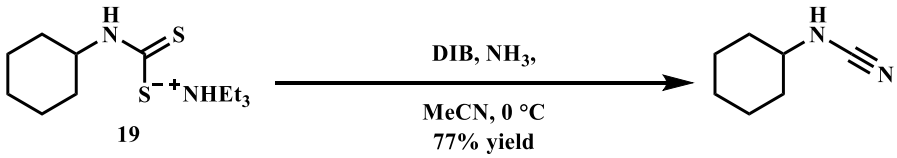
Scheme 1.9. Synthesis of o-chlorophenylcyanamide by desulfurisation of o*-chlorophenylthiourea*

In 2008 Schulz and co-workers published a more modern approach to desulfurisation of thioureas (Scheme 1.10).[36] In their work phenylthiourea **18** was first methylated with methyl iodide to form *N*-phenyl-*S*-methylisothiouronium iodide which on treatment with aqueous ammonia gives *N*-phenyl-*S*-methylisothiourea. Elimination with potassium hydroxide in isopropanol provides the phenylcyanamide potassium salt, which can be treated with hydrochloric acid to yield the cyanamide.

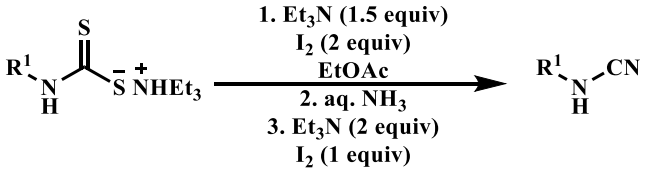


Scheme 1.10. Desulfurisation of phenylthiourea methylation and basic workup

A one-pot strategy from dithiocarbamic acid salts **19** using diacetoxyiodobenzene (DIB) has been developed (Scheme 1.11).[37] This work accesses isothiocyanates generated *in-situ* from the desulfurisation of dithiocarbamic acid salts. The isothiocyanates can react with aqueous ammonia forming alkyl or aryl thioureas. Further oxidative desulfurisation with DIB led to the corresponding cyanamides. Patel and co-workers reported a modification of this process using I_2 as a milder oxidant for the desulfurisation step (Scheme 1.12).[38]



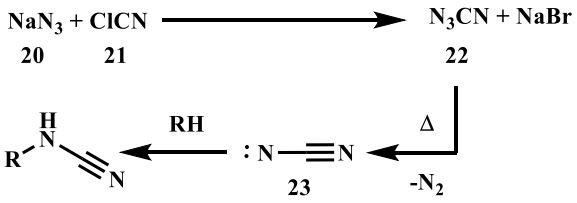
Scheme 1.11. Synthesis of cyanamides from dithiocarbamic acid salts by oxidative desulfurisation



Scheme 1.12. Synthesis of cyanamides from dithiocarbamic acid salts using I_2 as a mild oxidant

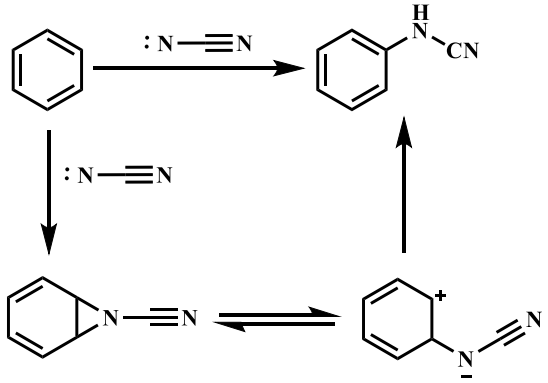
1.2.5 Addition of cyanonitrene to C-H bonds

Cyanogen azide can be synthesised by reaction of sodium azide **20** and chlorocyanogen **21**. Heating the cyanogen azide **22** to 40-50 °C provides a cyanonitrene **23** *via* thermolysis.[39] Simmons *et al*. found that the cyanonitrene can then react with a carbon hydrogen bond to form cyanamides (Scheme 1.13).[40]



Scheme 1.13. Synthesis of cyanamides with cyanonitrenes

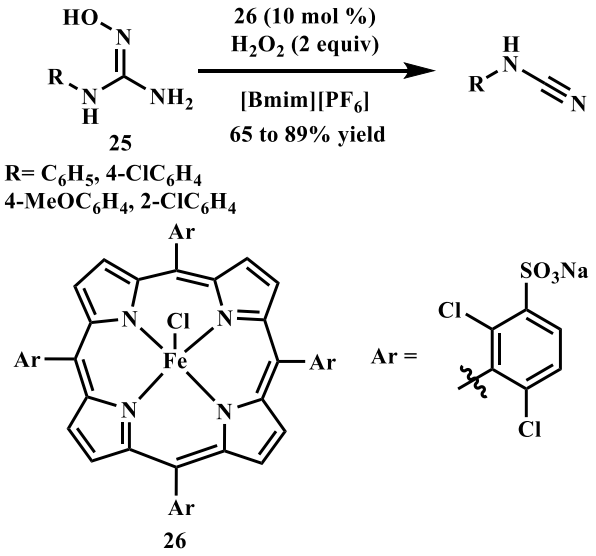
Cyanonitrenes have also been shown to react with carbon-carbon double bonds to form cyanamides (Scheme 1.14).[41] Whilst this technique can provide valuable secondary alkyl and aryl cyanamides, cyanogen azide must be handled with extreme caution. If neat, cyanogen azide can detonate with extreme violence and should therefore only be used in solution. Low solubility in apolar solvents mean that the concentration should not exceed 5% to avoid precipitation and resulting explosions.



Scheme 1.14. Synthesis of phenylcyanamides from aromatic carbon-carbon bonds an cyanonitrene

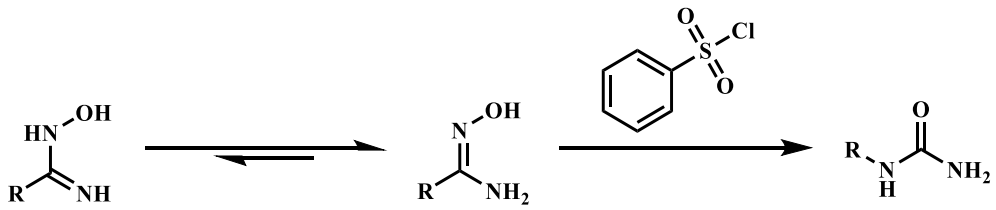
1.2.6 Synthesis of cyanamides from guanidoximes and amidoximes

Chauhan *et al*. have reported the synthesis of monosubstituted *N*-arylcyanamides from guanidoximes **25**.[42] Iron (III) porphyrins **26** have been found to be efficient catalysts for the hydrogen peroxide mediated oxidation of guanidoximes to the corresponding cyanamides (Scheme 1.15).



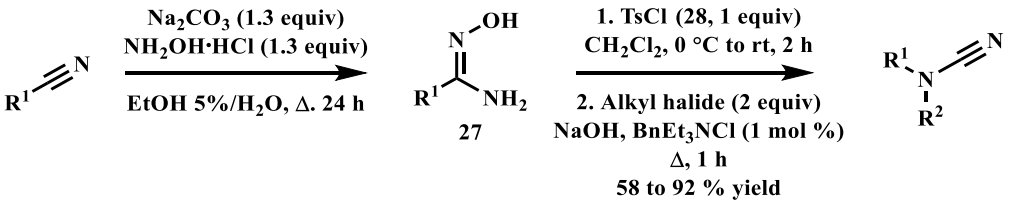
Scheme 1.15. Oxidation of guanidoximes with Fe(III) porphyrins in an ionic liquid with hydrogen peroxide to form secondary aryl cyanamides

In 1891 Tiemann reported the reaction of amidoximes with aryl sulfonyl halides to give *N*-phenylurea – known as the Tiemann rearrangement (Scheme 1.16).[43,44]



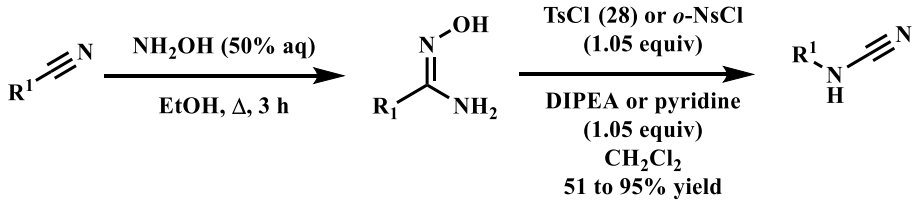
Scheme 1.16. General reaction scheme of the Tiemann rearrangement

116 years later in 2007, Tkachev and co-workers modified the conditions in order to yield symmetrical and non-symmetrical tertiary cyanamides (Scheme 1.17).[45] Amidoximes **27** were accessed from a range of nitrile compounds and subsequently reacted with tosyl chloride **28** to facilitate dehydration and alkylated with alkyl halides to yield tertiary cyanamides.



Scheme 1.17. Dialkylcyanamides synthesised from amidoximes

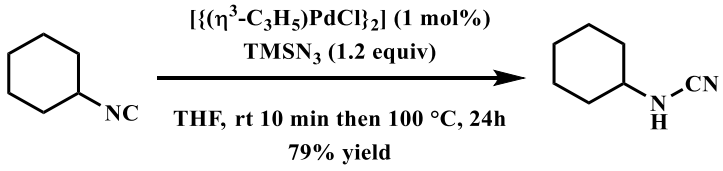
A further 7 years passed before Chien *et al*. in 2014 revisited this work and developed a procedure to form monosubstituted cyanamides from a series of aryl amidoximes (Scheme 1.18).[46] Treatment of amidoximes with tosyl chloride and a base yielded a range of *N*- substituted cyanamides in good to excellent yield. When electron rich aryl substrates were applied the reaction proceeded well with tosyl chloride. More challenging electron poor aryl or alkyl substrates required *o*-nosyl chloride as a better leaving group to facilitate the *N*-*O* bond cleavage to yield cyanamides.



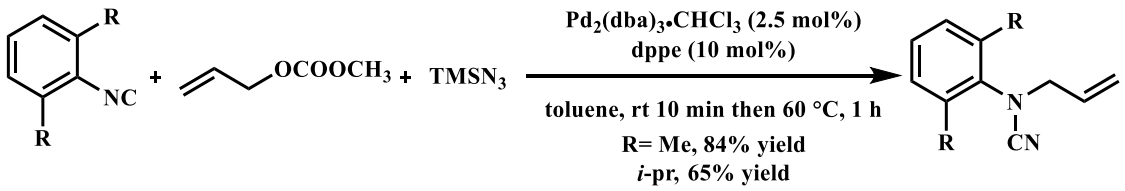
Scheme 1.18. Synthesis of primary cyanamides from amidoximes

1.2.7 Synthesis of cyanamides by metal catalysis

Aryl and alkyl cyanamides have been synthesised in good to high yield *via* the palladium catalysed reaction of isocyanides and trimethylsilyl azide (Scheme 1.19).[47,48] In a similar fashion allyl cyanamides have been synthesised by Yamamoto and co-workers by addition of allyl carbonates to the reaction mixture (Scheme 1.202).[49]

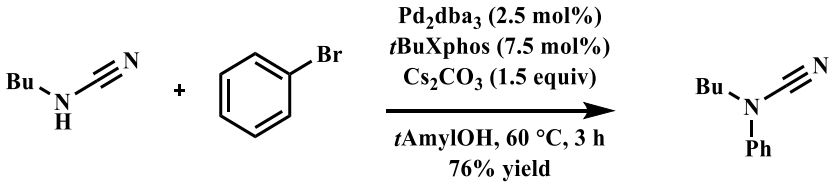


Scheme 1.19. Palladium catalysed synthesis of cyanamides



Scheme 1.20. Palladium catalysed synthesis of allyl cyanamides

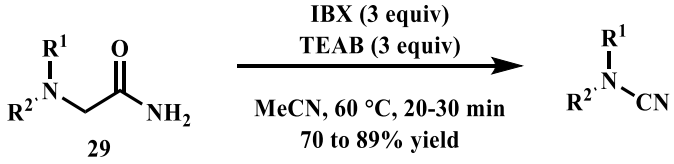
The derivatisation of cyanamides utilising palladium catalysis has also been developed. A range of alkyl cyanamides with a number of aryl, heteroaryl, vinyl halide or pseudohalide coupling partners can undergo Buchwald-Hartwig type cross coupling reactions (Scheme 1.21).[50,51] The reaction of alkyl cyanamides was optimised and it was found that 2.5 mol % of Pd_2dba_3 and 7.5 mol % *t*BuXPhos as ligand with caesium carbonate as base was optimal.[52]



Scheme 1.21. Derivatisation of cyanamides using a Buchwald-Hartwig type cross coupling

1.2.8 Transformation of *N*,*N*-disubstituted glycylamides into cyanamides

The transformation of *N*,*N*-disubstituted glycylamides **29** by reaction with 2-iodoxybenzoic acid (IBX) in the presence of tetraethylammonium bromide (TEAB) was developed by Akamanchi *et al*. (Scheme 1.22).[53] *N*,*N*-Disubstituted glycylamides can be readily transformed into cyanamides using this technique, with yields between 70 to 89%. Moreover, the reaction time is fast – between 20-30 minutes. Dess-Martin periodane was also found to be a suitable oxidant providing equal yields and reaction times.[53,54]

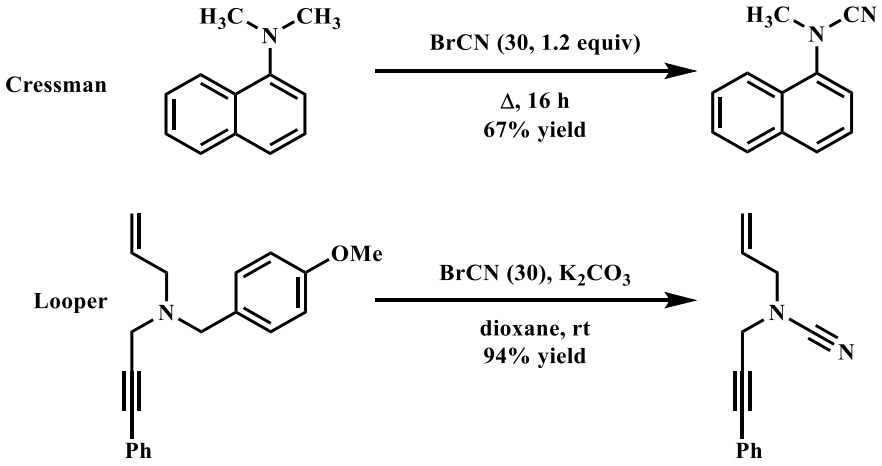


Scheme 1.22. Transformation of N,N-disubstituted glycylamides into cyanamides

1.2.9 Cyanation of amines

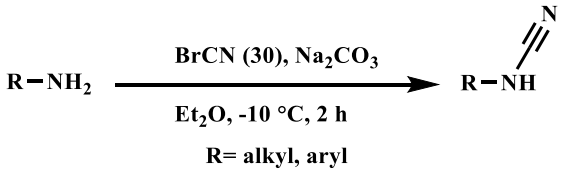
The direct cyanation of amines is regarded as the most common method to synthesise cyanamides. It is a direct route which can be accomplished in one step, from amines which are abundant in research laboratories. Furthermore, the most common method for this is utilising cyanogen bromide **30**.[55] The earliest example of cyanogen bromide in the synthesis of cyanamides comes from the work of Von Braun in 1900.[56] Tertiary amines were reacted with cyanogen bromide and potassium carbonate to yield cyanamides. This process has become known as the Von Braun reaction. Cressman utilised this technique in 1947 to form *N*-methyl-*N*-(naphthalen-1-yl)cyanamide eliminating methyl bromide,

and in 2009 Looper used the Von Braun reaction to form propargyl cyanamides (Scheme 1.23).[57]



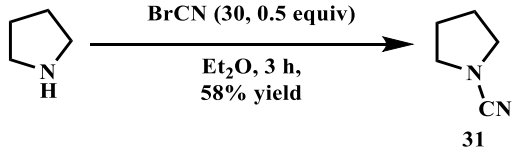
Scheme 1.23. Synthesis of cyanamides via the Von Braun reaction

The synthesis of cyanamides from primary amines utilising cyanogen bromide **30** was first disclosed by Harrison *et al*. in 1976 (Scheme 1.24).[58] A primary amine was added to a cooled (-10 to -20 °C) solution of cyanogen bromide in THF containing anhydrous sodium carbonate. The reactions were run for 2 hours before warming to room temperature. This procedure generally yields the cyanamides in >90% yield.



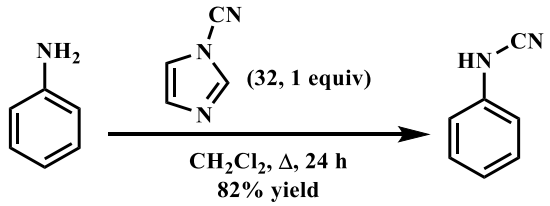
Scheme 1.24. Harrison's protocol for cyanation of primary amines

Secondary amines are also suitable reagents to react with cyanogen bromide to form cyanamides. An example is the synthesis of pyrrolidine-1-carbonitrile **31** (Scheme 1.25).[59] Notably, in the synthesis of cathepsin C inhibitor **6**, cathepsin K inhibitor **7** and PDE4 inhibitor **8** discussed in section 1.1 the cyanamide moiety is introduced by reaction of a secondary amine intermediate with cyanogen bromide.[14,16,18] Despite the ubiquity of the usage of cyanogen bromide in cyanamide synthesis, it has significant drawbacks, most significantly of which is toxicity. Cyanogen bromide has an LD_{50} of 25mg/kg (oral, rat) and is therefore highly toxic.[60] Cyanogen bromide is a crystalline solid with a melting point of 52 °C, however it readily sublimes at ambient temperature and pressure meaning toxic vapours are formed. Moreover the reaction of cyanogen bromide and aqueous acids forms HCN.[61]



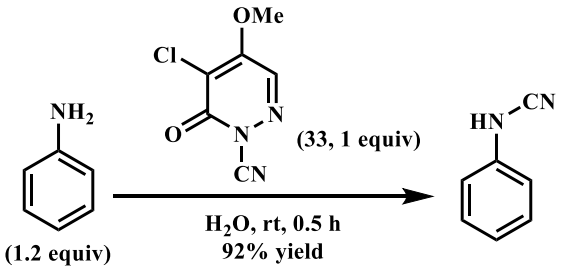
Scheme 1.25. Synthesis of a cyanamide from a secondary amine with cyanogen bromide

In recent years, a series of developments have been made in the cyanation of amines to avoid the use of cyanogen bromide. In 2000 Wu *et al*. developed 1-cyanoimidazole **32** as an effective cyanating agent (Scheme 1.26).[62] The reagent worked on a range of primary and secondary amines, however it must first be synthesised using cyanogen bromide.



Scheme 1.26. Cyanation of aniline with 1-cyanoimidazole

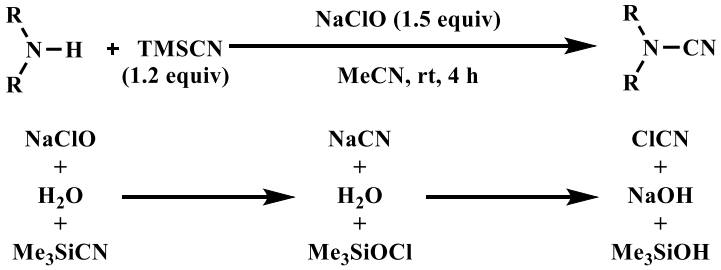
In 2005 2-cyanopyridazin-3(2H)-one **33** were developed as cyanating agents (Scheme 1.27).[63] A range of primary amines can be converted into cyanamides. The reagent can also be used with sulfur nucleophiles to form thiocyanates, or carbon nucleophiles to form nitriles. However, this compound must again be synthesised utilising cyanogen bromide.



Scheme 1.27. Synthesis of cyanamides using 2-cyanopyridazin-3(2H)-ones

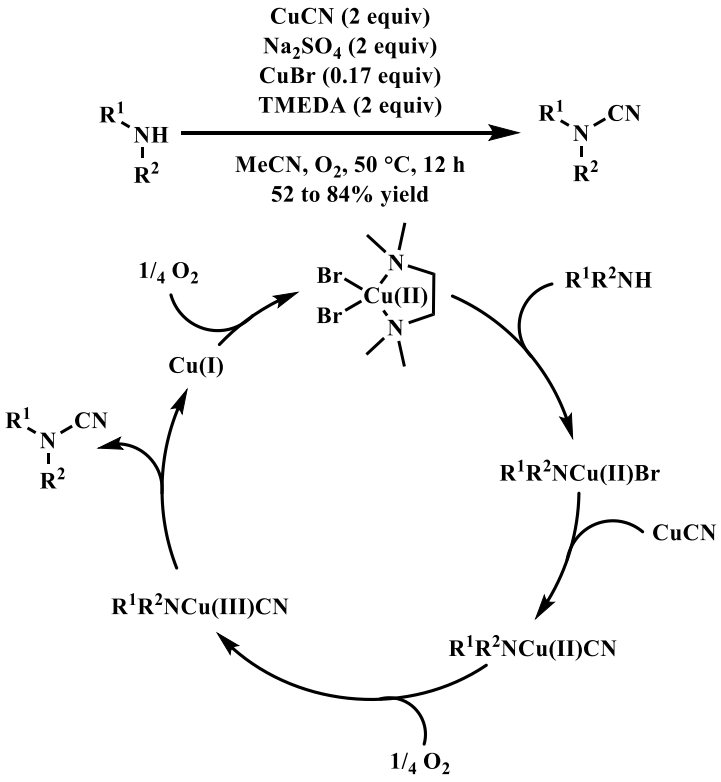
In 2014 Chen *et al*. demonstrated the cyanation of secondary amines employing the reaction between sodium hypochlorite (NaOCl) and trimethysilyl cyanide (TMSCN) to form an electrophilic cyanating agent *in situ* (Scheme 1.28).[64] Mechanistic studies showed that the reaction between NaOCl and TMSCN forms cyanogen chloride, which in the presence of a secondary amine can form a tertiary cyanamide. This work avoids the direct use of cyanogen compounds. Nevertheless, cyanogen chloride is accessed *in situ* and is comparably toxic to cyanogen bromide. The method also requires the use of highly

toxic trimethylsilyl cyanide which is fatal if the reagent is ingested, on skin or inhaled according to its hazard statements.[60]



Scheme 1.28. Electrophillic cyanation of secondary amines using TMSCN and NaOCl

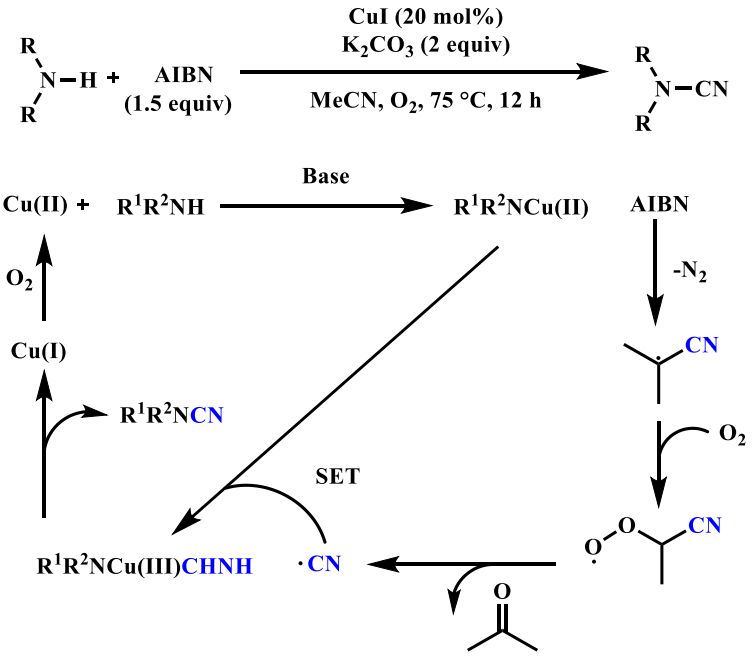
In the same year Cheng *et al*. reported a copper catalysed *N*-cyanation of aliphatic secondary amines by oxidative coupling (Scheme 1.29).[65] A range of aliphatic secondary amines can be transformed into the respective cyanamide using this approach with yields between 52 to 84%.



Scheme 1.29. Cyanation of secondary amines via an oxidative coupling approach

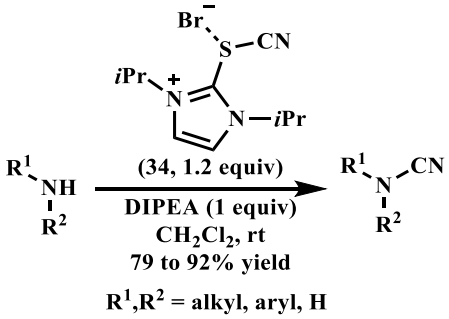
The following year Cheng and co-workers reported a second approach to the synthesis of cyanamides using azobisisobutyronitrile (AIBN) as a safer cyanide source (Scheme 1.30).[66] Both techniques by Cheng and co-workers provide excellent new routes to a

diverse array of cyanamides however the necessity for an oxygen atmosphere increases the complexity and requires more safety considerations.



Scheme 1.30. Synthesis of cyanamides using AIBN as a safe cyanide source

In 2015 Alcarazo *et al*. described a new type of dihalo(imidazolium)sulfurane **34** cyanating agent (Scheme 1.31).[67] This cyanating agent proved to be an exceptionally versatile reagent transferring CN^+ to nitrogen, sulphur and carbon nucleophiles. Both primary and secondary amines could be used to form cyanamides. The dihalo(imidazolium)sulfurane must be synthesised over three steps. There is no doubt that this compound has exceptional CN transfer qualities, however the three-step synthesis lowers this techniques accessibility in research laboratories.



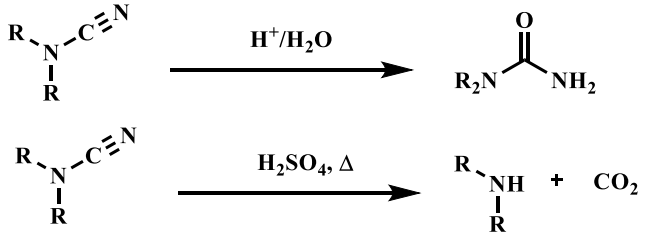
Scheme 1.31. Synthesis of cyanamides using dihalo(imidazolium)sulfurane

1.3 The chemistry of cyanamides

Owing to the cyanamides similarity to nitrile compounds they share some of the same reactivity. However, due to the conjugating amino nitrogen in cyanamides they are electronically distinct from nitriles. The donation of the lone pair means that cyanamides and carbodiimides are tautomers, as discussed briefly in section 1.0. The cyanamide form is more prevalent and the reactivity of cyanamides along with spectroscopic data support this.[3,4] The amino group basicity is strongly decreased and therefore in acidic conditions the cyanamide will be protonated on the terminal nitrogen. The presence of the electronegative amino nitrogen also helps the enhance the electrophilicity of the cyanamide carbon.[68] As a consequence nucleophiles attack at the carbon centre.

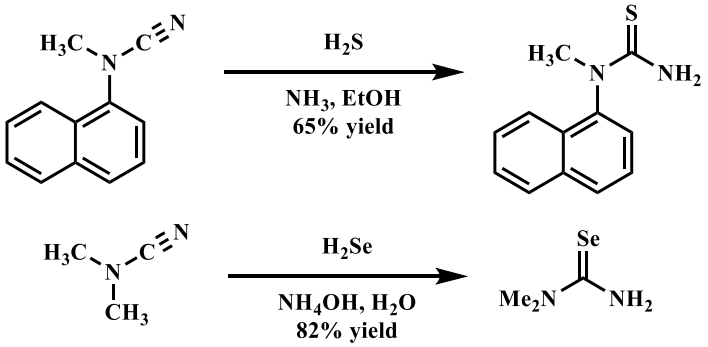
1.3.1 Hydrolysis

Cyanamides undergo hydrolysis in the presence of dilute hydrochloric or sulfuric acid to form urea (Scheme 1.32). When starting from a dialkylcyanamide, the reaction with concentrated acids will yield dialkylamines after hydrolytic cleavage of the urea.[69]



Scheme 1.32. Synthesis of ureas from cyanamides in the presence of dilute acid and dialkylamine from cyanamides and concentrated acid

Thioureas and selenoureas can also be synthesised from cyanamides *via* the reaction of a cyanamide with hydrogen sulphide or hydrogen selenide (Scheme 1.33).[70–72] The reaction of a cyanamide with H_2S in the presence of ammonia in ethanol yields the thiourea in 65% yield.[72] The reaction of a cyanamide with H_2Se in the presence of ammonium hydroxide in water yield the selenourea in 82% yield.[71]

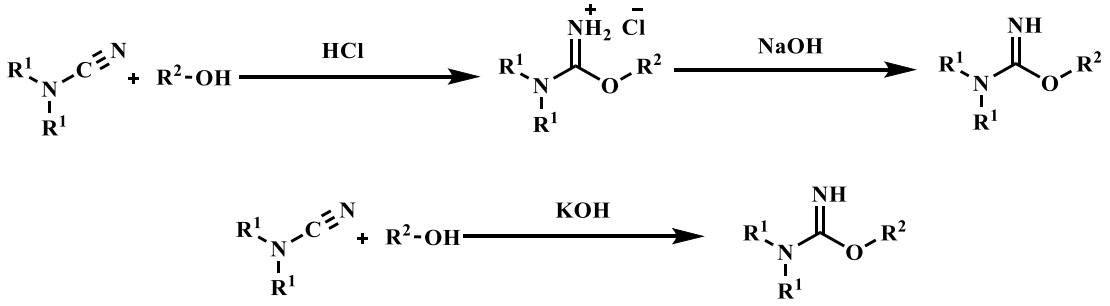


Scheme 1.33. The synthesis of thioureas and selenoureas

1.3.2 Nucleophilic addition

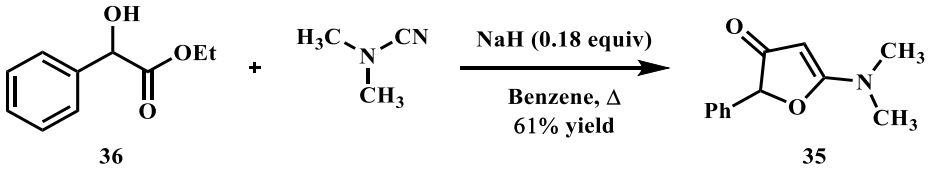
1.3.2.1 Oxygen nucleophiles

Cyanamides react with alcohols to form isourea derivatives, this chemistry generally requires a catalyst to proceed, such as Brønsted acid and Brønsted base catalysis (Scheme 1.34). In acidic conditions protonation of the nitrile nitrogen makes the carbon sufficiently electrophilic for the alcohol to attack. The product formed is the hydrochloride salt, which can be transformed into the isourea after addition of sodium hydroxide.[73,74] The reaction can also be catalysed by base to yield the isourea directly. The use of KOH as base was developed by Elderfield and Green in 1951.[75]



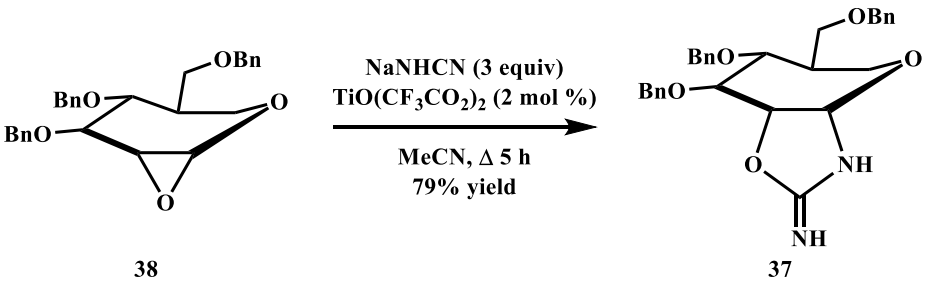
Scheme 1.34. Addition of alcohols to cyanamides in acidic and basic conditions

5-Aryl-2-dialkylamino-2-oxazolin-4-ones **35** can be synthesised from the condensation of mandelic acid derivatives **36** with dialkyl cyanamides in the presence of catalytic amounts of sodium hydride (Scheme 1.35).[76]



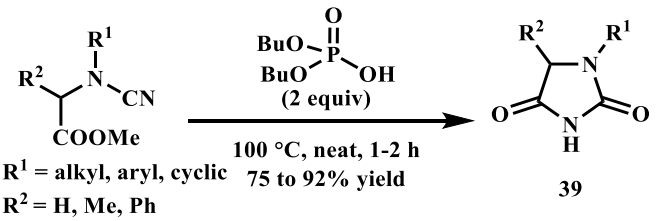
Scheme 1.35. Synthesis of 5-aryl-2-dialkylamino-2-oxazolin-4-ones with cyanamides

The formation of an alkoxide nucleophile from ring opening of an epoxide with Lewis acidic $TiO(CF_3CO_2)_2$ and subsequent reaction with a cyanamide was used in the synthesis of an imino-oxazolidine derivative **37** by Diaz and Castillon from epoxide **38** (Scheme 1.36).[77]



Scheme 1.36. Titanium alkoxide reacting with a cyanamide

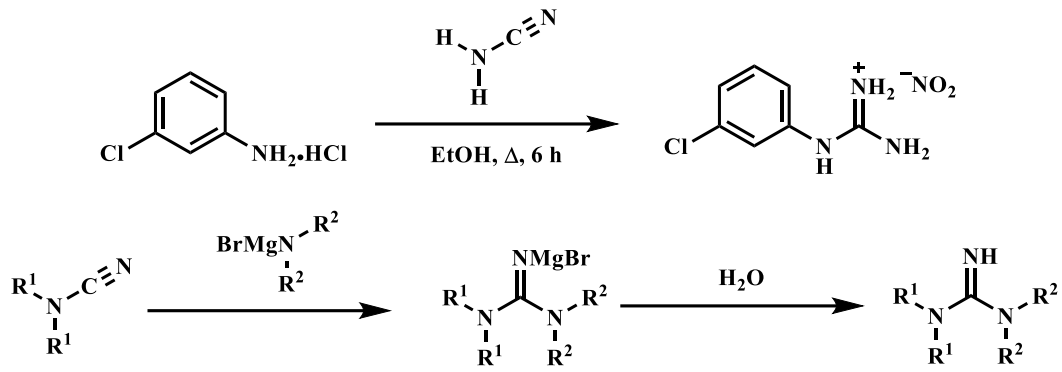
Kumar *et al*. have developed a synthesis for a series of diversely substituted hydantoins **39** from a cyanamide substrate (Scheme 1.37).[78] Dialkyl phosphates were used as a mild reagent to facilitate hydrolysis and cyclisation in one step to give hydantoins in excellent yield.



Scheme 1.37. Synthesis of hydantoins from cyanamides using dibutyl phosphate

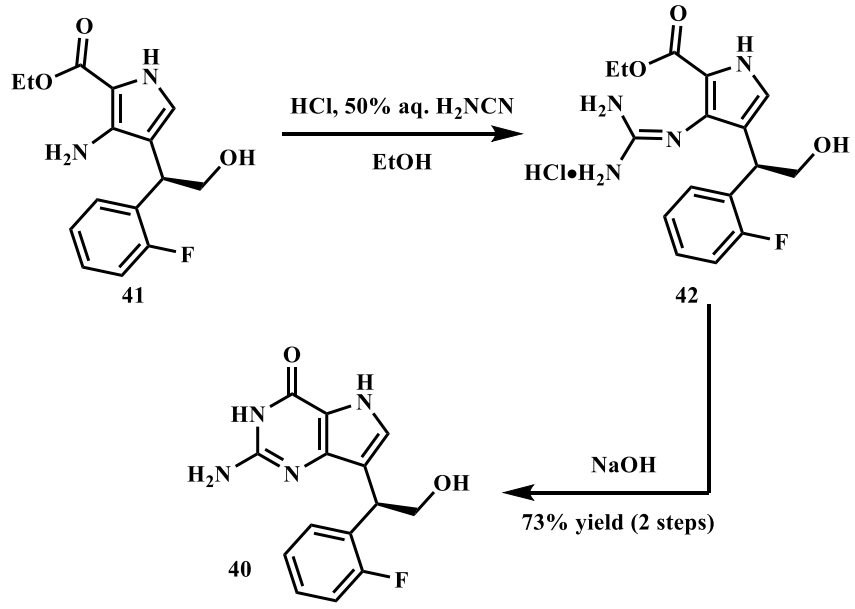
1.3.2.2 Nitrogen nucleophiles

Amines can also react with the C≡N bond of cyanamides. In 1946 King *et al*. described the reactivity of amine hydrochloride salts with cyanamide (Scheme 1.38).[79] Amine hydrochloride salts were reacted at reflux with cyanamide to form the corresponding guanidines as nitrate or hydrochloride salts. The synthesis of tetrasubsituted guanidines was also accomplished utilising dialkylaminomagnesium bromide compounds with disubstituted cyanamides by Hullin *et al.* (Scheme 1.38).[80]



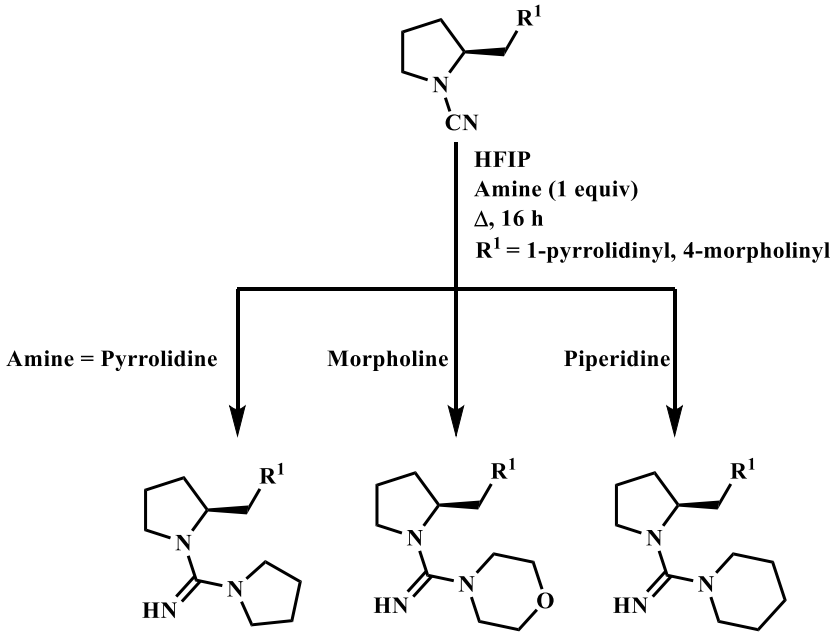
Scheme 1.38. The synthesis of guanidine compound by addition of nitrogen nucleophiles to cyanamides

More recently this chemistry has been applied to the synthesis of PNP405 purine nucleoside phosphorylase inhibitor **40** (Scheme 1.39).[81] Initially compound **41** was treated with 50% aqueous solution of cyanamide to form guanidine hydrochloride **42**. Treatment of the guanidine hydrochloride with NaOH yielded the target compound by cyclo-guanidinylation.



Scheme 1.39. Synthesis of PNP405 utilising guanidine formation with cyanamide

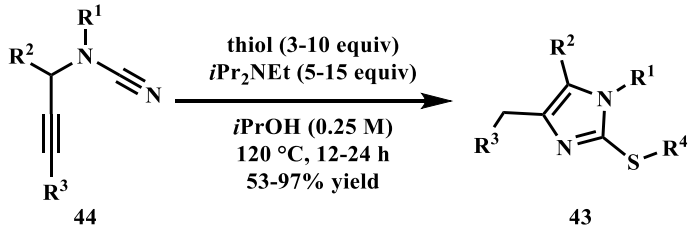
A series of chiral guanidine compounds were also synthesised from cyanamides by Anders and co-workers (Scheme 1.40).[82] Chiral cyanamide containing molecules are reacted with amines in hexafluoroisopropanol to yield a range of chiral guanidine compounds.



Scheme 1.40. Synthesis of chiral guanidines from a cyanamide

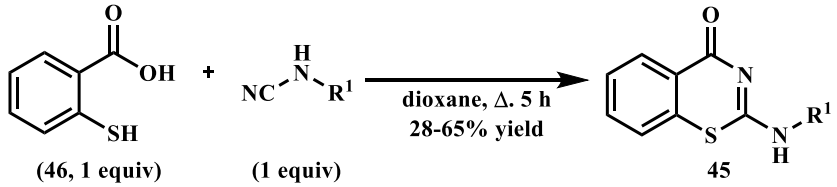
1.3.2.3 Sulfur nucleophiles

Sulfur nucleophiles can add to the electrophilic carbon of the cyanamide. One example is in the synthesis of thioimidazoles **43** by Looper and co-workers (Scheme 1.41).[83] A series of propargyl cyanamides **44** were synthesised using the Von Braun methodology. These cyanamides were then reacted with a series of thiols under basic conditions to form thioimidazole type compounds.



Scheme 1.41. Synthesis of thioimidazoles from cyanamides

Cyanamides have also been reacted with sulfur nucleophiles under acidic conditions to form 1,3-benzothiazinones **45** (Scheme 1.42).[84] 2-mercaptobenzoic acid **46** is reacted in dioxane at reflux with a range of cyanamides for 5 hours to form 1,3-benzothiazinones in moderate yield.

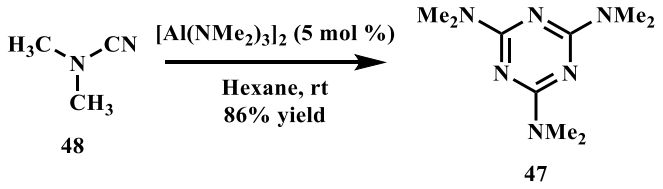


Scheme 1.42. The synthesis of 1,3-benzothiazinones from cyanamides

1.3.3 Cycloaddition

1.3.3.1 Cyclotrimerisation

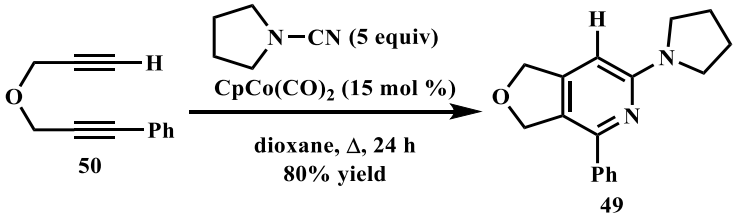
As discussed earlier cyanamide can trimerise to form melamine **4** (Scheme 1.1).[5] The cyclotrimerisation ability of cyanamides has been harnessed for the synthesis of hexamethylmelanine **47** an anti-tumour agent (Scheme 1.43).[85] Dimethylcyanamide **48** in the presence of a catalytic amount of $[Al(NMe_2)_3]_2$ will spontaneously cyclotrimerise.



Scheme 1.43. Synthesis of an antitumour agent via cyclotrimerization of dimethylcyanamide

1.3.3.2 [2+2+2] cycloadditions

Cyanamides are 2π partners for cycloadditions and can undergo [2+2+2] cycloadditions with other 2π species. Maryanoff *et al.* have developed a cobalt catalysed synthesis of a 2-aminopyridine species **49** (Scheme 1.44).[86] The reaction proceeds regioselectively with the unsymmetrical dialkyne **50**.

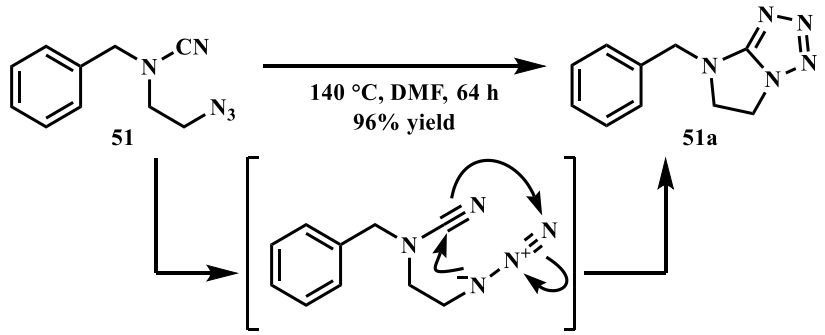


Scheme 1.44. Synthesis of 2-aminopyridines via [2+2+2] cycloadditions of cyanamides

1.3.3.3 [3+2] cycloadditions

In [3+2] cycloadditions cyanamides behave as dipolaraphiles and can react with suitable 1,3-dipoles to form cycloadducts.[87] Azides are suitable 1,3-dipoles as discovered by Sharpless in 2001 for the synthesis of tetrazoles (Scheme 1.45).[88] The group developed

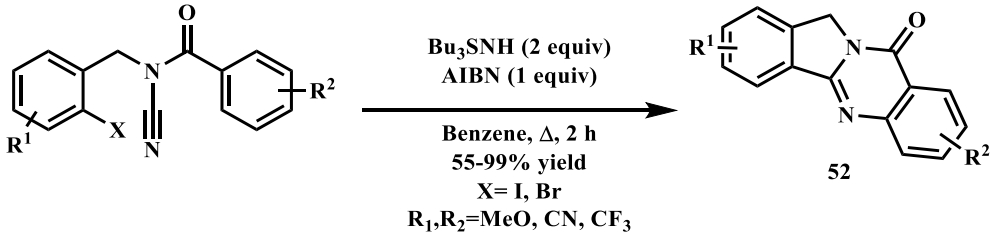
intramolecular cycloadditions of azidocyanamides **51**, yielding fused 5-heterotetrazoles **51a** in excellent yield.



Scheme 1.45. Synthesis of tetrazoles via intramolecular [2+3] cycloaddition with cyanamides

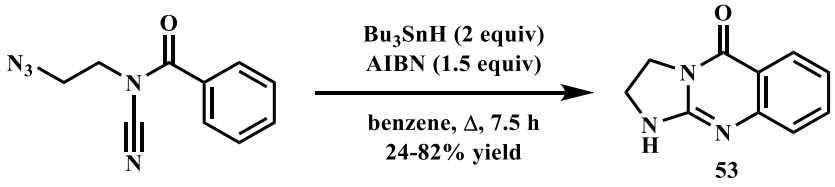
1.3.3.4 Radical reactions

Cyanamides have also found application in reactions involving radicals.[89] A range of polycyclic quinazolinones **52** were synthesised from bromo- and iodoaryl precursors with a *N*-acylcyanamide moiety utilising AIBN and tributyltin for radical formation and propagation (Scheme 1.46).[90]



Scheme 1.46. Synthesis of polycyclic quinazolinones via radical cascade reactions with cyanamides

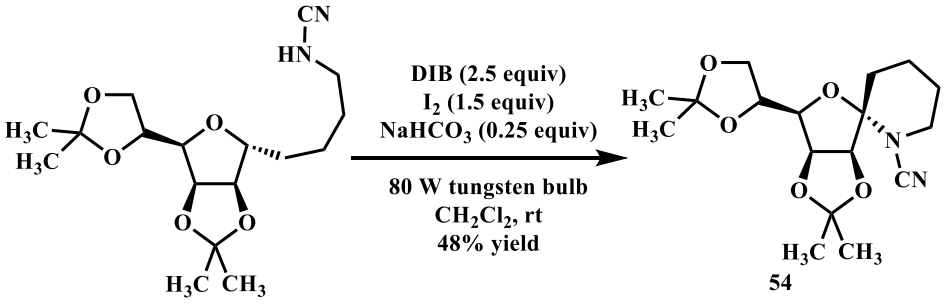
N-acyl cyanamides have also been converted into guanidines *via* radical chemistry developed by Fensterbank, Malacria and Lacôte (Scheme 1.47).[91] A range of highly substituted tricyclic guanidines **53** can be synthesised with this method.



Scheme 1.47. Guanidine synthesis by radical reaction with cyanamides

A report was published in 2009 where *N*-centred radicals from *N*-phosphoramidate or monosubstituted cyanamides attached to a tri- or tetramethylene tether on C1 of a carbohydrate could form oxa-azaspirobicyclic systems **54** (Scheme 1.48).[92] Using DIB

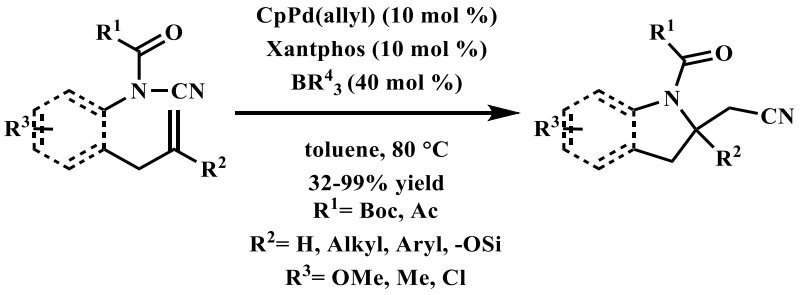
and iodine the reaction can undergo an intramolecular hydrogen atom transfer (HAT) reaction and ionic cyclisation to form the spirocyclic compounds. The cyanamide containing example was obtained with absolute regio- and stereoselectivity, although with a modest yield.



Scheme 1.48. Synthesis of oxa-azaspirobicyclic systems from cyanamides via a 1,6-HAT reaction

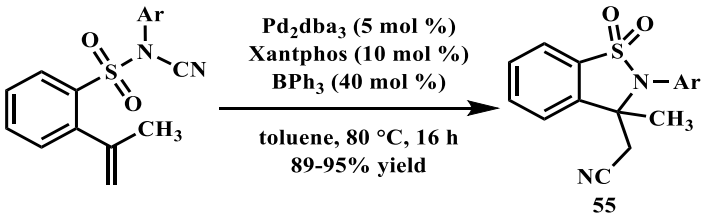
1.3.4 N-CN bond cleavage

In the past the N-CN bond has been viewed as an unreactive bond. However, a series of techniques have been developed to achieve the cleavage of the N-CN bond giving access to a range of interesting and useful reactivity. An early example of N-CN bond cleavage from Nakazawa *et al.* employed silyl-iron complexes.[93] More recently the cleavage of the N-CN bond of cyanamides has also been exploited for aminocyanation reactions. In 2014 Nakao and co-workers developed an intramolecular aminocyanation of alkenes by cooperative palladium and boron catalysis (Scheme 1.49).[94] The reaction begins with oxidative addition to the N-CN bond which is activated by coordination to the Lewis acidic boron species.[95] 5-Exo-trig cyclisation then forms the new 5-membered ring. Reductive elimination to reform the Pd(0) species yields the product.



Scheme 1.49. Aminocyanation by cooperative palladium and boron catalysis

In 2018 similar chemistry was developed by Douglas *et al*. in the palladium and Lewis acid catalysed intramolecular aminocyanation of alkenes for the synthesis of sultams **55** from cyanamides (Scheme 1.50).[96]



Scheme 1.50. Aminocyanation to form sultams from cyanamides

1.4 Thesis objectives

The chemistry of cyanamides has developed into a rich and diverse field since their first discovery 1838. Cyanamide containing molecules are highly valuable in pharmaceuticals, and especially so in agrochemistry. The cyanamide moiety has been exploited for the formation of many interesting compounds such as guanidines, ureas, isoureas and countless varieties of heterocycles.

The synthesis of cyanamides can be achieved from a range of starting materials such as ureas, guanidoximes and amidoximes. For the majority of the 19th and 20th century cyanation of amines was dominated by cyanogen bromide – however in recent years efforts have been made to avoid this compound. Despite this, many of the techniques are experimentally complex, or indeed utilise cyanogen compounds at one point or another. New methods for cyanamide synthesis using less toxic molecules *via* an operationally simple process would be valuable.

The aim of this thesis is to develop techniques to form cyanamides utilising less toxic cyano sources. It would be advantageous if the processes are simple and easy to carry out in a research laboratory. Further objectives are to investigate the broader reactivity of cyanamides and discover new reactivity.

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Chapter 2: *N*-cyanation of Secondary Amines using Trichloroacetonitrile

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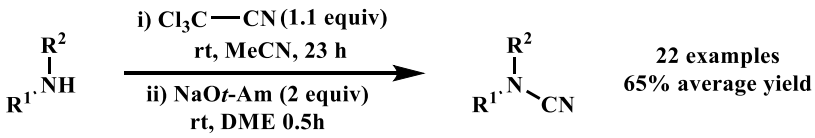
2.1 Preface

This chapter discusses the development of *N*-cyanation of secondary amines using trichloroacetonitrile. A one pot *N*-cyanation of secondary amines has been developed utilising trichloroacetonitrile as an inexpensive cyano source. A diverse range of cyclic and acyclic secondary amines can be readily transformed into the corresponding cyanamides in good isolated yields. The selectivity of this procedure was also investigated and demonstrated complementary reactivity to cyanogen bromide. The technique was also applied to the final synthetic step of a biologically active rolipram derived cyanamide.



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2.1.1 Acknowledgements

K. B. Ling - Syngenta, Jealott's Hill International Research Centre

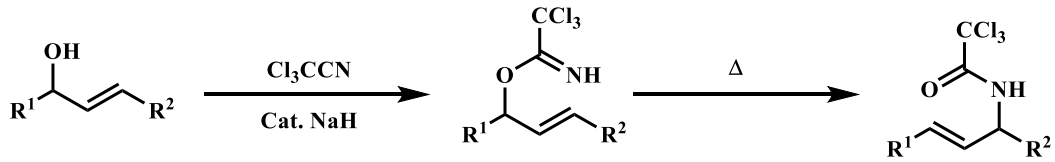
L. C. Morrill – Supervisor, Cardiff University.

2.2 Introduction

Inspiration for this project came from the work by Fischer in 1930.[1] Fischer took electron rich arenes in a Friedel-Crafts reaction with trichloroacetonitrile **56** (TCAN) and aluminium trichloride to form ketimines (Scheme 2.1).[2] Addition of KOH to the ketimine eliminates a trichloromethyl anion to form the nitrile arene.

Scheme 2.1. Cyanation of electron rich arenes using trichloroacetonitrile

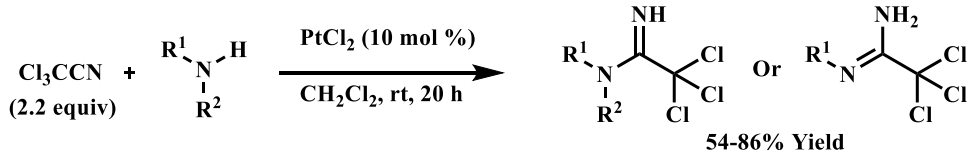
Based upon this work the proposal of reacting amines with TCAN to form amidines followed by treatment with base to form cyanamides was established. TCAN would be able to provide a safer alternative to cyanogen bromide. On comparison of the LD_{50} of each compound it is immediately clear that TCAN (250 mg/kg) is five to ten times less toxic than cyanogen bromide (25-50 mg/kg) orally for rats.[3,4] Moreover, cyanogen bromide readily sublimes at room temperature and pressure to provide a toxic gas. Furthermore, hydrogen cyanide and hypobromous acid is formed from cyanogen bromide *via* acid hydrolysis.[3] TCAN on the other hand is a high boiling (83-84 °C) liquid which can be handled with much greater safety. TCAN has an established utility in synthetic organic chemistry as demonstrated by the Overmann rearrangement.[5] In this reaction allylic alcohols can be transformed into allylic trichloroacetimidates (Scheme 2.2).



Scheme 2.2. The Overmann reaction using trichloroacetonitrile to form allylic trichloroacetimidates

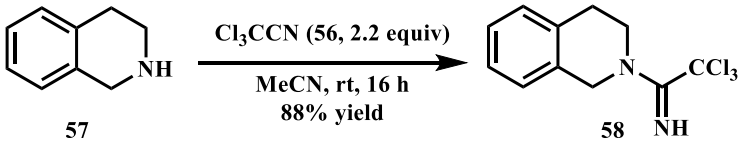
TCAN has also been reacted with amines such as for the synthesis of trichloroamidines. German patent 671,785 first mentioned the reactivity of trichloroacetonitrile with amines but it was first elaborated upon by Backer *et al.* in 1951 where they isolated *N*-methyl- and *N*-piperidyl-trichloroamidine only in the presence of methanol and as picrate salts.[6] Work by Taurins *et al.* developed this reactivity in aqueous conditions in 1958 and in 1978 Saari *et al.* used this technique to synthesise trichloroamidines as inotropic agents.[7,8] More recently Camp *et al.* have developed a platinum catalysed synthesis of trichloroamidines in non-polar aprotic solvents.[9] They discovered that a range of primary

and secondary amines can be reacted with TCAN in the presence of 10 mol % $PtCl_2$ (Scheme 2.3).



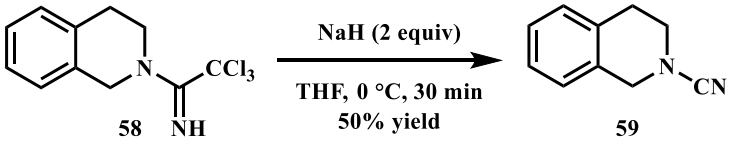
Scheme 2.3. Platinum catalysed synthesis of trichloromethylamidines by Camp et al.

The investigation began with the reaction of 1,2,3,4-tetrahydroisoquinoline **57** with trichloroacetonitrile (Scheme 2.4). 1,2,3,4-Tetrahydroisoquinoline **57** was reacted with 2.2 equivalents of TCAN **56** in acetonitrile to form 2,2,2-trichloro-1-(3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-imine **58**. The reaction proceeded to the trichloroamidine with an isolated yield of 88%.



Scheme 2.4. Initial investigations with trichloroacetonitrile to form a trichloroamidine

The trichloroamidine **58** was then treated with base to perform the elimination step. In the first case 2 equivalents of sodium hydride (NaH) were used in THF. This reaction after purification yielded the desired 3,4-dihydroisoquinoline-2(1H)-carbonitrile **59** in 50% yield (Scheme 2.5).

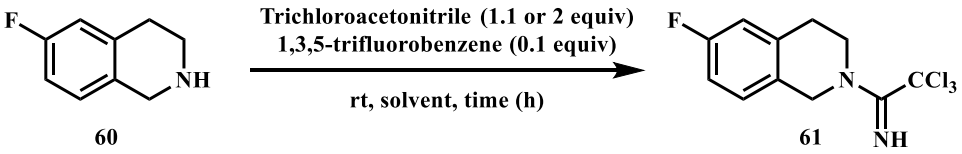


Scheme 2.5. Initial investigation of the elimination of a trichloroamidine to form a cyanamide

2.3 Optimisation

With these results in hand optimisation was initiated. For these reactions 6-fluoro-1,2,3,4-tetrahydroisoquinoline **60** was chosen as the model substrate. This substrate was chosen so the reaction could be monitored by *in situ* ^{19}F NMR (Scheme 2.6). The reactions would be run in a standard borosilicate glass 178 mm length, 4.97 mm O.D. x 4.20 mm I.D. NMR tube with 1,3,5-trifluorobenzene as internal standard. The contents of the NMR tube were mixed thoroughly and measured at 3 time points (T1 ≈ 30 mins, T2 = 5 hours,

T3 = 23 hours) by ^{19}F NMR. Initially the formation of the trichloroamidine was subjected to optimisation. Each ^{19}F NMR was analysed to determine the composition of the reaction, as a ratio of starting material to amidine **61** to unidentifiable products (UP). For this each NMR tube was loaded with 81.9 µL 6-fluoro-1,2,3,4-tetrahydroisoquinoline **60** (0.6 mmol, 1 equiv), 0.6 mL ([**60**] = 1 mol dm^{-3}) of the requisite solvent, 6.21 µL of 1,3,5-trifluorobenzene (0.06 mmol, 0.1 equiv) as internal standard and TCAN (1.1 or 2 equiv) (Table 2.1)



Scheme 2.6. Optimisation of the formation of the trichloroamidine

Entry	TCAN / eq.	Solvent	T= 30 min **60** : **61** : UP	T= 5 h **60** : **61** : UP	T= 23 h **60** : **61** : UP
1	2	Dioxane	94:03:03	69:27:04	18:78:4
2	2	Tol	92:05:03	48:48:04	0:96:4
3	2	TBME	91:06:03	48:48:04	7:90:3
4	2	MCPE	91:05:04	48:48:04	9:87:4
5	2	$CHCl_3$	95:02:03	75:21:04	36:61:3
6	2	EtOAc	94:03:03	59:38:03	12:83:5
7	2	DME	93:03:04	64:32:04	12:84:4
8	2	THF	88:07:05	40:56:04	9:87:4
9	2	CH_2Cl_2	95:02:03	47:50:03	0:96:4
10	2	*t*-BuOH	97:00:03	85:12:03	51:46:3
11	2	Acetone	67:26:07	0:47:63	0:66:34
12	2	MeOH	75:22:03	72:22:06	66:22:12
13	2	MeCN	68:28:04	0:97:3	0:96:4
14	**1.1**	**MeCN**	**80:17:03**	**18:79:3**	**0:97:3**
15	2	DMF	69:27:04	0:95:5	0:95:5
16	2	DMSO	59:37:04	0:94:6	0:95:5

Table 2.1. Optimisation data for the formation of the trichloroamidine

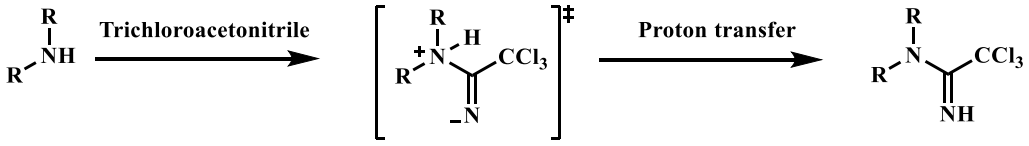
Initial reactions were performed with 2 equivalents of TCAN in a range of solvents. At the first time point it was evident that polar aprotic solvents favoured amidine formation. The data shows that reactions in acetone, acetonitrile (MeCN), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) with 2 equivalents of TCAN all proceed to 28-37% product formation after 30 minutes (Table 2.1, entries 11, 13, 15, 16). Reactions in non-polar solvents such as dioxane and toluene fail to provide more than 5% NMR yield

after the same amount of time (Table 2.1, entry 1 and 2). Acetone develops significant unidentifiable products, which could be attributed to iminium formation.

When the reactions are further analysed at 5 hours, those in polar aprotic solvents have increased very close to 100% product formation. MeCN, DMF and DMSO gave 97, 95 and 94% NMR yield to the product respectively. When compared again with non-polar solvents such as dioxane and toluene (27 and 48% respectively, T=5 h) there is up to 50% difference in NMR yield. The reaction in alternative solvents such as *t*-butyl methyl ether (TBME), cyclopentyl methyl ether (CPME), chloroform ($CHCl_3$), ethyl acetate (EtOAc), dimethoxy ethane (DME), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and *tert*-butanol (*t*-BuOH) (Table 2.1, entries 2-10) clearly perform less effectively at this time point.

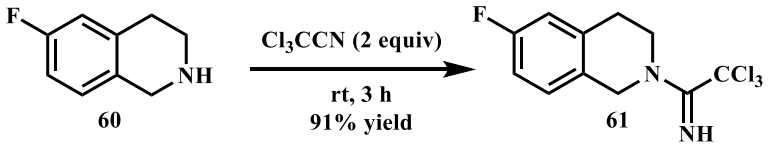
After 23 hours the reactions with polar aprotic solvents have equivalent results to that at 5 hours with product formation greater than 95%. Between 5 hours and 23 hours there are no signs of *in situ* product decomposition in either MeCN, DMSO or DMF. MeCN, DMSO or DMF would be suitable solvents for this reaction. Overall the optimisation process for the formation of the trichloroamidine showed that polar aprotic solvents were optimal.

It can be proposed that the transition state (Scheme 2.7) is more stabilised by polar solvents – therefore pushing the reaction towards product formation. Hughes-Ingold rules state that an increase in the polarity of the solvent can accelerate the rate of a reaction where charge is developed in the activated complex formed from neutral reactants.[10,11] This supports the increased rate of reaction when MeCN, DMF and DMSO are used as they are highly polar with dielectric constants of 36.64, 38.25 and 47 respectively.[12] On the contrary solvents such as dioxane and toluene are non-polar (ε = 2.21 and 2.38 respectively) and can better stabilise the reactants.[13] Moreover, use of an aprotic solvent eliminates hydrogen bonding interactions between the secondary amine nucleophile and the solvent, maintaining the amines nucleophilicity.[11]



Scheme 2.7. The reaction of a secondary amine and the proposed transition state

With efficient processes identified by ^{19}F NMR studies the optimal solvent selected was acetonitrile. As stated previously DMSO and DMF would both be suitable choices for this transformation. However difficulty with their use, specifically very high boiling points (DMSO = 189 °C / DMF = 153 °C) making solvent removal by evaporation challenging.[14] Whilst removal is possible, acetonitrile provides much easier removal with a boiling point of only 82 °C.[11] With acetonitrile chosen as the optimal solvent an investigation of whether it was possible to lower the equivalents of TCAN used was tested (Table 2.1, entry 14). An NMR yield of 97% was achieved with 1.1 equivalents TCAN after 23 hours and after purification by flash silica gel column chromatography gave an 88% isolated yield. It was also investigated whether it was possible to run the reaction neat in TCAN (Scheme 2.8).

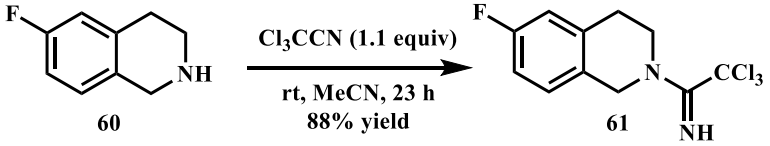


Scheme 2.8. An experiment to test whether the formation would occur in neat TCAN

Entry	TCAN	T= 30 min	T= 2 h	T= 3 h
	/ eq.	**60** : **61** : UP /%	**60** : **61** : UP /%	**60** : **61** : UP /%
1	2	39 : 60 : 1	3 : 96 : 1	0 : 99 : 1

Table 2.2. ^{19}F NMR studies for the reaction run neat in TCAN

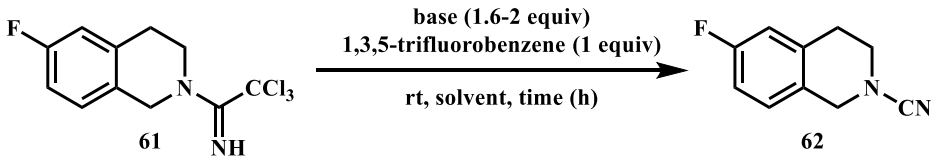
This experiment (Scheme 2.8, Table 2.2) showed it was possible for the reaction to proceed in neat TCAN, where TCAN is both reagent and solvent. After 3 hours 99% NMR yield was reached, and the product was isolated in 91% yield. Despite this, the optimal process chosen was utilising MeCN (Table 2.1, entry 14). The equivalents of more expensive TCAN could be lowered to 1.1 with equal performance. The final optimised conditions for the formation of the amidine provided the amidine in 88% isolated yield (Scheme 2.9).



Scheme 2.9. Final optimised conditions for the formation of the amidine

Attention was then turned to the elimination step of the reaction. For this a range of bases were examined. The reaction was analysed by *in situ* ^{19}F NMR using 1,3,5-

trifluorobenzene as internal standard and 2,2,2-trichloro-1-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-imine **61** as the model substrate (Scheme 2.10).



Scheme 2.10. Optimisation experiments for formation of the cyanamide

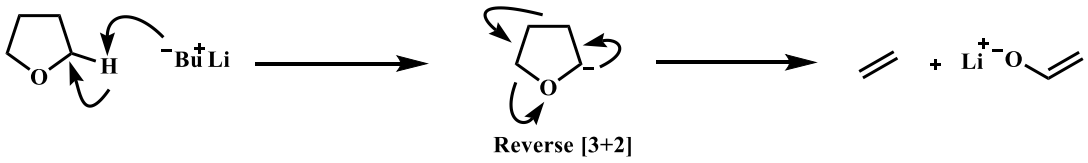
To a glass vial was charged 2,2,2-trichloro-1-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-imine **61** (29.6 mg, 0.10 mmol, 1 equiv) the required volume so that **61** was at concentration 0.20 mol dm^{-3}, 1,3,5-trifluorobenzene (10.3 µL, 0.10 mmol, 1 equiv) as internal standard and the requisite base (1.6 or 2 equiv). The reaction mixtures were stirred at room temperature and aliquots were taken at T1= 5 or 30 min, T2= 5 h, T3= 23 h. The reactions were analysed to determine reaction composition as ratios of starting material **61** to cyanamide **62** to unidentifiable-products (Table 3)

Entry	Base (equiv)	Solvent	T1 / min	**61** : **62** : UP /%	T= 5 h **61** : **62** : UP /%	T= 23 h **61** : **62** : UP /%
1	DBN (2)	THF	30	99 : 0 : 1	99 : 0 : 1	97 : 0 : 3
2	DBU (2)	THF	30	98 : 0 : 2	98 : 0 : 2	98 : 0 : 2
3	TBD (2)	THF	30	100 : 0 : 0	100 : 0 : 0	95 : 5 : 0
4	KO*t*-Bu (2)	THF	30	11 : 89 : 0	10 : 90 : 0	7 : 93 : 0
5	NaOAm (2)	THF	30	5 : 95 : 0	4 : 96 : 0	3 : 97 : 0
6	NaOAm (2)	DME	30	0 : 100 : 0	0 : 100 : 0	0 : 100 : 0
7	NaH (2)	THF	30	8 : 91 : 1	40 : 60 : 0	0 : 100 : 0
8	LHMDS (2)	THF	5	Complex mixture		
9	KHMDS (2)	Tol	5	Complex mixture		
10	KHMDS (1.6)	Tol	5	3 : 84 : 13	-	-

Table 2.3. ^{19}F optimisation data for the formation of the cyanamide

Investigations began with organic bases 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) (Table 2.3 entry 1), 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (Table 2.3, entry 2), and triazabicyclodecene (TBD) (Table 2.3, entry 3). A solvent swap was found necessary for this step with initial tests determining MeCN inhibited product formation. Moreover, it was found that any remaining TCAN would also inhibit the elimination step. To each reaction was added 2 equivalents of the requisite base in THF. With the organic bases, minimal conversion to the product was observed at T=30 mins, T=5 h, or T=23 h. Next alkoxide bases KO*t*Bu (Table 2.3, entry 4) and NaO*t*Am (Table 2.3, entry 5) were tested.

In each case 2 equivalents of base were used with the reaction running in THF. NaO*t*Am showed excellent NMR yield of 95% to the cyanamide after 30 minutes with KO*t*Bu slightly behind with 89% NMR yield. Over time the reaction with NaO*t*Am as base reached 96% NMR yield after T=5 h and reaching a peak of 97% after T=23 h. The case for KO*t*Bu however was poorer, after T=5 h the NMR yield had reached 90% however after 23 h significant decomposition to unidentifiable products had occurred. The reaction with NaO*t*Am was also not without flaws. Surprisingly in the proton NMR of this reaction decomposition of THF could be observed. More commonly seen when THF is reacted with butyl lithium at room temperature, one of the 4 protons adjacent to the oxygen of THF is removed by a base to facilitate a reverse [3+2] cycloaddition to form the enolate of acetaldehyde and ethylene gas (Scheme 2.11).[15]

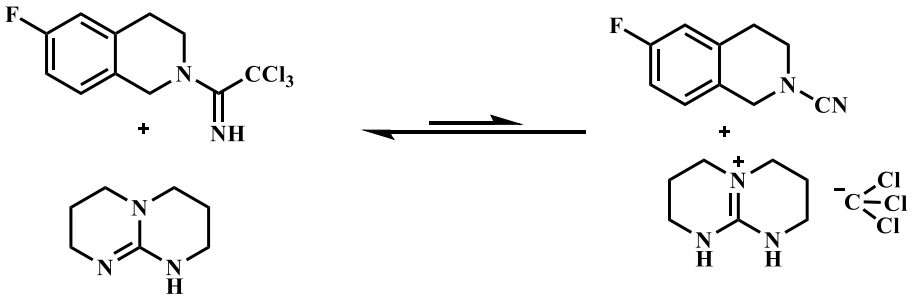


Scheme 2.11. The decomposition of THF when reacted with n-butyllithium

This could be overcome by a solvent switch to DME (Table 2.3, entry 6). The NMR yield observed in this reaction exceeded that of its counterpart in THF with 100% NMR yield at T=30 mins and stability of the product *in situ* all the way to T=23 h. The original attempt to facilitate the elimination step of this reaction as discussed earlier (Scheme 2.5) was using NaH and this reaction was also analysed by ^{19}F NMR (Table 2.3, entry 7). At T=30 min the reaction with NaH had proceeded to 91% product formation. After T= 5 h however the data showed a 60:40 ratio of starting material to product which is an anomalous result, this may have been caused by a sampling issue. The reaction with NaH was particularly heterogeneous possibly due to its addition as a 60% mixture with paraffin oil. After T=23 h, the product conversion had reached 100%. With alkoxide bases providing excellent conversion it was decided that NaH would be less ideal for our reaction for safety reasons, especially if carried out on large scales and was therefore not investigated further.[16] Lastly lithium bis(trimethylsilyl)amide (LiHMDS, 1 M THF) and potassium bis(trimethylsilyl)amide (KHMDS, 1 M toluene) were tested and each gave complex mixtures by ^{19}F NMR and were therefore determined not suitable for this reaction.

To understand the suitability of each base it is important to compare the relative pK_a values. Amidine bases typically have a pK_aH of 12-14 (EtOH).[17] DBU and DBN are both amidine bases and the results show that they cannot promote the reaction.[18] It can be proposed that neither are basic enough to deprotonate the trichloroamidine.

Guanidine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) provided only 5% product after 23 h and was therefore marginally more successful than the amidine bases. Guanidines are also recognised as strong organic bases and even more so than amidines. Guanidine has an experimental pK_a (H_2O) of 13.6. TBD has an experimental pK_aH (H_2O) value of 14.5.[19] Again, it may be possible that TBD cannot deprotonate the amidine, however it is expected that guanidines are more basic than amidines. It may be the case however that in this reaction there is a significant amount of reversibility and the amidinium ion can be readily protonated by the guanidium conjugate acid to provide the starting materials.

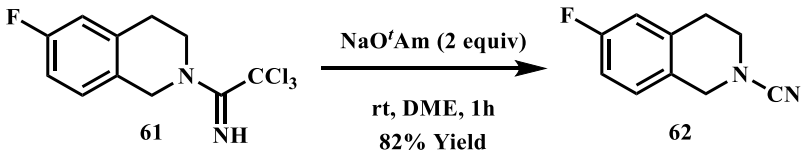


Scheme 12. Possible equilibrium when TBD is used as base

The alkoxide bases provided the product readily because of their higher pK_aH values. KO*t*Bu has a pK_aH of the conjugate acid (H_2O) of 17 – significantly higher than that of any amidine.[20–22] Experimental data for the pK_aH of NaO*t*Am is not available, but it can be presumed it is comparable to KO*t*Bu and is therefore a strong enough base to deprotonate the amidine.

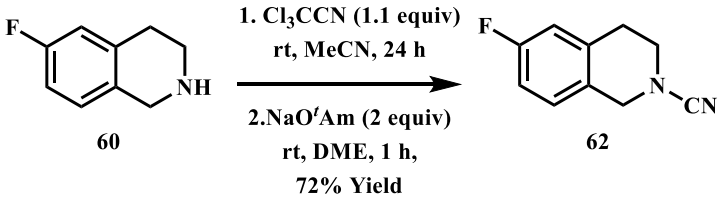
NaH is a strong base (pK_a H_2=42). This base can readily deprotonate the amidine to form H_2. This formation of H_2 is one of the reasons it was discounted for safety precautions. LHMDS and KHMDS were expected to readily promote the formation of the cyanamide however in each case this was not observed. Both have pK_aH (THF) values of ~26 which is significantly higher than the amidine proton which is required to be removed.[23] These reactions yielded very complex mixtures by ^1H and ^{19}F NMR with significant degradation of starting material to unidentifiable products. With effective bases for this procedure

already discovered limited investigation was given to understand this phenomenon. Lowering the equivalents of KHMDS to 1.6 was tested and much more product could be observed (84% NMR yield T=30 min) however many unidentifiable products were present in the NMR spectra. The optimal conditions for the elimination step of this reaction is shown in scheme 2.13 below and the cyanamide was isolated with a yield of 82%.



Scheme 2.13. Optimised conditions for the elimination of the amidine to form a cyanamide

With the two steps optimised it was then investigated whether it was possible for this reaction to be run in one pot and avoid isolation of the amidine in the first step. For this to work it would be necessary to remove the MeCN solvent and excess TCAN from the first step as it was known that this inhibited product formation and replace with DME for the second step. Practically the reaction to form the amidine was run in a thick-walled microwave vial under the optimised conditions for 23 h. The vial was then placed under vacuum ensuring that all MeCN and TCAN has been removed – this could be achieved *via* a Schlenk line or rotary evaporator. The residue was then dissolved in DME before NaO*t*Am was added and stirred for 1 h. The reaction could then be quenched by dropwise addition of saturated aqueous $NaHCO_3$ and extraction with EtOAc. Purification of the crude product by flash column chromatography yields the pure cyanamide product **62** (Scheme 2.14).



Scheme 2.14. The final optimised one pot-two step cyanation reaction with trichloroacetonitrile

2.4 Substrate scope

With the one pot-two-step process optimised the generality of this process was then tested with a range of cyclic amines (Figure 2.1).

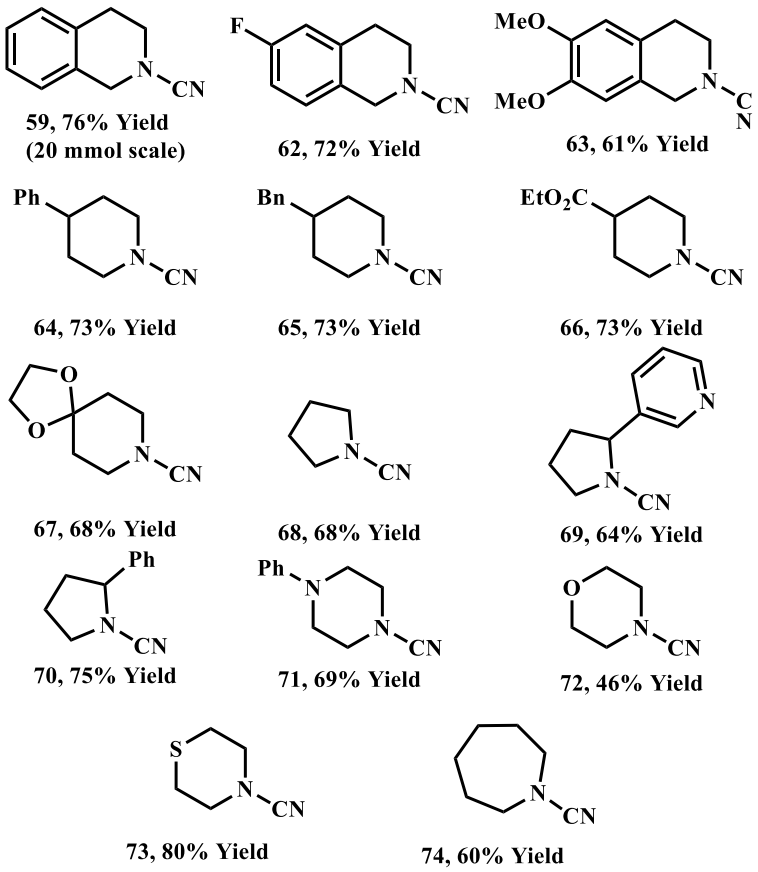


Figure 2.1. Cyclic amine substrate scope

A range of cyclic amines were tested with a 5-,6- and 7- membered nitrogen heterocycles working well. More specifically a series of tetrahydroisoquinolines were tolerated and several 4- substituted piperidines (Compounds **59**, **62-67**, 61-76% yield). 1,2,3,4-tetrahydroisoquinoline **57** was tested on a 20 mmol scale and the cyanamide **59** was obtained in a 76% yield (2.42 g). 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carbonitrile **63** was synthesised from the commercially available corresponding HCl salt starting material. This was possible with a modification to the first step. Initially addition of triethylamine and potassium carbonate in acetonitrile was tested in an effort access the free base *in situ*. The reaction was then diluted with water and extracted with EtOAc and dried over $MgSO_4$. The EtOAc was removed *in vacuo*, prior to addition of DME and NaO*t*Am. Whilst the cyanamide was isolated in each case the isolated yields using triethylamine or potassium carbonate in the first step were 35 and 22% respectively. The

reaction was then tested with 1:1 MeCN/Sat. Aq. $NaHCO_3$. in the first step, again it was necessary in this case to workup the reaction to remove the water and salts leftover before the residue was then dissolved in DME and treated with NaO*t*Am to yield the cyanamide **63** in an acceptable 61% yield. Pyrrolidine afforded cyanamide **68** in a 68% yield. Formation of the nicotine analogue **69** in 64% yield demonstrates that the method is tolerant of additional basic nitrogen atoms within the molecule.[24,25] A second 2-substituted 2-phenylpyrrolidine yielded cyanamide **70** in 75% yield both indicating that an increase in steric demand around the amine can be tolerated. Further heterocycles such as 1-phenylpiperazine (**71,** 69% yield), morpholine (**72,** 46% yield) thiomorpholine (**73,** 80% yield) and azepane (**74,** 60% yield) were tolerated and formed the respective cyanamides in high yield. A lower isolated yield for morpholine derived **72** was due to product volatility rather than poor conversion. The reaction with morpholine was run with mesitylene as internal standard and the ^{1}H NMR yield was determined as 75% after 2 steps.

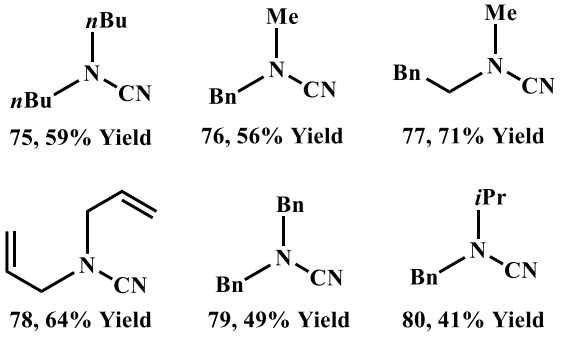
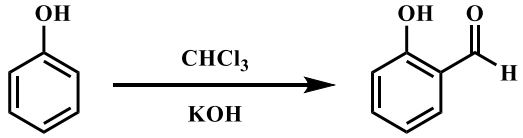


Figure 2.2. Acyclic amine substrate scope under optimised conditions

Having successfully demonstrated *N*-cyanation with a series of cyclic secondary amines a series of acyclic secondary amines were tested (Figure 2.2). It was found that a range of symmetrical and orthogonally substituted acyclic amines could be cyanated with this process. For example, dibutylamine, *N*-benzylmethylamine and *N*-methylphenethylamine can be readily converted to the corresponding cyanamides in good to high yields (**75,** 59%, **76** 56% and **77** 71% respectively). Under the standard reaction conditions diallylamine only provided cyanamide **78** in 33% yield. In this case it was suspected that the formation of a dichlorocarbene in the presence of an alkene containing substrate may be causing undesirable side reactions.

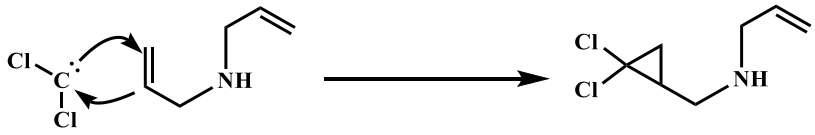
In the presence of base, it is possible to form dichlorocarbenes from choroform.[26] This chemistry has in fact been used in several synthetic transformations productively such as

the Reimer-Tiemann reaction.[27–29] The Reimer-Tiemann reaction is used for *ortho*-formylation of phenols (Scheme 2.15).



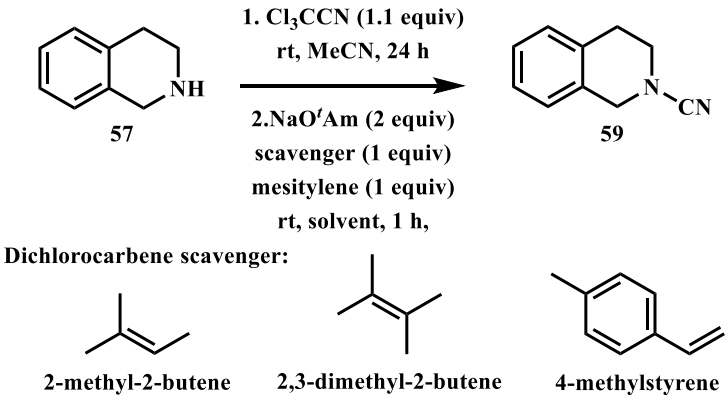
Scheme 2.15. The Reimer-Tiemann formylation of phenol by dichlorocarbene formation

The dichlorocarbene is formed from the deprotonation of chloroform in strong base to form a trichloromethyl carbanion followed by the loss of a chlorine anion to provide the dichlorocarbene. In an *N*-cyanation system with diallylamine it can be proposed that the dichlorocarbene can react with the alkenes to form dichlorocyclopropanes (Scheme 2.16).



Scheme 2.16. The possible side reaction with dichlorocarbenes in the presence of an alkene containing substrate

To limit the loss of desired cyanamide **78** to this side reaction it was proposed that addition of a sacrificial dichlorocarbene scavenger could be used. To test this, it was first investigated whether the proposed scavengers have any detrimental effect upon the reaction. This was tested with the reaction of 1,2,3,4-tetrahydroisoquinoline **57** with the addition of a scavenger in the elimination step. The first step of the reaction was run as standard to yield the trichloroamidine. In the elimination step a dichlorocarbene scavenger (1 equiv) was added along with mesitylene as an internal standard (Scheme 2.17). The NMR yield would be measured and compared to reactions with no scavenger to observe any detrimental effect (Table 2.4).

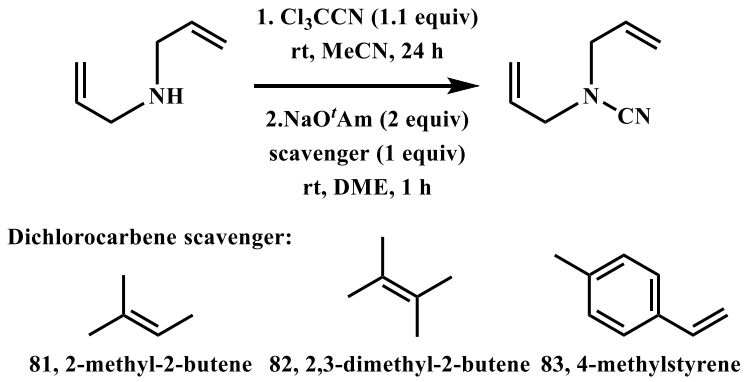


Scheme 2.17. Investigation to limit side reactivity of alkene containing substrates with dichlorocarbenes

Dichlorocarbene scavenger	Solvent	NMR yield **59**/ % (T= 23h)
2-methyl-2-butene	THF	71
	DME	79
2,3-dimethyl-2-butene	THF	69
	DME	80
4-methystyrene	THF	78
	DME	76
No scavenger	THF	77
	DME	75

Table 2.4. NMR Yield results for addition of dichlorocarbene scavenger to standard N-cyanation reaction

The data collected showed that the addition of a dichlorocarbene scavenger to the standard reaction had no detrimental effects upon the NMR yield of the reaction. It is also noteworthy that the reaction became significantly less black/brown when a dichlorocarbene scavenger was present. With these results showing the reaction worked effectively it was then tested on the diallylamine substrate. Each of the three proposed scavengers was tested in the second step and the NMR yield was observed after 23 hours with mesitylene as internal standard. In this case only DME as solvent was tested (scheme 2.18).



Scheme 2.18. NMR Yield results for the addition of a dichlorocarbene scavenger to a substrate containing an alkene

Dichlorocarbene scavenger	NMR yield **78** /% (T= 23 h)
2-methyl-2-butene **81**	52
2,3-dimethyl-2-butene **82**	62
4-methylstyrene **83**	69
No scavenger	40

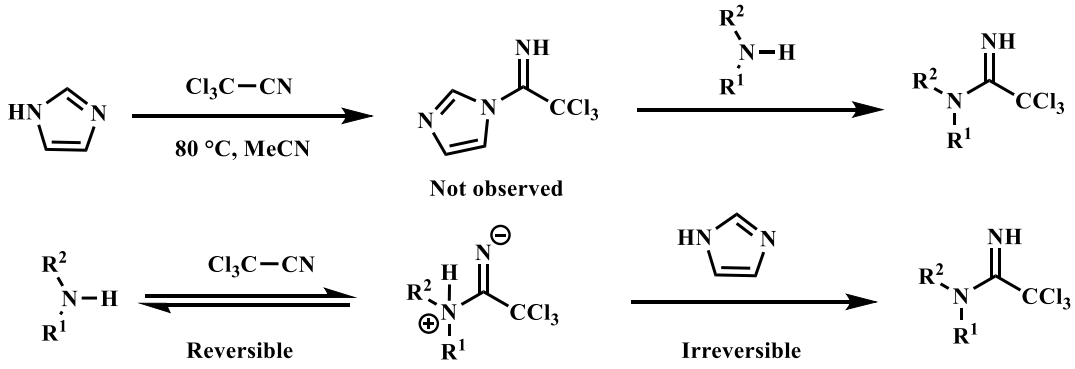
Table 2.5. NMR Yield data for the addition of a dichlorocarbene scavenger to a reaction with an alkene containing substrate

The data shows that the presence of a dichlorocarbene scavenger is highly beneficial to product formation in the reaction with diallylamine (Table 2.5). In the absence of a

scavenger an NMR yield of 40% was observed, consistent with the 33% isolated yield for this process. Addition of 2-methyl-2-butene **81** or 2,3-dimethyl-2-butene **82** was beneficial with NMR yields of 52 and 62% respectively. The reaction with 4-methylstyrene **83** showed the greatest NMR yield of 69% after 23 h and subsequently an acceptable 64% isolated yield for the two-step procedure when included in the second step.

More sterically encumbered amines such as dibenzylamine and *N*-isopropylbenzylamine gave no conversion to the corresponding amidines after stirring with TCAN after 23 h (Figure 2.2). To promote the formation of the amidine the reaction was tested at reflux in acetonitrile. After 24 h the reaction NMR yield could be observed as 38% and after 40 h at 52% by ^{1}H NMR. To further accelerate the reaction a series of Lewis bases were then tested – imidazole, 4-dimethylamino pyridine (DMAP), pyridine and 4-pyrollopyridine (PPY). The first tests were run with 1 equivalent of the Lewis base and it was found that imidazole had the desired effect with 84% NMR yield after 16 h at 80 °C. Imidazole was then tested in catalytic quantities (10 mol %) and was found to be equally as effective. When applied in the overall 2 step procedure the addition of imidazole in the first step provided a 49% isolated yield for the dibenzylamine derived cyanamide **79** and isolated yield 41% for *N*-isopropylbenzylamine derived cyanamide **80** (with a 50 and 49% NMR yield respectively)

This enhancement was first thought to be through the formation of a more reactive species by the reaction of the Lewis base with TCAN (Scheme 2.19). However, when imidazole and TCAN were mixed together with MeCN at 80 °C no reactivity was observed. Subsequently it was suggested that the imidazole was acting as a shuttle base to push the reaction to completion by promoting the conversion of the zwitterion to the corresponding amidine. Further evidence for the shuttle base behaviour is found when imidazole was replaced with triethylamine, providing the amidine with 34% conversion. Triethylamine was chosen to provide evidence for shuttle base behaviour as it doesn't generally behave as a Lewis base because of steric hindrance.



Scheme 2.19. A reaction between the Lewis base and TCAN was not observed. Imidazole was proposed to act as a shuttle base

Limitations for the reaction were also discovered. During the amine substrate scope, it was found that cyclic aniline type secondary amines 1,2,3,4-tetrahydroquinoline **84** and indoline **85** and acyclic aniline type secondary amines diphenylamine **86** and *N*-cyclohexylaniline **87** did not undergo amidine formation (Figure 2.3).

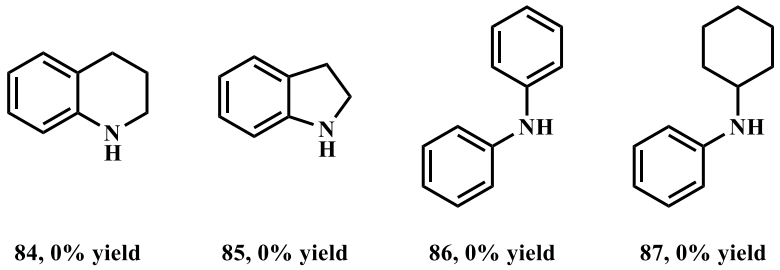
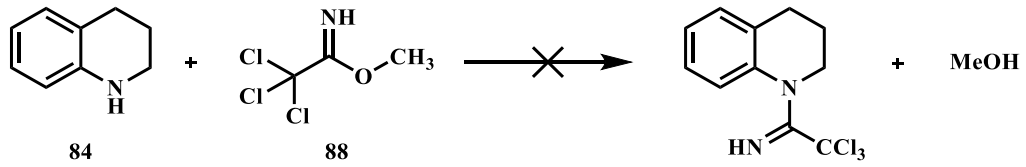


Figure 2.3. Aniline type secondary amines do not form the amidine

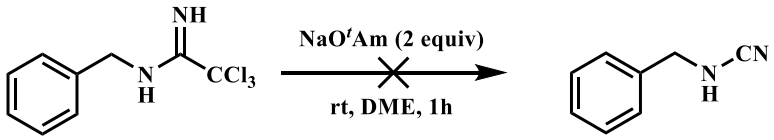
Aniline type amines are less nucleophilic due to their lone pair donation into the aromatic ring and therefore do not attack TCAN. A range of Lewis acid additives were tested in the first step to try and increase the electrophilicity of TCAN inspired by the work of Camp *et al* that used $PtCl_2$ (10 mol %) to catalyse the reaction of secondary amines with TCAN in non-polar solvents.[9] The additives tested in the first step were CuCl, AuCl, AgOTf and $PtCl_2$ (10 mol %) however no reaction between the aniline type amines and TCAN in MeCN could be observed. Subsequently commercially available methyl-2,2,2-trichloroacetimidate **88** was tested as a more electrophilic cyanating agent with 1,2,3,4-tetrahydroquinoline (Scheme 2.20). A series of conditions such as elevated temperatures and the presence of acetic acid were tested however, a productive reaction between the amines and methyl-2,2,2-trichloroacetimidate could not be developed.



84 88

Scheme 2.20. Methyl-2,2,2-trichloroacetimidate was tested as a more electrophilic cyanating agent

Primary amines were also found to be unsuitable for this reaction. Reactions between benzylamine and TCAN to form a trichloroamidine are known and it also worked under the standard conditions for step 1, this substrate was chosen for investigation.[30,31] However, under the standard conditions for step 2, primarily decomposition to unidentifiable compounds was observed (Scheme 2.21). This may be attributed to an additional labile proton in the amidine. Further bases, LHMDS, NaH and DBU were tested for the elimination involving a primary amine at rt, 80 °C and -78 °C however no reaction provided the cyanamide.

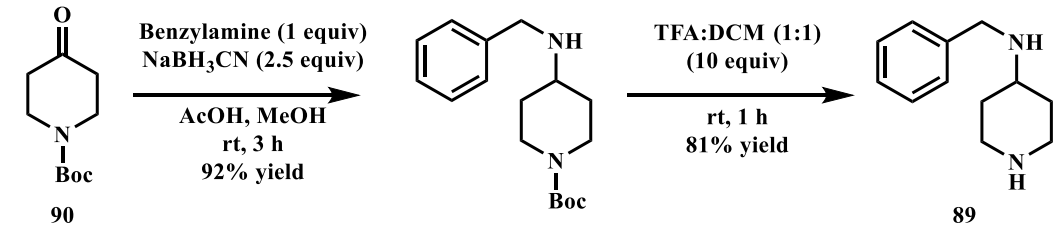


Scheme 2.21. The elimination step with primary amines provided decomposition products

2.5 Selectivity studies

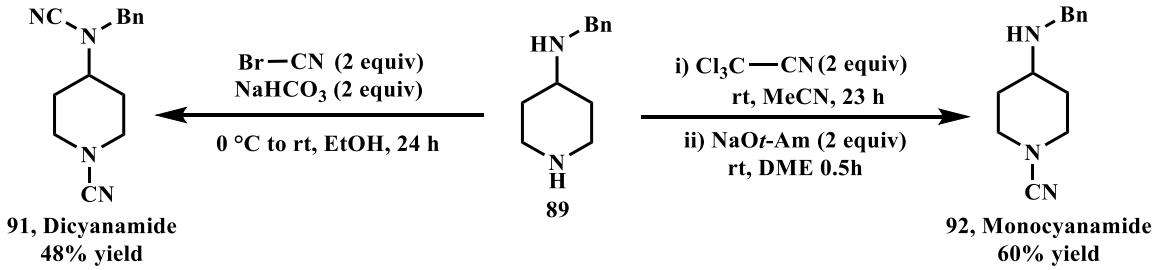
Having established the substrate scope it was clear that some secondary amines required different conditions to facilitate trichloroamidine formation. Moreover, it was clear that TCAN was less reactive than cyanogen bromide. Based upon this observation it was proposed that cyanogen bromide and TCAN should have distinct selectivity profiles. To test this hypothesis, it was necessary to synthesise a model diamine.

N-Benzylpiperidin-4-amine **89** was chosen as the target, it was proposed that cyanogen bromide will cyanate both amine positions. However, TCAN will only cyanate at the cyclic amine position, due to the increased steric bulk of the α-branched amine. *N*-benzylpiperidin-4-amine **89** was synthesised *via* a reductive amination of commercially available 1-Boc-4-piperidone **90** followed by tert-butyloxylcarbonyl (Boc) deprotection with trifluoroacetic acid (Scheme 2.22).



Scheme 2.22. Synthesis of N-benzylpiperidin-4-amine

With the model amine **89** in hand it was treated with 2 equivalents of cyanogen bromide to yield the dicyanamide **91** in 48% isolated yield. Subsequently, treatment with 2 equivalents of TCAN yielded the monocyanamide **92** in 60% isolated yield. Confirmation of cyanation at the piperidine nitrogen was confirmed by HMBC NMR studies and the presence of only one cyanamide peak in the ^{13}C spectrum. It is also significant that utilising 1 equivalent of cyanogen bromide does not result in clean monocyanation, instead yielding a mixture containing both **91** and **92**. This distinct selectivity and complementary reactivity between the two cyanating agents could prove beneficial in systems with multiple reactive sites.

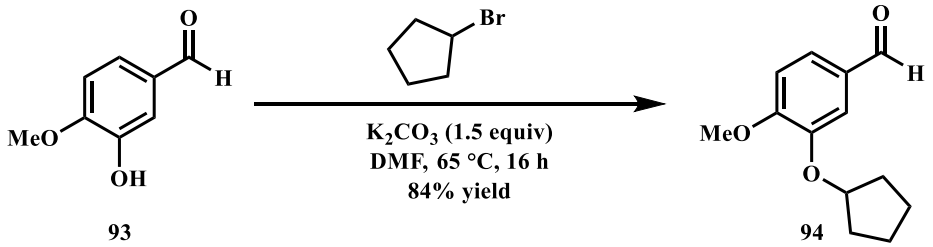


Scheme 2.23. Monocyanation with TCAN and dicyanation with BrCN

2.6 Synthesis of PDE4 inhibitor

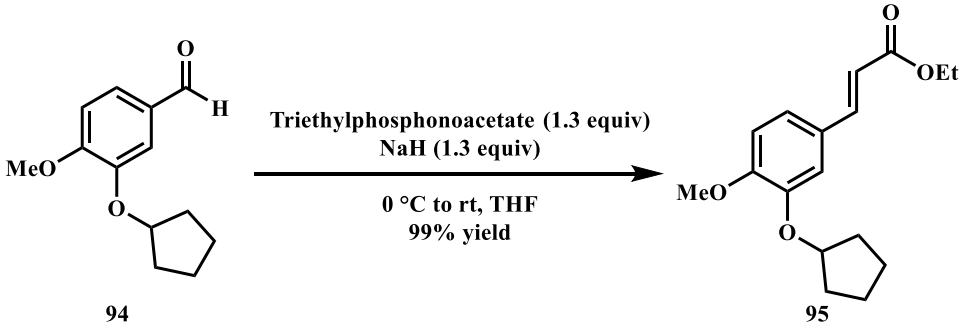
To further demonstrate the utility of this procedure it was applied in the synthesis of a medicinally relevant cyanamide. The chosen target molecule was Rolipram derived PDE4 inhibitor **8**. PDE4 inhibitors have found use in the treatment of depression. Rolipram continues to be researched with potential applications in Alzheimer's disease, autoimmune diseases and respiratory diseases such as COPD and asthma.[32]

Synthesis of the Rolipram derivative started with 3-hydroxy-4-methoxy benzaldehyde **93** following a modified procedure from Feldman *et al.* (Scheme 2.24).[32] After purification 3-(cyclopentyloxy)-4-methoxybenzaldehyde **94** was obtained (30 g, 136 mmol, 84% yield) as an orange oil.



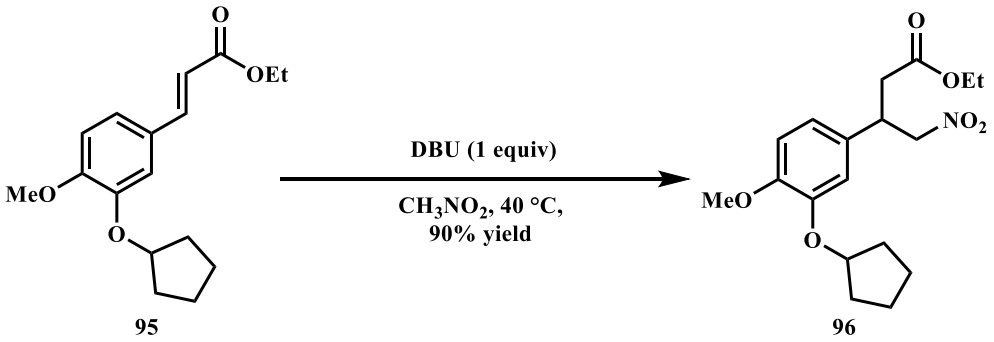
Scheme 2.24. Synthesis of 3-(cyclopentyloxy)-4-methoxybenzaldehyde

The second step was to functionalise the aldehyde by a Horner-Wadsworth-Emmons reaction following a modified procedure from Jiang and co-workers (Scheme 2.25).[33,34] After purification ethyl (*E*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)acrylate **95** was isolated (19.7 g, 68 mmol, 99% yield) as a clear oil.



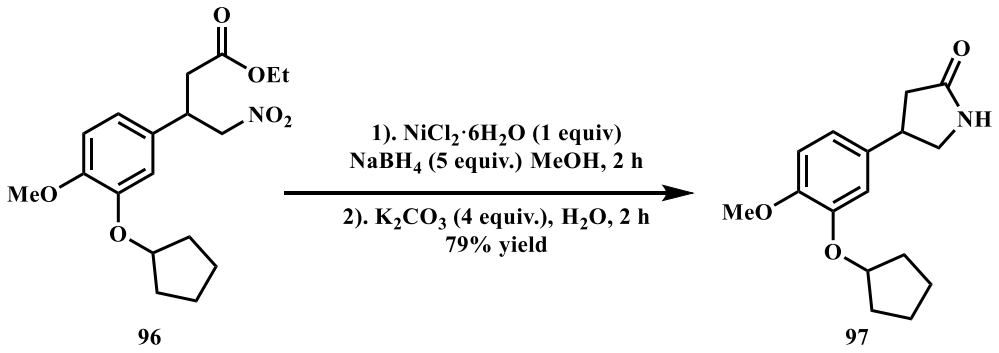
Scheme 2.25. Horner-Wadsworth-Emmons reaction to install a new carbon-carbon double bond

The next step was a nitro-Michael/Henry addition of nitromethane utilising DBU as the base (Scheme 2.26).[35] Following a literature procedure for similar compounds initial attempts with this reaction with MeCN as solvent at room temperature showed no product formation.[34] However productive conditions were soon found (Scheme 2.26) with nitromethane as reagent and solvent. Ethyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate **96** was obtained (16.4 g, 46.5 mmol, 90% yield) as a yellow solid.



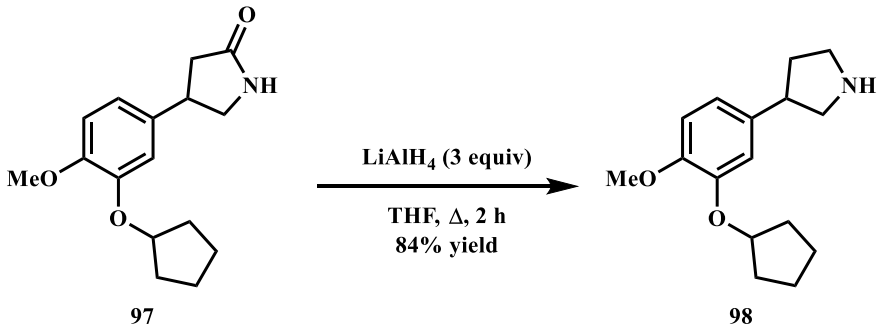
Scheme 2.26. Nitro-Michael addition of Nitromethane

Formation of Rolipram was achieved in the next step *via* reduction of the nitro group with $NiCl_2$ and sodium borohydride and subsequent base promoted 5-exo-trig cyclisation following a modified literature procedure from Hou and co-workers (Scheme 2.27).[36] Rolipram **97** was obtained (7.5g, 27.1 mmol, 79% yield) as a white solid.



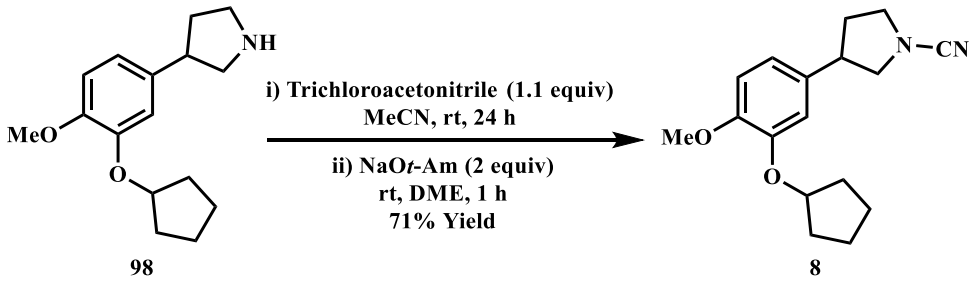
Scheme 2.27. Nickel borohydride reduction of the nitro group and base catalysed cyclisation to form the γ-lactam

The final step of the synthesis of 3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine **98** was the reduction of the γ-lactam (Scheme 2.28). Several conditions were attempted to provide the cyclic amine and it was eventually determined 3 equivalents of $LiAlH_4$ were required. After purification 3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine **98** was obtained (220 mg, 0.84 mmol, 84%) as a yellow oil.



Scheme 2.28. Reduction of the γ-lactam to form the cyclic secondary amine

With 3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine **98** in hand the TCAN cyanation protocol was tested to form biologically active **8** (Scheme 2.29). Treatment of the amine **98** with 1.1 equivalents of TCAN in MeCN followed by solvent removal/swap to DME and addition of NaO*t*Am gave 3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine-1-carbonitrile **8** as an off white solid. This represented a significant improvement over the established synthesis utilising cyanogen bromide providing 3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine-1-carbonitrile **8** in only 38% yield.[32]



Scheme 2.29. Synthesis of a biologically active cyanamide

2.7 Conclusion and outlook

A new synthetic methodology for the synthesis of cyanamides from secondary amines has been developed utilising trichloroacetonitrile as a less toxic and cheap cyano source. This method avoids the use of cyanogen bromide and is experimentally simple. A range of secondary amines have been shown to be applicable with good to excellent yields. Moreover, the technique provides distinct selectivity and has been successfully applied to a biologically relevant molecule.

The limitations of this protocol have also been established, with aniline type amines not sufficiently nucleophilic to form trichloroamidines. Additionally, primary amines have been found unsuitable due to difficulties in the elimination step. Future work could investigate the use of protecting groups with primary amines to form secondary amines. The protected primary amine could then be tested in the TCAN protocol to form a tertiary cyanamide. Deprotection of the tertiary cyanamide would yield a secondary cyanamide. Careful consideration of the protecting group would need to be made, balancing sterics and electronics. Electron withdrawing protecting groups such as tosyl, or Boc may lower the nucleophilicity of the amine such that is cannot form the trichloroamidine. Silyl protecting groups may be more suitable electronically due to the mild inductive donation however, sufficiently stable silyl protecting groups may sterically encumber the amine.

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Chapter 3: Deoxycyanamidation of Alcohols with *N*-Cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS)

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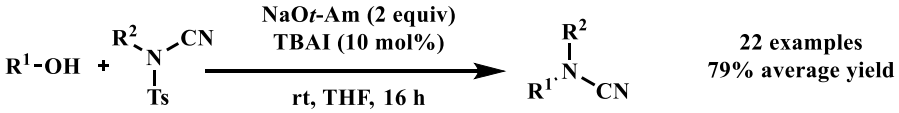
3.1 Preface

This chapter will describe early efforts to discover a synthetic pathway towards cyanates and thiocyanates using trichloroacetonitrile. Within this work alternative cyanating agents would eventually be sought and *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) was chosen. The first one-pot deoxycyanamidation of alcohols using NCTS was discovered. NCTS was used as both a sulfonyl transfer reagent and cyanamide source. The technique accesses a diverse range of tertiary cyanamides in excellent isolated yields. This approach exploits the underdeveloped desulfonylative (N-S) bond cleavage reactivity pathway of NCTS.



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J. A. Platts, and L. C. Morrill, *Org. Lett.*, 2017, **19**, 3835–3838

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K. B. Ling - Syngenta, Jealott's Hill International Research Centre

J. A. Platts – Dr. James Platts undertook all computational calculations for this project.

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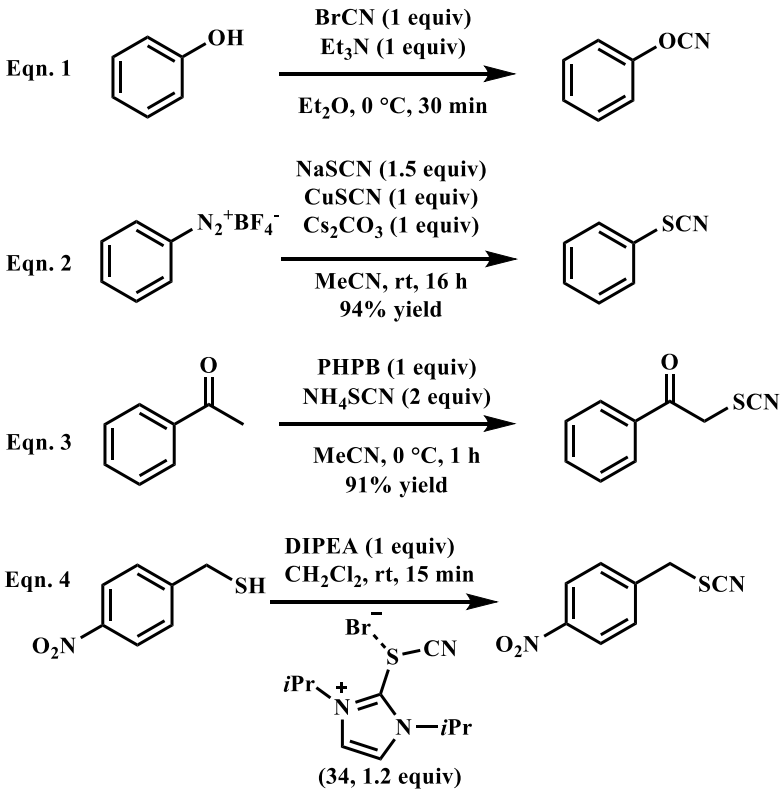
3.2 Introduction

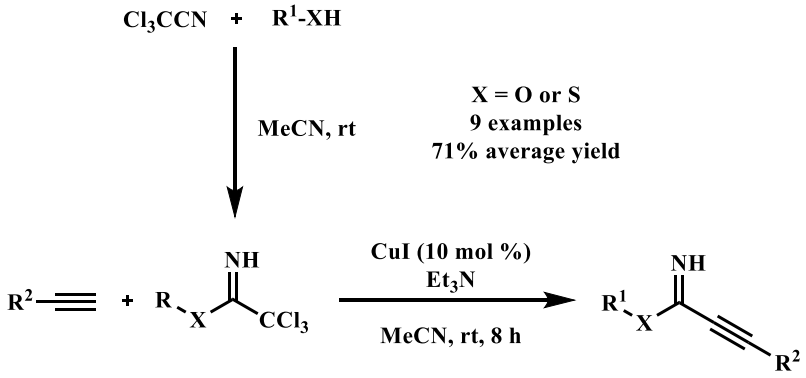
With the development of cyanation of secondary amines with trichloroacetonitrile, interest turned to whether it would be possible to synthesise cyanates from alcohols, or thiocyanates from thiols utilising the same methodology. Cyanates are primarily synthesised using cyanogen bromide much like their amine counterparts and therefore a new method for their synthesis would be valuable (Scheme 3.1, Eqn 1). Thiocyanates however cannot be synthesised from thiols with cyanogen bromide, this reaction yields only disulfides.[1] More typical introduction of a thiocyanate moiety utilises Sandmeyer type reactions with sodium thiocyanate as nucleophilic source of thiocyanate (Scheme 3.1, Eqn 2).[2] Electrophillic sources of thiocyanate can be formed from ammonium thiocyanate and an activating agent. An example is the use of pyridinium tribromide to form a NCS^+ species *in situ*.[3] (Scheme 3.1, Eqn 3). More recently Alcarazo and co-workers developed an imidazolium thiocyanate **34** cyanating agent that allows synthesis of thiocyanates directly from thiols (Scheme 3.1, Eqn 4).[4] This cyanating agent also demonstrated reactivity with nitrogen and carbon nucleophiles – however formation of cyanates was not demonstrated.



Scheme 3.1. The synthesis of cyanates and thiocyanates

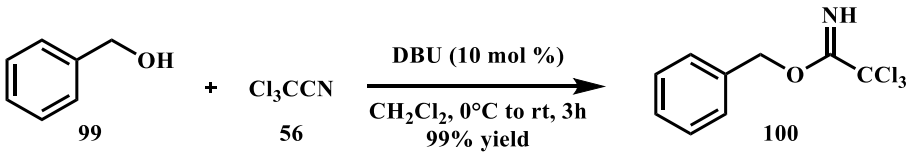
It was hypothesised that the reaction of TCAN with either an alcohol or thiol and a subsequent elimination step with base would provide the cyanate or thiocyanate respectively. This would provide a new simple technique, avoiding cyanogen bromide in the case of cyanates or more complex reactions with toxic metal salts in the case of thiocyanate synthesis.

The reactivity of TCAN with alcohols and thiols was already established by Yavari *et al.*[5] In their work alknyl imidates and thioimidates were synthesised via coupling reactions of trichloroimidates and terminal alkynes. (Scheme 3.2).



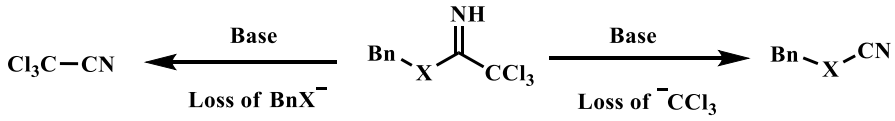
Scheme 3.2. The reaction of TCAN with alcohols and thiols and subsequent coupling reaction

With this precedent, benzyl alcohol **99** was subjected to the standard conditions for *N*-cyanation with TCAN **56** however none of the desired cyanate was observed showing only starting materials. Moreover, analysis of the first step in isolation showed no reactivity between benzyl alcohol **99** and TCAN **56** in MeCN at room temperature overnight. Conditions developed by Ionescu and co-workers were then tested. Their synthesis included catalytic DBU as a base, and provided the desired benzyl 2,2,2-trichloroacetimidate **100** in 99% yield (Scheme 3.3).[6]



Scheme 3.3. Ionescu and co-workers acetimidate synthesis

With acetimidate **100** synthesised, attention turned to testing a range of bases for the elimination. Bases tested were NaO*t*Am, NaH, KHMDS. In each case it was found that the leaving group in the elimination was phenylmethanolate, yielding benzyl alcohol **99** and trichloroacetonitrile **56** (Scheme 3.4).

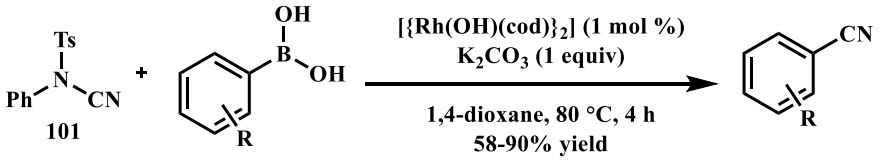


Scheme 3.4. Possible elimination routes

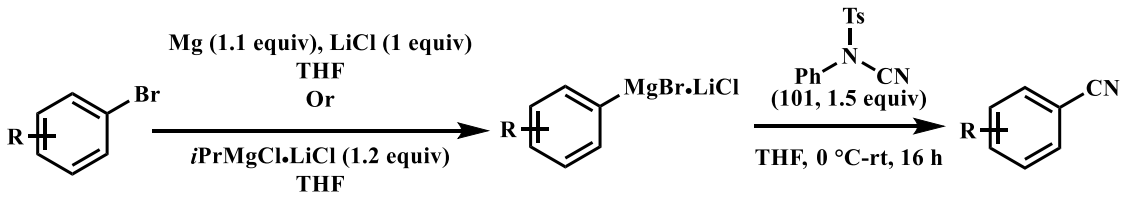
The observed reactivity can be understood by the relative pK_a of each leaving group. The pK_a of chloroform in H_2O is reported as 25. However, benzyl alcohol and benzyl mercaptan are 15.4 and 10.1 respectively and therefore phenylmethanolate and phenylmethanethiolate are better leaving groups.[7] This is because when the labile proton is lost from either benzyl alcohol or benzyl mercaptan, the anionic oxygen or sulfur species is more stable than the trichloromethyl anion. With this result investigations of alternative cyanating agents were started.

3.3 *N*-Cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS)

NCTS **101** has often found itself the reagent of choice for cyanation reactions *via* an N-CN bond cleavage pathway.[8,9] Despite first being reported by Kurzer in 1949, NCTS has only recently found use in modern synthetic chemistry.[10] In 2011 Beller *et al*. disclosed a rhodium catalysed synthesis of aryl nitriles (Scheme 3.5).[11] In the same year they showed that aryl nitriles could also be synthesised using aryl Grignard reagents (Scheme 3.6).[12]



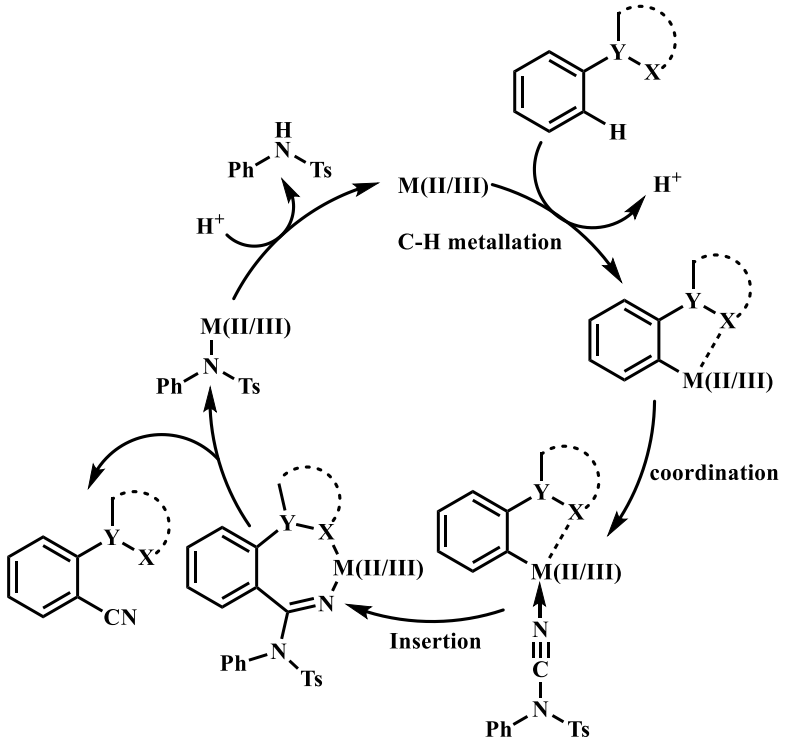
Scheme 3.5. Synthesis of aryl nitriles using NCTS as the cyano source



Scheme 3.6. Synthesis of aryl nitriles with Grignard reagents using NCTS as the cyano source

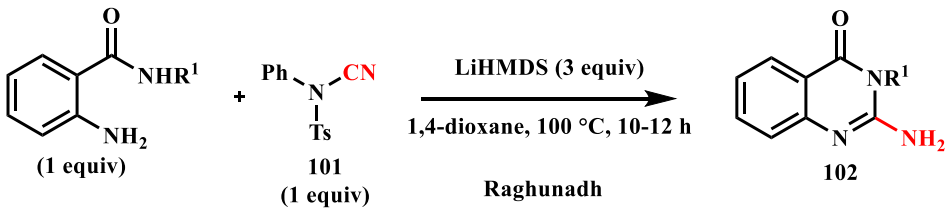
Since these pioneering studies utilising NCTS, many new techniques have been developed using NCTS. For example, a range of C-H cyanation reactions utilising transition metal catalysts such as rhodium, cobalt and ruthenium have been developed.[13–21]

A general mechanism for C-H cyanation with rhodium, cobalt and ruthenium with NCTS is shown (Scheme 3.7).[9] The reaction begins with C-H metalation guided by the directing group prior to coordination of the terminal nitrogen of the cyanamide before insertion. Formation of the C-H cyanated product occurs after elimination. NCTS **101** reacts *via* an N-CN bond cleavage pathway. C-H cyanation using NCTS provides an excellent and modern alternative to reactions such as the Rosenmund-von Braun reaction using copper cyanide with aryl iodides or the Sandmeyer reaction with aryl diazoniums to form aryl nitrile compounds.[22–24]

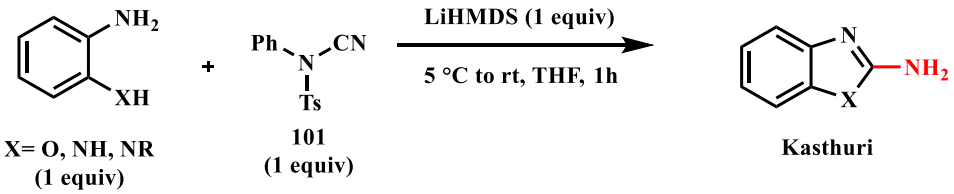


Scheme 3.7. General mechanism for C-H cyanation with NCTS

In 2011 Ragunadh *et al.* reported the use of NCTS **101** in *N*-cyanation where they were able to access quinazolines **102** upon intramolecular cyclisation of a cyanamide intermediate (Scheme 3.8).[25] In 2015 Kasthuri *et al.* also reported the synthesis of 2-aminobenzoxazoles and 2-aminobenzimidazoles in a similar fashion (Scheme 3.9).[26]

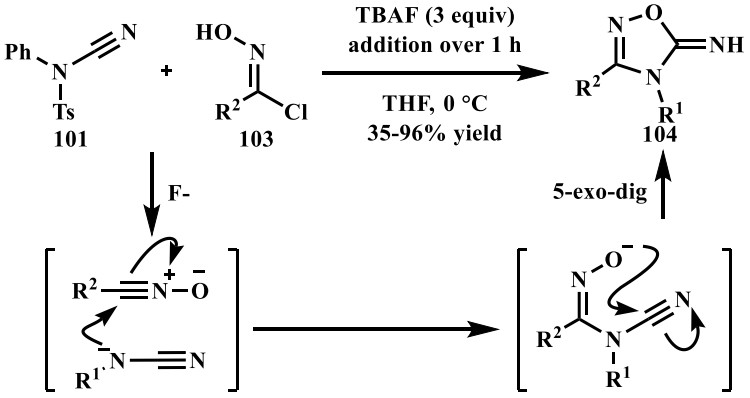


Scheme 3.8. Synthesis of quinazolines with NCTS



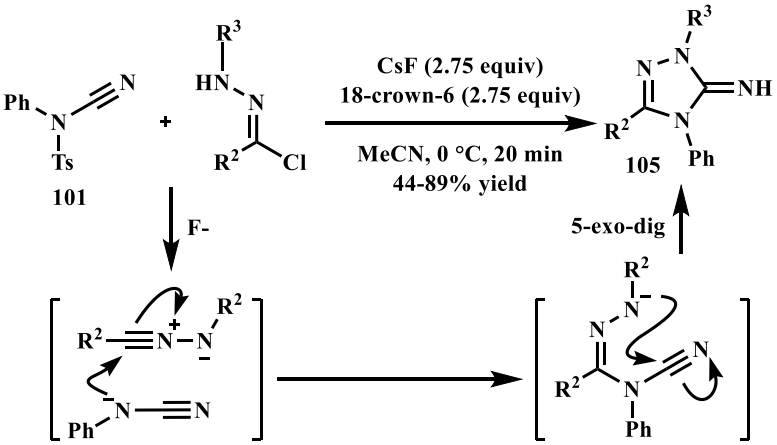
Scheme 3.9. Synthesis of 2-aminobenzoxazoles and 2-aminobenzimidazoles with NCTS

In 2016 Sharma *et al.* demonstrated the synthesis of 1,2,4-oxadiazol-5(4H)-imines with NCTS and nitrile oxides (Scheme 3.10).[27] The nitrile oxide was formed *in situ* from fluoride mediated dehydrochlorination of the *N*-hydroximoyl chloride **103**, the fluoride was also used to remove the tosyl group of NCTS **101** to form the second reactive species. With both reactive species formed *in situ* a 1,3-dipolar cycloaddition readily occurs to form the desired 1,2,4-oxadiazol-5(4H)-imines **104**. At the time of this work only the 2016 publication from Sharma reported a desulfonylative reaction pathway with NCTS.



Scheme 3.10. Synthesis of 1,2,4-oxadiazol-5(4H)-imines from cyanamides

In 2018 the scope of this reactivity was further developed to include the synthesis of 1,2,4-triazol-3-imines **105** (Scheme 3.11).[28] Again Sharma and co-workers utilised the desulfonylative reactivity pathway of NCTS **101** to form the reactive cyanamide species, this time intercepting a nitrile imine 1,3-dipole. A range of 1,2,4-triazol-3-imines could be obtained in good to excellent yields in 20 minutes.

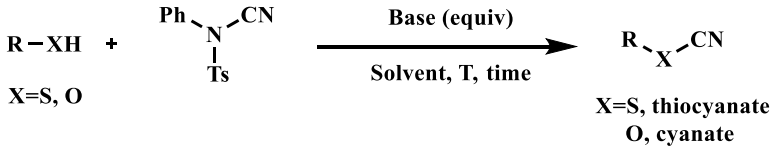


Scheme 11. Synthesis of 1,2,4-triazol-3-imines from cyanamides

3.4 Results and discussion

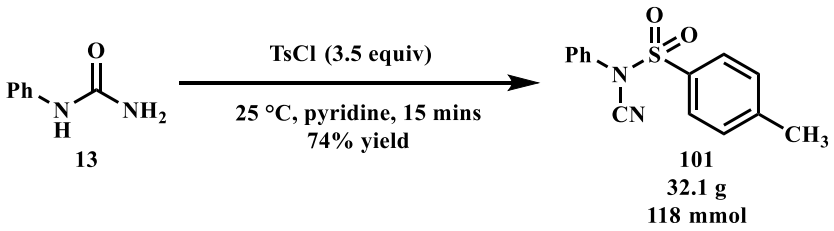
3.4.1 Introduction

NCTS has been used in a variety of different ways to afford a range of interesting and valuable compounds. Despite the broad investigation of NCTS reactivity that had already been reported, interest turned to how NCTS reacts with oxygen or sulfur nucleophiles. It was proposed that reaction with alcohols or thiols would provide acetimidates and thioacetimidates, *via* attack at carbon which could then undergo elimination in the presence of a base to form the cyanate or thiocyanate. This would provide another simple cyanation technique avoiding cyanogen bromide or techniques with operational complexity (Scheme 3.12).



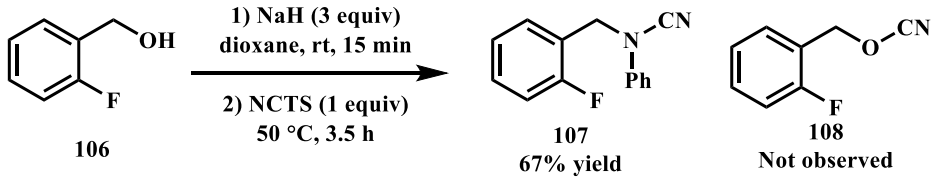
Scheme 3.12. Proposed reaction of alcohols and thiols with NCTS

Another reason for investigating the chemistry of NCTS is that it can be readily synthesised from phenyl urea **13** – a cheap and abundant starting material with low toxicity.[10] The procedure is also very simple and NCTS can be isolated on multiple gram scale after purification in under 1 hour (Scheme 3.13). NCTS is also a bench stable crystalline solid and cyanogen bromide is avoided in the synthetic procedure.



Scheme 3.13. Synthesis of NCTS

A test reaction with 2-fluorobenzyl alcohol **106** was undertaken. 2-fluorobenzyl alcohol **106** was stirred with 3 equivalents of NaH in dioxane for 15 minutes. After 15 minutes one equivalent of NCTS **101** was added and the reaction was heated to 50 °C and stirred for 3.5 hours (Scheme 3.14). After this time all NCTS had been consumed as visible by TLC. After purification by silica gel column chromatography a single product **107** was isolated in 67% yield.

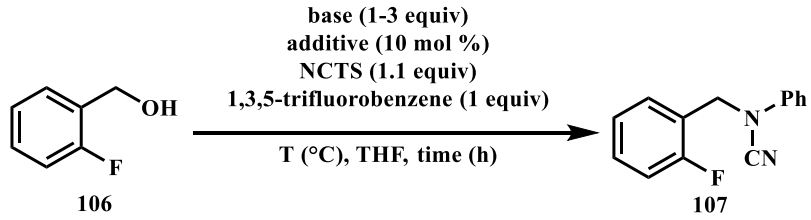


Scheme 3.14. Initial reaction with NCTS did not yield the proposed product

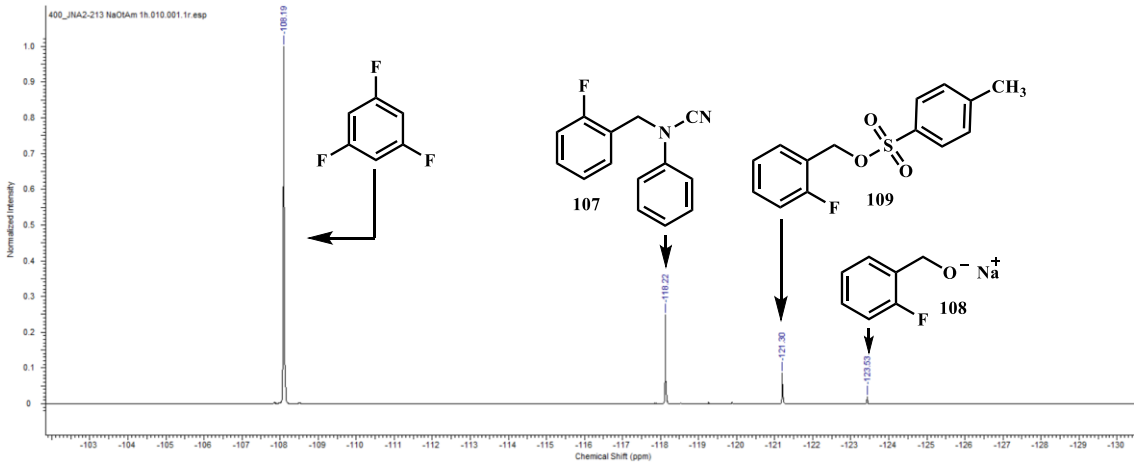
Instead of the proposed cyanate **108** a cyanamide *N*-(2-fluorobenzyl)-*N*-phenylcyanamide **107** was isolated in good yield. The overall transformation that occurs is an alcohol being substituted with a cyanamide or deoxycyanamidation - which has not been reported previously. Despite not achieving *O*-cyanation this reaction proved interesting and a potentially useful method to synthesise cyanamides from alcohol starting materials. As a valuable transformation, the reaction would be optimised, the scope investigated, and the mechanism probed.

3.5 Optimisation

To optimise the deoxycyanamidation reaction 2-fluorobenzyl alcohol **106** was used as the parent substrate due to the ability to monitor the reactions by *in-situ* ^{19}F NMR (Scheme 3.15). Each reaction vial was loaded with 2-fluorobenzyl alcohol **106** (110 µL, 1 mmol, 1 equiv) followed by THF (5 mL), base (1.1, 2 or 3 equiv) and additive as required (10 mol %) and stirred for 15 minutes at the desired temperature. NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) and 1,3,5-trifluorobenzene (104 µL, 1 mmol, 1 equiv) as internal standard were added and the reaction stirred at a constant temperature. At 5 time points (T1 ≈ 30 mins, T2 = 1 h, T3 = 3 h, T4 = 6 h, T5 = 23 h) aliquots were taken and added to a standard borosilicate glass 178 mm length, 4.97 mm O.D. x 4.20 mm I.D. NMR tube and diluted with $CDCl_3$. The ratio of product **107** to other materials was observed by ^1H NMR. In this case other materials refers to the population of starting material **106**, alkoxide **108** or tosylate intermediate **109**. A representative NMR spectrum is shown where each compound is visible with known chemical shift values having been previously synthesised and characterised (Spectrum 3.1).



Scheme 3.15. Optimisation procedure for deoxycyanamidation



Spectrum 3.1. Identification of each species present by 19F NMR

Entry	Base (eq.)	Additive (mol %)	[SM] /mol dm-3	T / °C	**T1 = 30 min 107:other /%**	**T2 = 1 h 107:other /%**	**T3 = 3 h 107:other /%**	**T4 = 6 h 107:other /%**	**T5 = 23 h 107:other /%**
1	NaH (3)	-	0.2	50	84 : 0	84 : 0	84 : 0	84 : 0	84 : 0
2	NaH (3)	-	0.2	rt	71 : 18	76 : 12	81 : 0	81 : 0	81 : 0
3	NaH (2)	-	0.2	rt	44 : 32	50 : 33	72 : 11	80 : 0	80 : 0
4	NaOtAm (2)	-	0.2	rt	42 : 30	42 : 23	67 : 12	78 : 0	78 : 0
5	KOtBu (2)	-	0.2	rt	39 : 41	52 : 30	65 :20	85 : 0	85 : 0
6	LHMDS (2)	-	0.2	rt	44 : 40	55 : 17	75 : 0	75 :0	75 : 0
7	KHMDS (2)	-	0.2	rt	0 : 100	0 :100	0 : 100	0 : 100	0 : 100
8	DBU (2)	-	0.2	rt	11 : 82	33 : 63	54 : 46	60 : 40	86 : 14
9	DBN (2)	-	0.2	rt	0 : 100	0 : 100	0 : 100	0 : 100	0 : 100
10	TBD (2)	-	0.2	rt	19 : 81	20 : 80	20 : 80	30 : 68	47 : 53
11	NaH (1.1)	-	0.2	rt	34 : 53	43 : 46	52 : 36	56 : 32	62 : 35
12	NaO*t*Am (1.1)	-	0.2	rt	33 : 53	39 : 43	50 : 36	55 : 32	59 : 34
13	NaH (1.1)	-	0.2	50	65 : 26	66 : 25	67 : 24	68 : 21	71 : 19
14	NaO*t*Am (1.1)	-	0.2	50	58 : 30	60 : 29	59 : 33	61 : 28	66 : 28
15	NaH (1.5)	-	0.2	rt	64 : 23	75 : 18	89 : 9	89 : 9	89 : 9
16	NaO*t*Am (1.5)	-	0.2	rt	63 : 33	68 : 24	88 : 10	88 : 10	88 : 10
17	DBU (2)	-	1	rt	67 : 33	69 : 31	77 : 23	77 : 23	77 : 23
18	NaO*t*Am (2)	TBAB (10)	0.2	rt	89 : 11	99 : 1	100 : 0	100 : 0	100 : 0
19	**NaO*t*Am (2)**	**TBAI (10)**	**0.2**	**rt**	**99 : 1**	**100 : 0**	**100 : 0**	**100 : 0**	**100 : 0**
20	NaO*t*Am (1.1)	TBAB (10)	0.2	rt	46 : 54	57 : 43	61 : 39	63 : 37	63 : 37
21	NaO*t*Am (1.1)	TBAI (10)	0.2	rt	52 : 48	62 : 38	68 : 32	70 : 30	70 : 30
22	NaO*t*Am (2)	$TBABF_4$ (10)	0.2	rt	92 : 8	100 : 0	100 : 0	100 : 0	100 : 0
23	NaO*t*Am (2)	$TBAPF_6$ (10)	0.2	rt	90 : 10	100 : 0	100 : 0	100 : 0	100 : 0
24	NaO*t*Am (2)	NaI (10)	0.2	rt	90 : 10	100 : 0	100 : 0	100 : 0	100 : 0

Table 3.1. Optimisation data for the deoxycyanamidation process

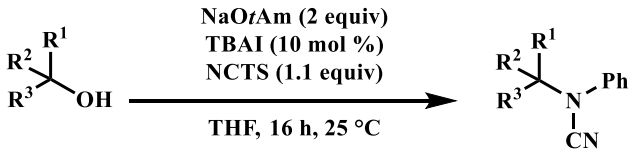
Investigations began with the original conditions used when this reaction was discovered (Table 3.1, entry 1). Only 84% NMR yield of **107** was achieved after 23 h reaching this maximum after only 30 minutes, the remainder of the material in the reaction was also not identifiable as the alkoxide or tosylate intermediate **109**. Running the reaction with sodium hydride at room temperature slowed the reaction and again neither provided a high NMR yield (Table 3.1, entries 2 and 3). In entries 4 to 10 a range of different bases were tested with 2 equivalents. NaO*t*Am and KO*t*Bu work equally well to provide a maximum 85% NMR yield after 6 h, however the ^{19}F NMR spectrum for KO*t*Bu showed significant unidentifiable impurities when compared to NaO*t*Am. LHMDS (1.0 M THF) did not provide such high NMR yield with a maximum of 75% reached after 3 h (Table 3.1, entry 6). KHMDS (1.0 M toluene) provided only small amounts of the alkoxide and therefore the NMR yield was low (Table 3.1, entry 7). This may be because the KHMDS

was supplied as a solution in toluene rather than THF. Amidine base DBU gave a maximum NMR yield of 86% after 23 h, however the process was significantly slower than previous entries (Table 3.1, entry 8). When DBN was used no alkoxide could be observed and the reaction did not proceed (Table 3.1 entry 9). Guanidine base TBD only provided 47% maximum NMR yield after 23h (Table 3.1, entry 10)

No reaction had reached the desired 100% conversion. A possible explanation was inefficient mixing observed in the reaction vials. In cases with a metal salt base (NaO*t*Am, NaH, KO*t*Bu) the reactions were not homogeneous, and the stirrer-hotplate struggled to turn the stirrer bar and often couldn't. The equivalents of base were then lowered to 1.1 or 1.5 equivalents (Table 3.1, entries 11-15) to see if higher NMR yield could be achieved aware of the fact only 1 equivalent of base should be necessary to form the alkoxide and fewer metal salts could free up the solution to stir more efficiently. With 1.1 equivalents the reactions were slower and NaH reached a 62% maximum NMR yield at T= 23 h (Table 3.1, entry 11) and NaO*t*Am (Table 3.1, entry 12) reached a 59% maximum NMR yield at T= 23 h. The reactions with 1.5 equivalents of NaH (Table 3.1, entry 12) and NaO*t*Am (Table 3.1, entry 13) achieved maximum NMR yields 89 and 88% respectively. Lowering the loading of base did not increase the NMR yield sufficiently, again a significant issue with these reactions was poor mixing.

With the heterogeneity of the reaction mixture the most significant issue, a range of phase transfer catalysts were tested to aid stirring. At this point, NaH was also discounted due to safety implication especially when used on a large scale.[29] NaO*t*Am was equally as effective as NaH so it was decided this base was to be tested with the phase transfer catalysts. A series of tetrabutylammonium salts were tested (Table 3.1, entries 17-22) with 10 mol % loading. It was evident from observing the reaction mixtures that the addition of the phase transfer catalysts was providing improved reaction homogeneity and therefore better stirring/mixing. The reactions proved more efficient with the addition of tetrabutylammonium bromide providing 100% NMR yield in 3 hours (Table 3.1, entry 17). Tetrabutylammonium tetrafluoroborate and tetrabutylammonium hexafluorophosphate (Table 3.1, entries 21 and 22) achieved 100% NMR yield after 1 hour. However, tetrabutylammonium iodide showed greater reactivity with 99% NMR yield after 30 minutes (Table 3.1, entry 18).[30] Sodium iodide was also tested and this reaction reached 100% NMR yield after 1 hour (Table 3.1, entry 23). The role of the additive and how it improves the rate of the reaction will be discussed in greater detail in

section 3.7. The optimised conditions for the process were chosen as entry 18 (Table 3.1). The reactions would be run with 1 equivalent of the alcohol and stirred in THF ([alcohol] = 0.2 mol dm^{-3}), with NaO*t*Am (2 equiv) and TBAI (10 mol %) for 15 minutes at room temperature. The requisite sulfonamide (1.1 equiv) would then be added and the reaction would be stirred for 16 hours (overnight) at room temperature. A 16-hour reaction time was chosen so that the different reactivities of substrates should go to completion and for operational simplicity (Scheme 3.16).



Scheme 3.16. Optimised conditions for deoxycyanamidation

3.6 Mechanistic investigations

The preliminary proposal for the mechanism could follow two pathways (Figure 3.1). Pathway 1 *via* alkoxide attack at carbon and subsequent intramolecular *N*- to *O*- sulfonyl transfer. Pathway 2 was *via* intermolecular *N*- to *O*- sulfonyl transfer *via* direct attack of the alkoxide at sulfur. Computational data provided an insight into the mechanism. The data revealed that attack at carbon forming a carbamimidate (pathway 1) is the lower energy pathway with an activation energy of 24.3 kJ mol^{-1}. Attack at sulfur has an activation energy of 39.5 kJ mol^{-1} (Pathway 2) which is 15.8 kJ mol^{-1} greater than attack at carbon. However, the large energy barrier associated with intramolecular *N*- to *O*- sulfonyl transfer to phenyl cyanamide and methyl tosylate (Ga = 161.7 kJ mol^{-1}) is unlikely to be overcome at 25 °C. Furthermore, the lack of any observable products resulting from *O*-cyanation (the lowest energy pathway from the carbamimidate intermediate) suggests that the observed sulfonyl transfer proceeds via direct attack at S (pathway 2).

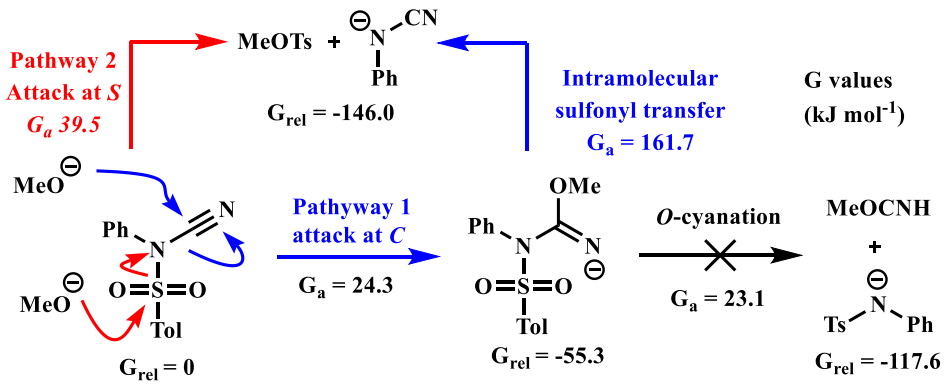
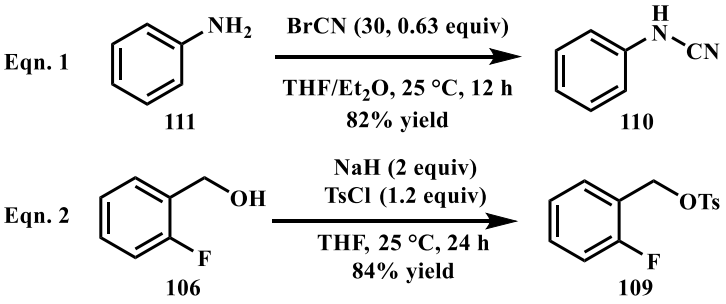


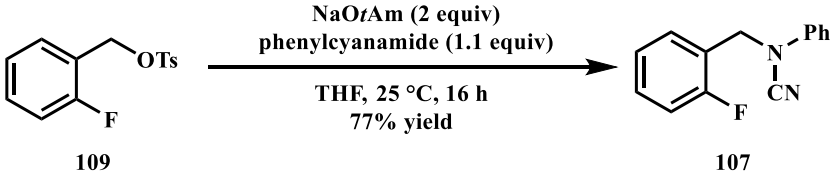
Figure 3.1. Computational investigation of the deoxycyanamidation mechanism

To further investigate the mechanism the intermediate products were synthesised. It would be tested whether it was possible to access the cyanamides by reaction of these compounds. The first intermediate compound synthesised was phenyl cyanamide **110** (Scheme 3.17, Eqn 1) which was synthesised using cyanogen bromide **30** (0.63 equiv) and aniline **111** in 82% yield. Secondly 2-fluorobenzyl 4-methylbenzenesulfonate **109** was synthesised by tosylation of 2-fluorobenzyl alcohol **106** with sodium hydride in 84% yield (Scheme 3.17, Eqn 2). This compound was observable in the ^{19}F NMR spectra as discussed in section 3.5.



Scheme 3.17. The synthesis of phenylcyanamide and 2-fluorobenzyl 4-methylbenzenesulfonate

2-fluorobenzyl 4-methylbenzenesulfonate **109** was then reacted with phenylcyanamide **110** (1.1 equiv) in the presence of NaO*t*Am (2 equiv) in THF. The reaction yielded the expected cyanamide **107** product in 77% yield, confirming the potential involvement of these intermediates in the reaction mechanism (Scheme 3.18).



Scheme 3.18. The reaction of the proposed intermediates to form the cyanamide

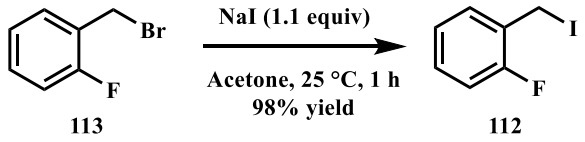
3.7 Role of additive

The additive phase transfer catalyst in this reaction was very important to obtain a high yield. It was readily observed that in the absence of this additive the reaction would not stir effectively, and yields were low. To investigate the role of the additive *in-situ* ^{19}F NMR was used. In the absence of any additive the reaction would proceed to 42% NMR yield after 30 minutes (Table 3.2, entry 1). However, on addition of 10 mol % tetrabutyl ammonium bromide this increased to 89% NMR yield after the same time period (Table 3.2, entry 2). Subsequently tetrabutyl ammonium tetrafluoroborate (Table 3.2, entry 3) and tetrabutyl ammonium hexafluorophosphate (Table 3.2, entry 4) were tested and these provided 92 and 90% NMR yield after 30 minutes respectively. Further acceleration of the reaction was observed when tetrabutyl ammonium iodide (Table 3.2, entry 5) was used.[30] This reaction proceeded to 99% conversion after 30 minutes. It was proposed that the iodine counter ion could exchange with the tosyl group of the 2-fluorobenzyl 4-methylbenzenesulfonate **109** producing 1-fluoro-2-(iodomethyl)benzene **112**, a more reactive species. To test this further NaI was added as an additive and it was found that the reaction containing 10 mol % of this additive reached 90% NMR yield after 30 minutes (Table 3.2, entry 6). NaI should not behave as a phase transfer catalyst as cation exchange will not occur, however it can promote conversion to 1-fluoro-2-(iodomethyl)benzene **112.**

		T1 = 30 min	T2= 1 h	T3= 3 h	T4= 6 h	T5 = 23h
Entry	Additive (10 mol %)	**107**:other/ %	**107**:other / %	**107**:other / %	**107**:other / %	**107**:other / %
1	No additive	42 : 30	42 : 23	67 : 12	85 : 0	85 : 0
2	TBAB	89 : 11	99 : 1	100 : 0	100 : 0	100 : 0
3	TBA BF_4	92 : 8	100 : 0	100 : 0	100 : 0	100 : 0
4	TBA PF_6	90 : 10	100 : 0	100 : 0	100 : 0	100 : 0
5	TBAI	99 : 1	100 : 0	100 : 0	100 : 0	100 : 0
6	NaI	90 : 10	100 : 0	100 : 0	100 : 0	100 : 0

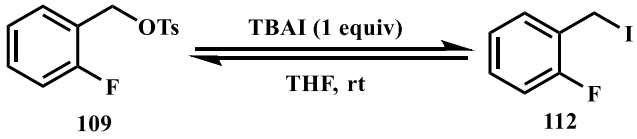
Table 3.2. Table showing the effect of additive on the deoxycyanamidation process

To further verify if the proposed formation of 1-fluoro-2-(iodomethyl)benzene **112** was occurring it was first synthesised (Scheme 3.19) from 1-(bromomethyl)-2-fluorobenzene **113** by a Finkelstein reaction to obtain characteristic data.[31]



Scheme 3.19. Synthesis of 1-fluoro-2-(iodomethyl)benzene

2-fluorobenzyl 4-methylbenzenesulfonate **109** was then stirred with 1 equivalent of TBAI in THF (Scheme 3.20). The reaction was monitored by ^{19}F NMR at different time points (T= 30 min, T= 1 h, T= 3 h, T= 6 h and T= 23 h) to observe the proposed equilibrium (Scheme 3.20)



Scheme 3.20. Proposed equilibrium between 2-fluorobenzyl 4-methylbenzenesulfonate and 1-fluoro-2-(iodomethyl)benzene in the presence of TBAI

	Reaction composition/ %		
Time	2-fluoro-4- methylbenzene sulfonate **109** /%	1-fluoro-2-(iodomethyl)benzene **112** /%	Other/ %
30 min	14	86	0
1 h	16	84	0
3 h	16	84	0
6 h	16	84	0
23 h	16	74	10

Table 3.3. The reaction composition as measured by ^{19}F NMR of the equilibrium in scheme 35

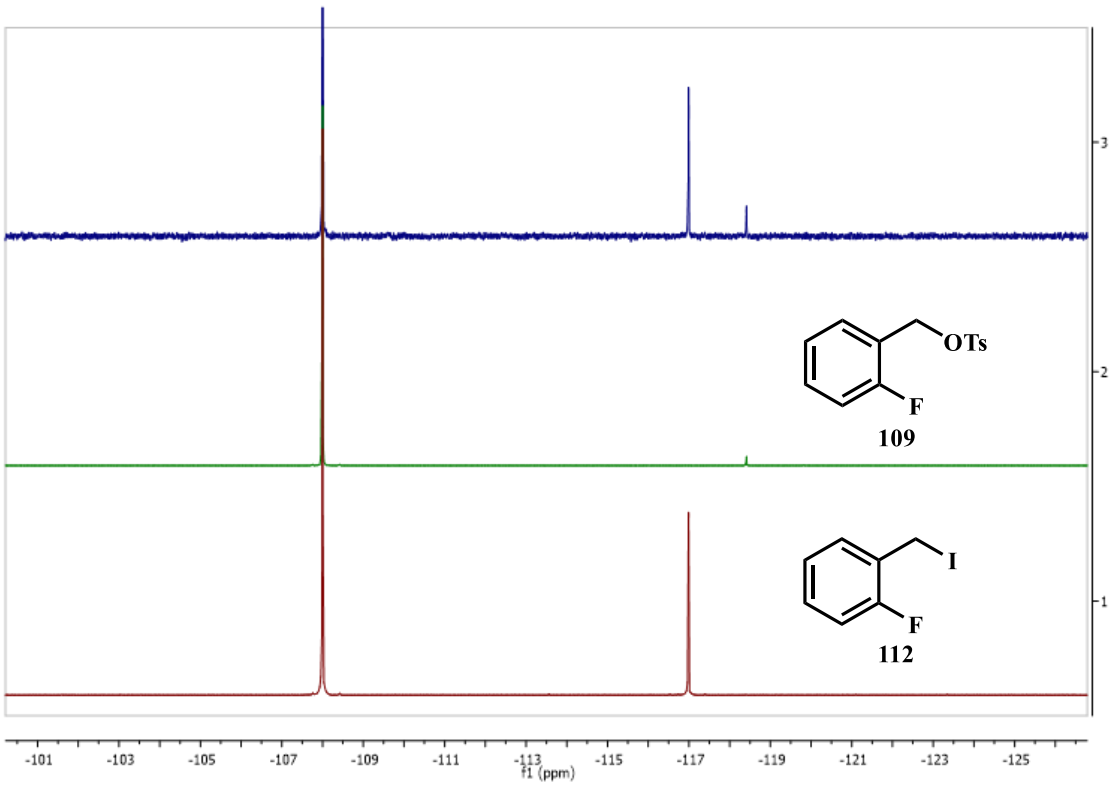


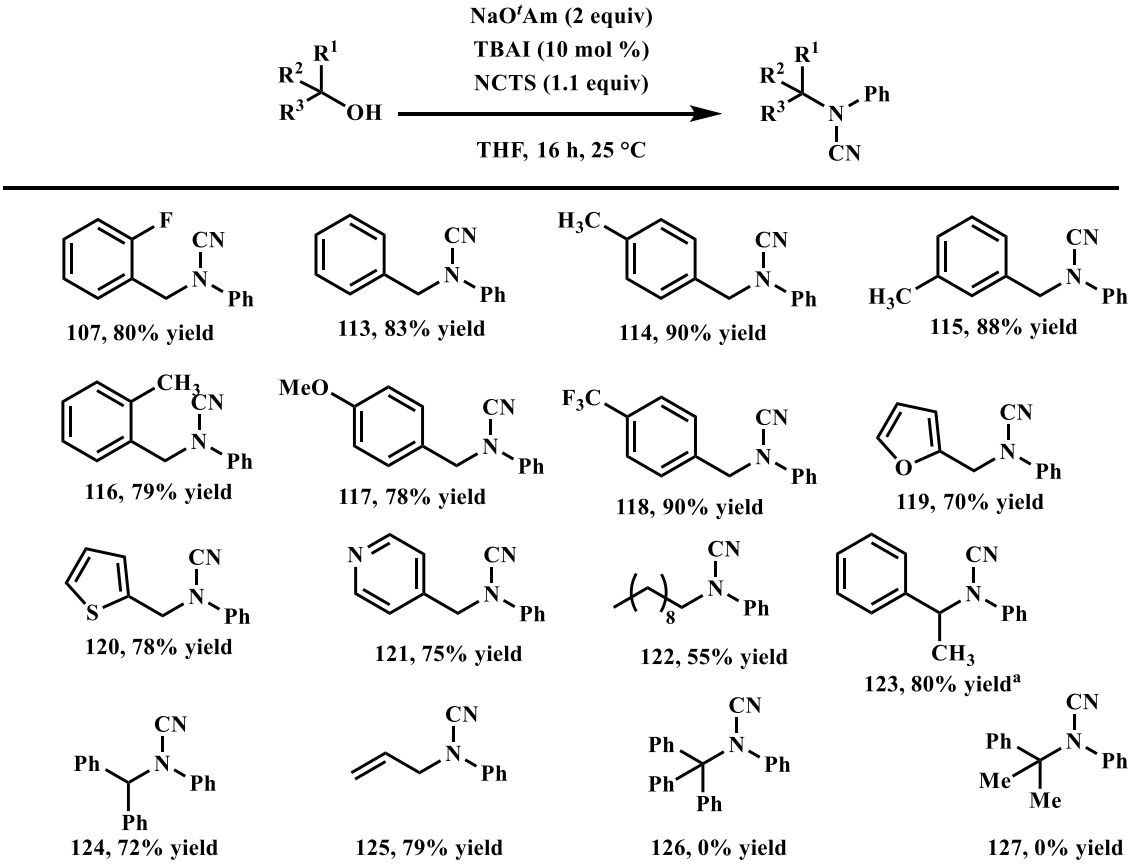
Figure 2. The NMR of the equilibrium reaction in scheme 22 at 3 h

The NMR spectra showed considerable conversion to 1-fluoro-2-(iodomethyl)benzene **112** from 2-fluorobenzyl 4-methylbenzenesulfonate **109**. With 1,3,5-trifluorobenzene (σ -108 ppm) as standard it was observed that 1-fluoro-2-(iodomethyl)benzene **112** had formed in 84% NMR yield after 1 hour. This NMR yield was stable, although after 23 hours some unidentifiable products did arise on the NMR spectra. The enhanced reaction rate when TBAI was used as an additive is attributed to both phase transfer catalysis (cation exchange) and interconversion to the more reactive 1-fluoro-2-(iodomethyl)benzene **112**.

3.8 Substrate scope

3.8.1 Alcohol scope

With the reaction optimised the generality of deoxycyanamidation was then tested on a range of substrates to obtain a variety of cyanamide compounds (Scheme 3.21).

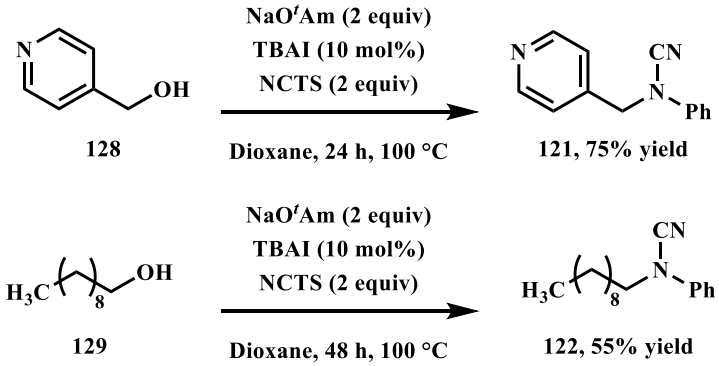


Scheme 3.21. Alcohol substrate scope for deoxcyanamidation, [a] 2 equiv NCTS, 100 °C, dioxane

The substrate investigation began with a series of aryl substituted benzyl alcohols. The product of the optimisation substrate *N*-(2-fluorobenzyl)-N-phenylcyanamide **107** was isolated in 80% yield. *N*-Benzyl-*N*-phenylcyanamide **113** was isolated in 83% yield. A series of methyl substituted benzyl alcohols all work well (**114**, 90% yield and **115**, 88% yield). However, the more hindered *N*-(2-methylbenzyl)-*N*-phenylcyanamide **116** has a slightly reduced isolated yield of 79%. An electron rich benzyl alcohol 4-methoxybenzyl alcohol provided **117** with a 78% isolated yield. An electron poor benzyl alcohol, 4-trifluoromethyl benzyl alcohol can be converted to cyanamide **118** in an excellent 90% yield. Furfuryl alcohol and thiophen-2-ylmethanol can be converted to the cyanamides **119** and **120** in 70% and 78% respectively. Secondary alcohols 1-phenylethan-1-ol and diphenylmethanol can also be converted to the respective cyanamides (**123** and **124**) in

good yield. However, 1-phenylethan-1-ol requires 2 equivalents of NCTS in dioxane at 100 °C for 24 h to achieve an isolated yield of the respective cyanamide **123** in 80% yield. An increase in steric hindrance may account for the necessity of modified conditions, as the rate of S_N2 reactions is strongly affected by steric bulk at the reactive site. Allyl alcohol tolerates the system well and the cyanamide *N*-allyl-*N*-phenylcyanamide **125** can be isolated in 79% yield.

N-Phenyl-*N*-(pyridin-4-ylmethyl)cyanamide **121** required harsher reaction conditions of 2 equivalents of NCTS in dioxane at 100 °C and was obtained in 75% isolated yield from pyridin-4-ylmethanol **128** (Scheme 3.22). Alkyl alcohol decanol **129** was employed to form **122,** requiring 2 equivalents of NCTS in dioxane at 100 °C for 48 h to obtains a 55% isolated yield (Scheme 3.22). The mass balance for the reaction with decanol was unreacted starting material.



Scheme 3.22. Elevated reaction conditions for 4-pyridinemethanol and decanol

A limitation of the reaction is tertiary alcohols, it was found that these more hindered alcohols, triphenylmethanol to form **126** and 2-phenylpropan-2-ol to form **127** do not react with NCTS. The harsher reaction conditions developed for several of the substrates were tested however only starting materials were returned. In an S_N2 reaction steric hindrance around site of reaction has significant effects. In general, tertiary centres are too hindered to undergo S_N2 reactions. However, it seems that the alcohols simply do not undergo *N*- to *O*- sulfonyl transfer.

In addition to spectroscopic data for the products, the structures above were also ratified by X-ray diffraction of *N*-(4-methylbenzyl)-*N*-phenylcyanamide **114**, the single crystal was obtained via vapour diffusion of hexane into *N*-(4-methylbenzyl)-*N*-phenylcyanamide **114** dissolved in $CDCl_3$ (Figure 3.3).

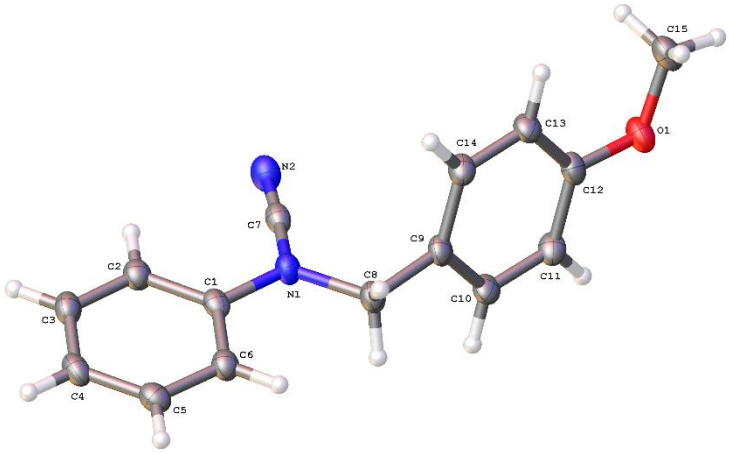
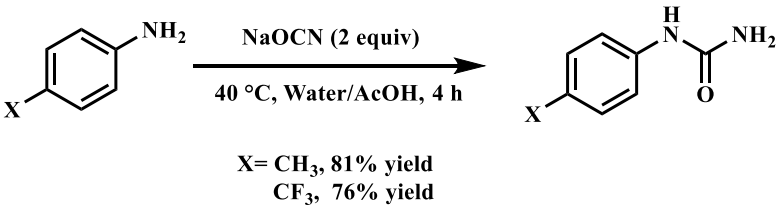


*Figure 3.3. Crystal structure of N-(4-methylbenzyl)-N-phenylcyanamide **114** determined by X-ray diffraction*

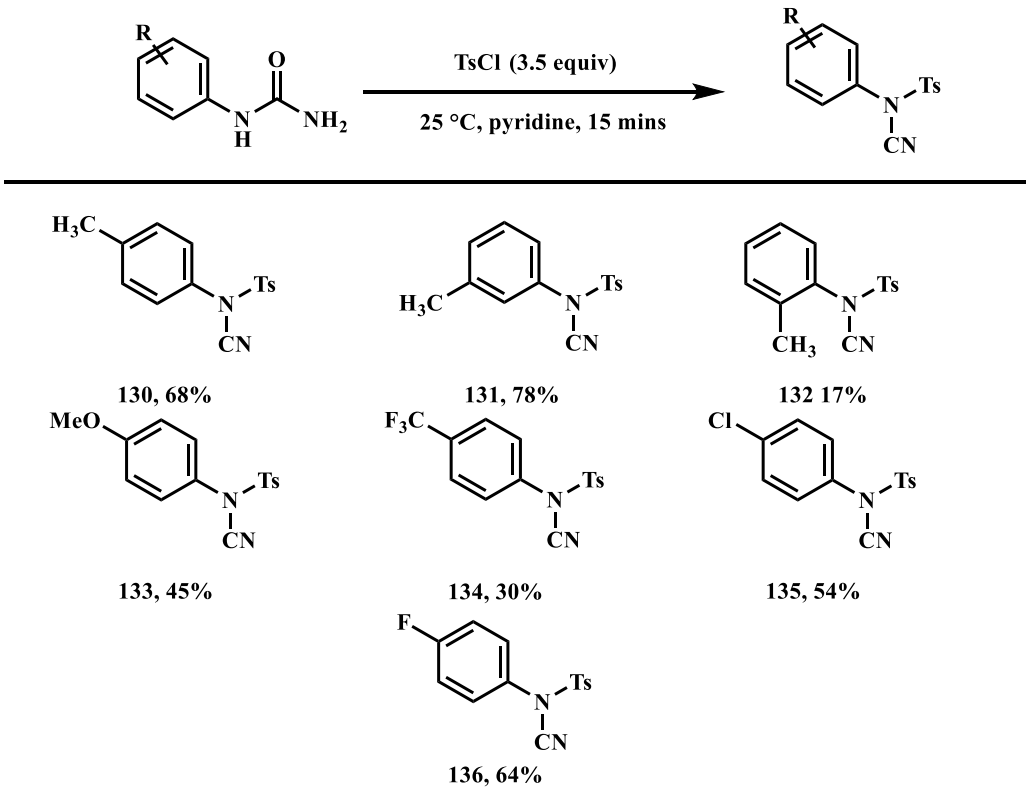
3.8.2 Sulfonamide scope

Having successfully demonstrated deoxycyanamidation with a variety of primary and secondary alcohols, the reaction scope with respect to the sulfonamide was then investigated. Under the standard reaction conditions with benzyl alcohol it was found that a range of *N*-aryl substituents within the sulfonamide could be incorporated, giving aryl/alkyl cyanamides in excellent yields.

A range of NCTS derivates were synthesised and the general procedure for NCTS synthesis would be followed and therefore the aim was to synthesise the sulfonamides from a range of urea derivatives. Depending upon availability and price some ureas were required to be synthesised. This was achieved from the aniline with the desired substitution reacting with 2 equivalents of sodium cyanate (2 equiv) in water/AcOH (1:1) at 40 °C (Scheme 3.23).[32]



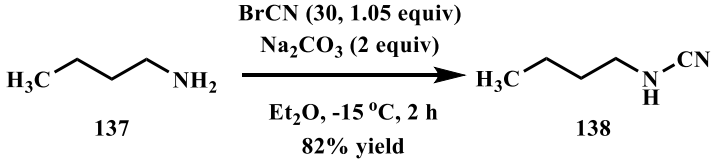
Scheme 3.23. Synthesis of phenylurea derivatives



Scheme 24. Synthesis of a range of NCTS derivatives from ureas

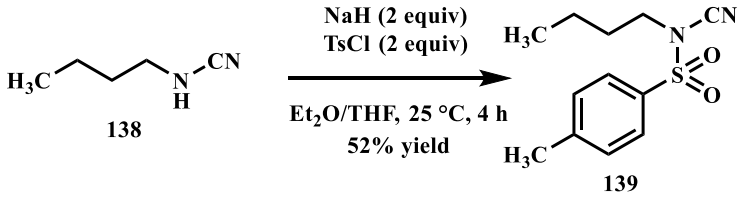
The synthesis of a range of NCTS derivates was successful with variable yields (**130-136**, 17-78% yield, Scheme 24). This process was not optimised for variation of the urea and therefore some yields were low. This is most likely because the isolation procedure where water is added to the reaction to precipitate the sulfonamide. The varying solubility of each compound may have caused low isolation in some cases. Despite this all compounds were isolated in sufficient yield to test at 1 mmol scale in the sulfonamide substrate scope.

An alkyl example, *N*-butyl-*N*-cyano-4-methylbenzenesulfonamide **136** was also attempted but it was found that alkyl ureas do not form the sulfonamide under the standard conditions. In this case butylamine **137** was treated with cyanogen bromide **30** (1.05 equiv) and sodium carbonate (2 equiv) in diethyl ether at -15 °C for 2 hours (Scheme 3.25).



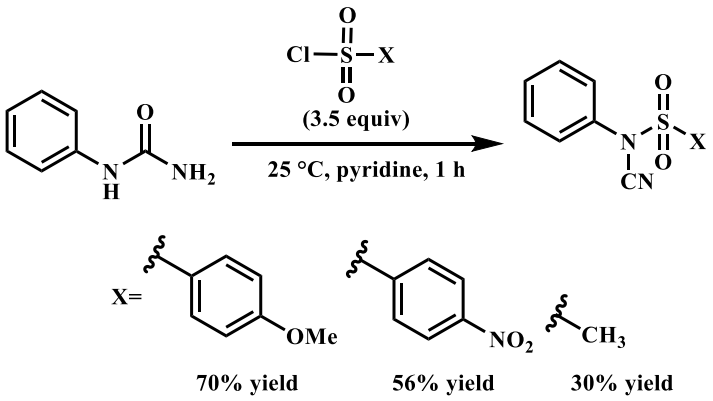
Scheme 3.25. Cyanation of N-butylamine towards N-butyl-N-cyano-4-methylbenzenesulfonamide

The secondary alkyl cyanamide **138** could then be treated with sodium hydride (2 equiv) and tosyl chloride (2 equiv) in diethyl ether/THF (10:1) at 25 °C for 4 hours to yield the sulfonamide **139** (Scheme 3.26).



Scheme 3.26. Tosylation of N-butylcyanamide to form N-butyl-N-cyano-4-methylbenzenesulfonamide

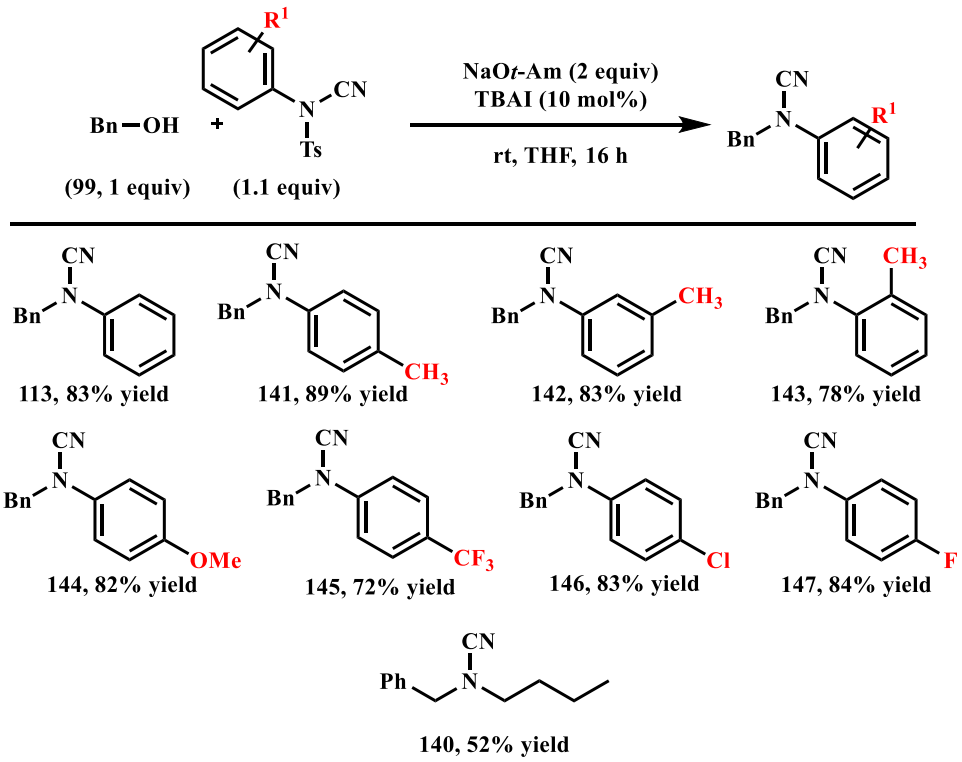
The effect of electronics within the *S* substituent of the sulfonamide would also be investigated. To do this phenylurea **13** was treated with 4-methoxybenzenesulfonyl chloride (electron donating), 4-nitrobenzenesulfonyl chloride (electron withdrawing). Methanesulfonyl chloride was also tested (Scheme 3.27).



Scheme 3.27. Synthesis of S-substituent modified NCTS derivatives

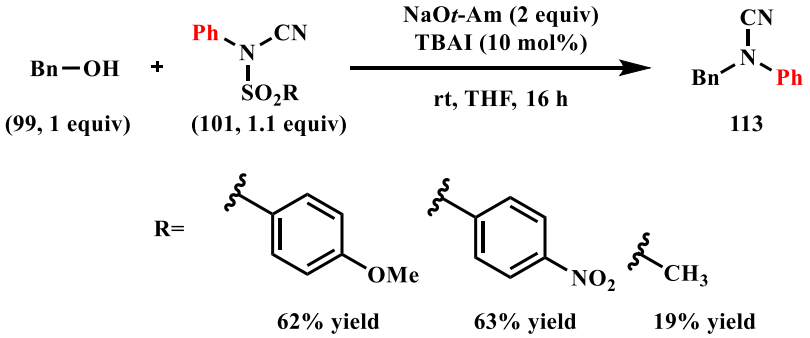
With the sulfonamides synthesised they were then subjected to the optimised reaction conditions using benzyl alcohol **99** as the standard alcohol substrate (Scheme 3.28). All sulfonamides worked well and provided a series of *N*-aryl substituted cyanamides in excellent yield. For example, 4-methyl (**141**), 3-methyl (**142**) and 2-methyl (**143**) substituents could be incorporated with 89, 83 and 78% yields respectively. *N*-Benzyl-*N*-(4-methoxyphenyl)cyanamide **144** bearing an electron donating methoxy group can be accessed in 82% yield. *N*-Benzyl-*N*-(4-(trifluoromethyl)phenyl)cyanamide **145** was obtained in 72% with an electron withdrawing trifluoromethyl group. Halogen containing *N*-(4-chlorophenyl)-*N*-cyano-4-methylbenzenesulphonamide **135** and *N*-(4-fluorophenyl)-*N*-cyano-4-methylbenzenesulphonamide **136** provided 4-chloro and 4-

fluoro *N*-aryl substituted cyanamides **146** and **147** in 83% and 84% respectively. Cyanamide **140** bearing an alkyl chain could be synthesised in 52% yield.



Scheme 3.28. Sulfonamide substrate scope

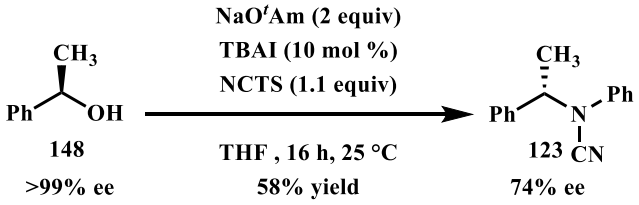
When the NCTS derivatives with modified *S* substituents were tested it was found that none improved upon NCTS **101** (Scheme 3.29). It was predicted that the nosyl sulfonamide would react more effectively due to the more electrophilic sulfur in this compound (electron withdrawn) however when this reaction was run there were significant solubility issues which may have negated any gains. A sulfonamide bearing a *p*-CF_3 electron withdrawing group could be tested, however this is prohibitively expensive to synthesise. The sulfonamide bearing an electron donating methoxy group provided the sulfonamide in 62% yield. *N*-cyano-*N*-phenylmethanesulfonamide worked poorly under the optimised conditions with the cyanamide isolated in 19% yield. The poor yield can be attributed to poor stability of the sulfonamide anion with the phenyl group replaced with a methyl group, the reaction is less favourable.



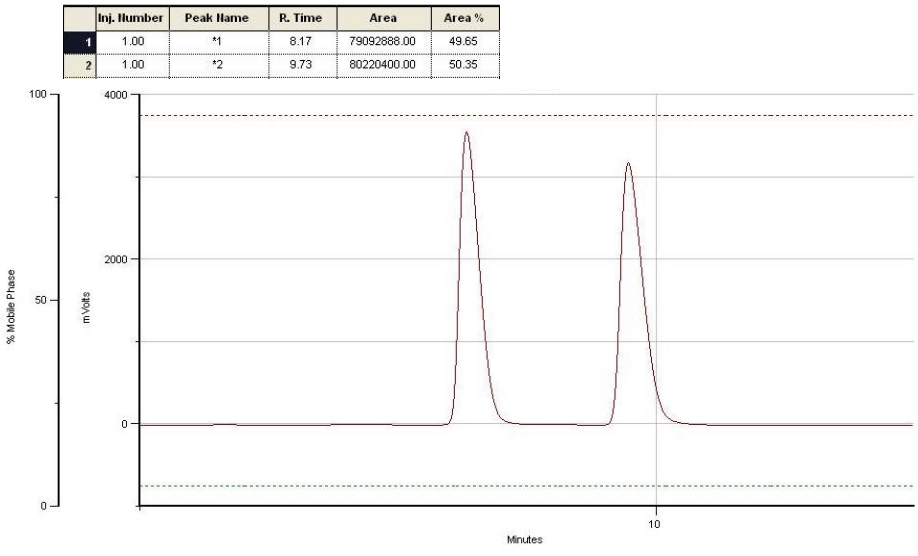
Scheme 3.29. Modification of the sulphonyl group

3.9 Stereospecificity

The stereospecificity of the reaction was investigated using commercially available (*R*)-1-phenylethan-1-ol **148**. It was proposed that the reaction should be stereospecific with inversion of stereochemistry in the S_N2 step. To test this hypothesis (*R*)-1-phenylethan-1-ol **148** was subjected to the standard reaction conditions for deoxycyanamidation (Scheme 3.30). The reaction was also carried out with racemic 1-phenylethan-1-ol to identify both enantiomers by chiral HPLC (Chiral HPLC, Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm)).



Scheme 3.30. Investigating the stereospecificity of the deoxycyanamidation process



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	8.17	79092888.00	49.65
2	1.00	*2	9.73	80220400.00	50.35

Figure 3.4. Chiral HPLC chromatogram of the racemic reaction

	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	8.16	55022120.00	86.96
2	1.00	*2	9.78	8253515.00	13.04

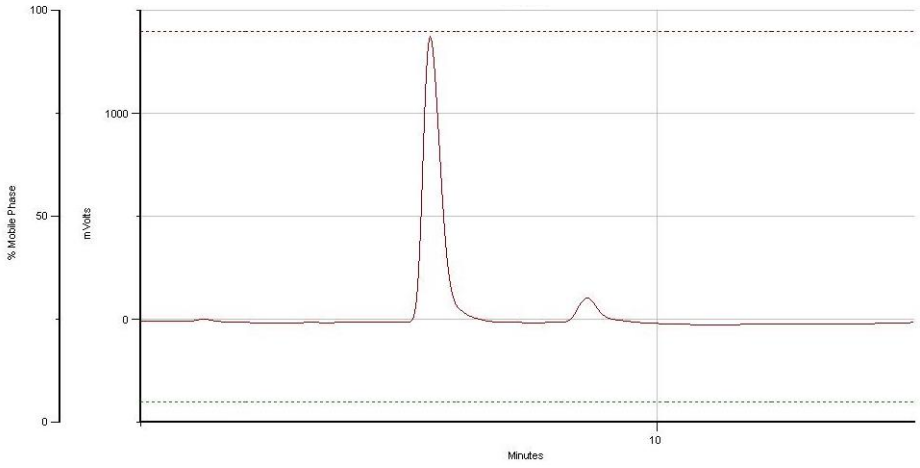
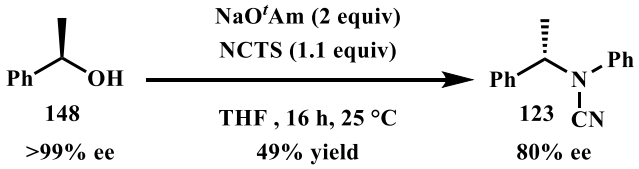


Figure 3.5. Chiral HPLC chromatogram with an enantiopure starting material

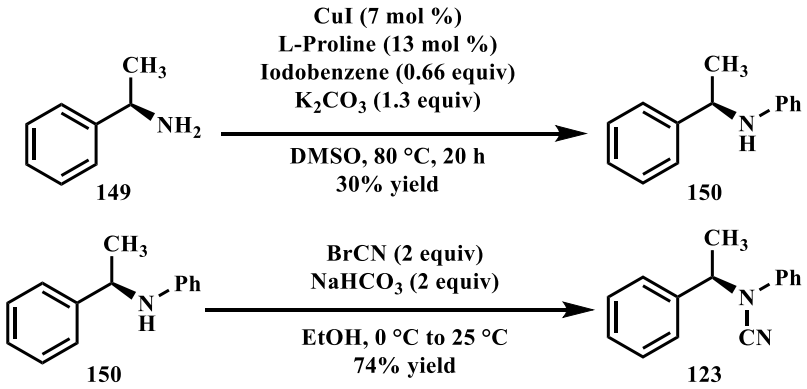
As shown by the chromatograms (Figure 3.4 and 3.5) the reaction does not proceed stereospecifically as expected with an S_N2 reaction. In the presence of TBAI it possible that a double inversion process could take place, which would retain the original stereochemistry. The interconversion of the tosylate intermediate to the alkyl iodide will invert the stereocentre, the alkylation step will invert it again. The ee for this process was determined as 74%. This provides evidence that there is a competing S_N1 pathway. This reaction was also tested in the absence of TBAI and it was found that the ee was retained marginally better at 80% (Scheme 3.31).



Scheme 3.31. Investigating the stereospecificity of the deoxycyanamidation process in the absence of TBAI

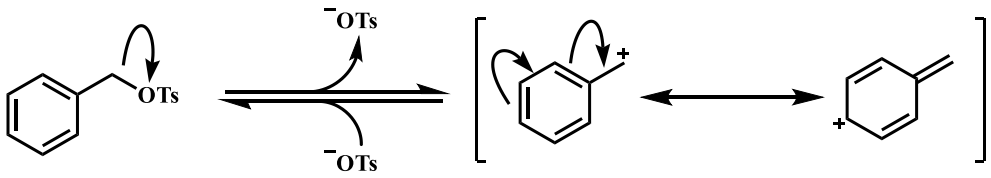
Enantiopure (*R*)-*N*-phenyl-*N*-(1-phenylethyl)cyanamide **123** was then synthesised (Scheme 3.32). (*R*)-1-phenylethan-1-amine **149** underwent an Ullmann type coupling reaction with iodobenzene (0.66 equiv) in the presence of catalytic copper iodide (7 mol %) and L-proline (13 mol %) to yield (*R*)-*N*-(1-phenylethyl)aniline **150** in a 30% yield.[33] This was then cyanated with cyanogen bromide to form (*R*)-*N*-phenyl-*N*-(1-phenylethyl)cyanamide **120** with a 74% yield.

(*R*)-*N*-phenyl-*N*-(1-phenylethyl)cyanamide was then treated with NaO*t*Am (2 equiv) in THF for 16 hours in order to determine if any epimerisation was taking place in the reaction. It was found that after 16 h no epimerisation had occurred, and the product remained enantiopure. This adds evidence that the ee is falling because of a competing S_N1 pathway and not due to *in-situ* epimerisation in basic conditions.



Scheme 3.32. The synthesis of (R)-N-phenyl-N-(1-phenylethyl)cyanamide

The occurrence of competing S_N1 pathway is possible due to the nature of the substrate. In an S_N1 pathway the leaving group leaves before nucleophilic attack. For this to occur the stability of the carbocation is of great importance. The carbocation is formed at the benzylic position (Scheme 3.33). This position can be stabilised by resonance from the aromatic ring. This enhancement of the stability of the carbocation accounts for the presence of the competing S_N1 pathway. The nature of the substrate will have a significant effect upon the whether an S_N1 or S_N2 pathway is followed. If the carbocation formed is tertiary, more S_N1 reactivity would be expected, due to the enhanced stability. Primary or secondary centres will favour S_N2 reactions more, however steric hindrance has significant effects upon S_N2 reactions.

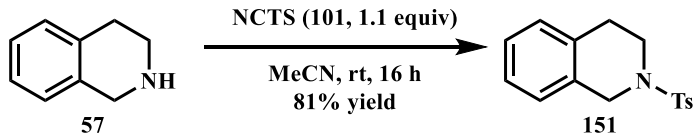


Scheme 3.33. Resonance stabilisation of the carbocation formed in an S_N1 reaction

3.10 Further investigations into the reactivity of NCTS

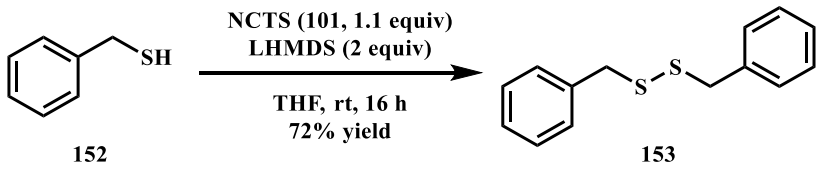
The deoxycyanamidation protocol yields cyanamides from the reaction of alcohols with NCTS, *via* a desulfonylative pathway. Initially reactivity was sought at the carbon of the nitrile, similar to the work of Ragunadh and Kasthuri.[25,26] Because of this observation an investigation into the reactivity of NCTS with other nucleophiles and modification of the structure of NCTS was initiated.

Investigations began with verifying how nitrogen and sulfur nucleophiles react with NCTS. It has been proposed that nitrogen nucleophiles attack at the carbon of the nitrile however based upon the deoxycyanamidation work it was predicted that attack at sulfur could occur. To test this 1,2,3,4-tetrahydroisoquinoline **57** was reacted with NCTS **101** (1.1 equiv) in MeCN (polar aprotic) for 16 h. The reaction proceeds to give 2-tosyl-1,2,3,4-tetrahydroisoquinoline **151** *via* attack at sulfur (Scheme 3.34).



Scheme 3.34. Reaction of tetrahydroisoquinoline with NCTS.

A similar experiment utilising benzyl thiol **152** as the nucleophile was tested however it was soon determined that a base was necessary to facilitate the reaction. After a short series of test reactions (bases (2 equiv) = NaO*t*Am, NaH, LHMDS) it was found that LHMDS promoted the reaction between benzyl mercaptan **152** and NCTS **101** yielding dibenzyl disulfide **153** as the only product (Scheme 3.35). The formation of dibenzyl disulfide can occur *via N*- to *S*- sulfonyl transfer followed by attack of a second thiol displacing the sulfonyl group forming a highly stable disulfide compound.

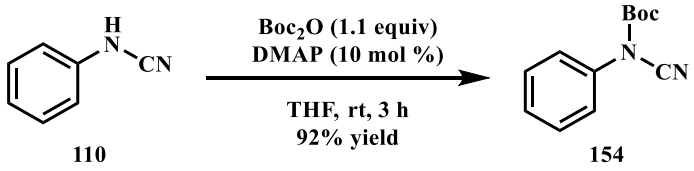


Scheme 3.35. Reaction of benzyl mercaptan with NCTS

At this point it was established within this work that oxygen, nitrogen and sulfur nucleophiles react with NCTS *via* a desulfonylative pathway. A number of people within the Morrill group (Yannick Stöckl, Matthew Ashford, James Ayres) tried to replicate the

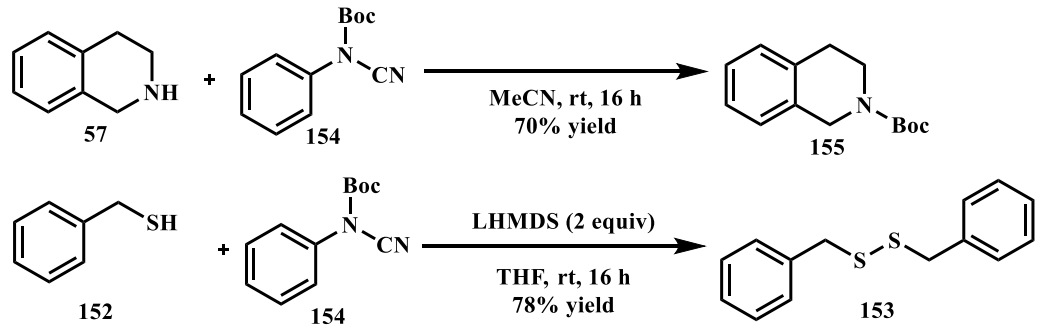
work of Raghunadh and Kasthuri and hence observe attack at the carbon centre of the nitrile, however the proposed products could not be isolated.[25,26]

Attention then turned to whether it would be possible to modify NCTS to alter the reactivity. Inspiration was taken from the work of Gosmini *et al*. where they synthesised NCTS derivatives with carboxyl protecting groups instead of the standard sulfonyl group.[21] In this work phenyl cyanamide **110** was treated with Boc anhydride to yield *N*-Boc-phenylcyanamide **154** (Scheme 3.36).



Scheme 3.36. Synthesis of N-Boc-phenylcyanamide

N-Boc-phenylcyanamide **154** was then tested with 1,2,3,4-tetrahydroisoquinoline **57** and benzyl mercaptan **152** under the same conditions developed with NCTS **101**. In each case the *N*-Boc-phenylcyanamide **154** reacted by transferring the Boc group, to form tert-butyl 3,4-dihydroisoquinoline-2(1H)-carboxylate **155** and dibenzyldisulfide **153** respectively (Scheme 3.37).

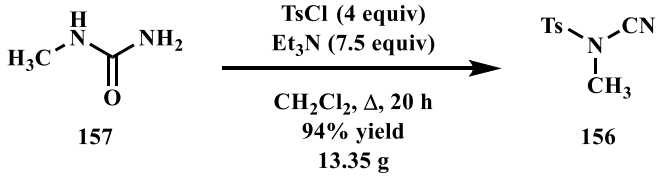


Scheme 3.37. Reaction of 1,2,3,4-tetrahydroisoquinoline and benzyl mercaptan with N-Boc-phenylcyanamide

Further investigations involved the modification of the phenyl group of NCTS to a smaller less hindering group and a methyl group was targeted to form *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156**. Initial endeavours to isolate this compound were from the reaction of methyl urea **157** and tosyl chloride, however no reaction occurred through this tosylation-dehydration method. Subsequently cyanation of methylamine with cyanogen bromide followed by tosylation in a one pot procedure gave the desired *N*-cyano-*N*,4-dimethylbenzenesulfonamide in 12% yield. Initial investigations with this sulfonamide proved interesting and therefore a more efficient method was sought to

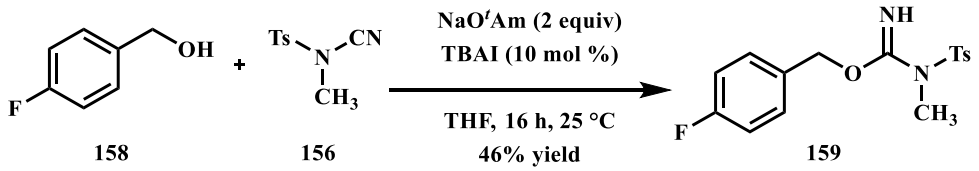
synthesise it. Inspiration for a better process came from the work of Wagenaar and Kerwin where alkyl ureas were transformed into cyanamides with tosyl chloride and triethylamine in dichloromethane at reflux.[34]

Methylurea **157** was treated with tosylchloride (2 equiv) and triethylamine (3.75 equiv) in CH_2Cl_2 at reflux for 3 hours. At this point a further 2 equivalents of tosylchloride and 3.75 equivalents of triethylamine were added, and the reflux continued overnight. After cooling and concentration *in vacuo* the crude mixture was purified by flash silica gel column chromatography to yield the desired *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** in an excellent 94% yield (Scheme 3.38).



Scheme 3.38. Synthesis of N-cyano-N,4-dimethylbenzenesulfonamide

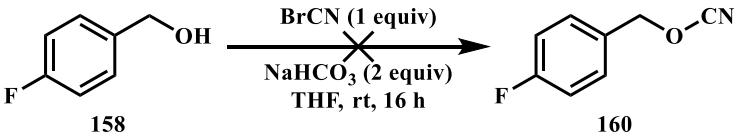
The first reaction carried out with *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** was to investigate how it reacts under deoxycyanamidation conditions. 4-Fluorobenzyl alcohol **158** was chosen as the test substrate which on treatment with *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** (1.1 equiv), NaH (2 equiv) in the presence of TBAI (10 mol %) yielded 4-fluorobenzyl methyl(tosyl)carbamimidate **159** *via* attack at the carbon of the cyanamide as a bench stable white solid in 46% yield, with the balance remaining starting material. (Scheme 3.39).



Scheme 3.39. Synthesis of benzyl methyl(tosyl)carbamimidate

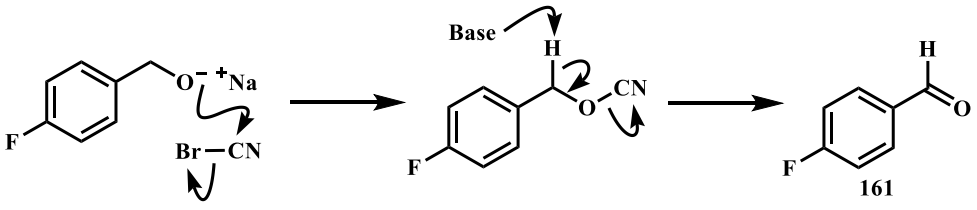
4-Fluorobenzyl alcohol **158** was chosen with a view to monitor this reaction and subsequent reactions by ^{19}F NMR. Treatment of the 4-fluorobenzyl methyl(tosyl)carbamimidate with base could promote elimination of methyl(tosyl)amide anion and formation of 1-(cyanatomethyl)-4-fluorobenzene **160**. The synthesis of 1-(cyanatomethyl)-4-fluorobenzene **160** was then attempted from 4-fluorobenzyl alcohol **158** reacting with cyanogen bromide **30** in the presence of sodium hydrogen carbonate so

that the characteristic peak could be observed in ^{19}F NMR, however, no reactivity was observed with only starting materials remaining (Scheme 3.40).



Scheme 3.40. Attempts to synthesise 1-(cyanatomethyl)-4-fluorobenzene

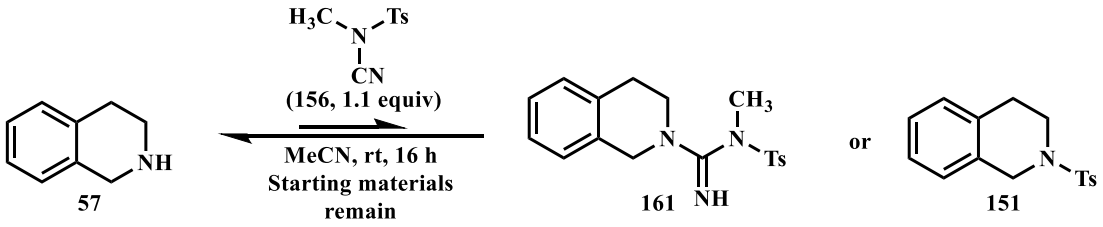
Benzyl cyanate type molecules are mostly unknown with only one paper by Lebedev *et al.* reporting an average yield of 6% (6 examples) as a by-product in an isocyanate synthesis.[35] A second reaction to access 1-(cyanatomethyl)-4-fluorobenzene **160** was run with NaO*t*Am as a stronger base, capable of deprotonating the alcohol and forming an alkoxide. If the reason for no reaction is due to poor nucleophilicity of the alcohol, deprotonation will enhance the nucleophilicity and may help the reaction proceed. 4-fluorobenzyl alcohol **158** was added to a reaction vial with 5 ml THF and 1.1 equivalent of NaO*t*Am and stirred at room temperature for 15 minutes. Cyanogen bromide **30** (1 equiv) was then added and the reaction monitored by TLC. TLC was inconclusive, so the reaction was stopped after 16 hours. The reaction was diluted with H_2O and extracted with CH_2Cl_2. Crude NMR shows 4-fluorobenzyl alcohol remaining with trace formation of 4-fluorobenzaldehyde **161**. The formation of 4-fluorobenzaldehyde **161** was confirmed against an NMR of a commercially available sample however it was not isolated. Formation of 4-fluorobenzaldehyde **161** could occur from formation of the cyanate, followed by elimination of CN^- (Scheme 3.41). At this point it became clear that the synthesis of the benzyl cyanates was challenging and that the possibility for elimination and aldehyde formation was possible. Further computational investigation could be carried out into the feasibility/stability of these molecules.



Scheme 3.41. Elimination of the cyanate to form 4-fluorobenzaldehyde

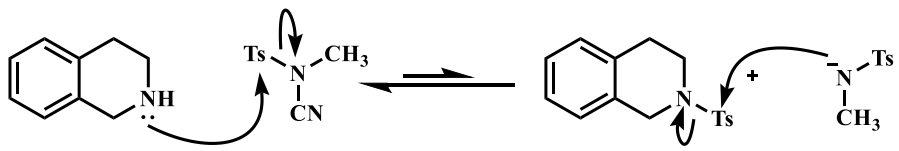
A final further investigation was carried out with the reaction of 1,2,3,4-tetrahydroisoquinoline **57** with *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** to find out whether a nitrogen nucleophile would react at the carbon centre of the cyanamide.

1,2,3,4-Tetrahydroisoquinoline **57** (1 equiv) was added to a reaction vial with MeCN and *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** was added (1.1 equiv) and stirred at room temperature for 16 h. It was predicted that one of two products would form. Either attack at the carbon centre to form *N*-methyl-*N*-tosyl-3,4-dihydroisoquinoline-2(1H)-carboximidamide **161** or tosyl transfer to form 2-tosyl-1,2,3,4-tetrahydroisoquinoline **151** (Scheme 3.42).



Scheme 3.42. The reaction of 1,2,3,4-tetrahydroisoquinoline with N*-cyano-*N*,4-dimethylbenzenesulfonamide*

However only starting materials were observed after 16 h. It seems likely that a reaction should occur between these reagents, which if true suggests that the reaction is in equilibrium and strongly favours the starting materials. 2-tosyl-1,2,3,4-tetrahydroisoquinoline **151** could behave as a tosyl transfer reagent itself (Scheme 3.43). The leaving group in this case is the anion of *N*,4-dimethylbenzenesulfonamide which will be more reactive than the leaving group when NCTS is used. This is because the anion is more electron rich due to inductive donation from the methyl group, rather than resonance withdrawal by a phenyl ring. At this point there is no evidence that the nitrogen nucleophile attacks at the carbon centre.

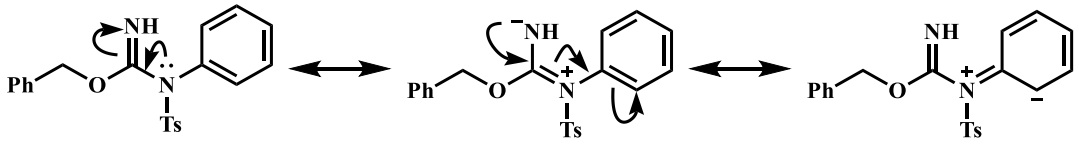


Scheme 3.43. Potential equilibrium between 1,2,3,4-tetrahydroisoquinoline and N*-cyano-*N*,4-dimethylbenzenesulfonamide*

3.10.1 Rationalising attack at sulfur or carbon

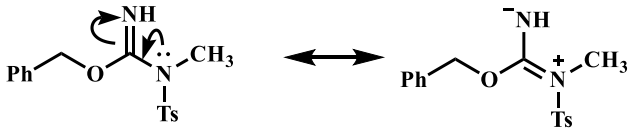
As discussed in this chapter in deoxycyanamidation attack of an oxygen nucleophile with NCTS was only observed at sulfur, moreover further investigation found that nitrogen and sulfur nucleophiles attacked at sulfur. In more recent work with *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** attack at carbon with alcohol nucleophiles has been observed and the products of this reaction are isolable.

With alcohol nucleophiles the isolation could potentially be rationalised by understanding the resonance structures of the compounds formed by attack at carbon. In the three resonance structures (Scheme 3.44), donation of the nitrogen lone pair can take place into the C=NH bond and into the aromatic ring. With the lone pair delocalised into the aromatic ring, elimination to reform the starting materials can occur. Throughout the reaction an equilibrium may occur with attack at carbon, however when the alcohol attacks at sulfur to form the tosylate and subsequent alkylation the reaction does not proceed in reverse ultimately providing the product of the reaction through attack at sulfur. pK_as of the leaving groups should also be considered. The pKa of benzyl alcohol is 15.1 whereas the pK_a of the sulfonamide is around 16.1 and therefore the anion of benzyl alcohol is a marginally better leaving group.[7]



Scheme 3.44. Resonance structures of benzyl phenyl(tosyl)carbamimidate

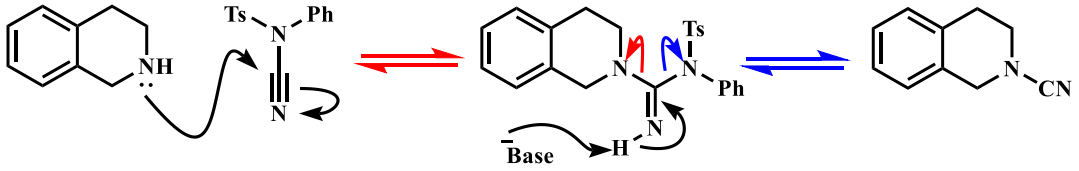
In contrast when an alcohol is reacted with *N*-cyano-*N*,4-dimethylbenzenesulfonamide **156** fewer resonance forms occur, for example with benzyl methyl(tosyl)carbamimidate (Scheme 3.45). The position with the phenyl group is now occupied by an inductively donating methyl group. The stability of this molecule could be attributed to the donation of the tertiary nitrogen lone pair into the C=NH bond, inhibiting elimination, the nitrogen cation is stabilised by inductive donation from the methyl group.



Scheme 3.45. Resonance structures of benzyl methyl(tosyl)carbamimidate

When 1,2,3,4-tetrahydroisoquinoline **57** is reacted with NCTS **101**, the product is 2-tosyl-1,2,3,4-tetrahydroisoquinoline **151**. If the nitrogen nucleophile was to attack at carbon based upon pK_a it would seem likely that it would be possible to form the cyanamide *via* a base catalysed elimination, like step 2 of the TCAN work. Data for the pK_a of 1,2,3,4-tetrahydroisoquinoline could not be obtained, but will be comparable to pyrrolidine which has at pK_a of 44.[36] If 1,2,3,4-tetrahydroisoquinoline attacks the carbon centre it would be

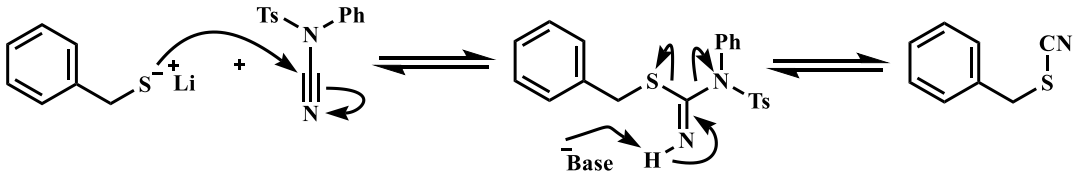
predicted (by relative pK_a values) that the sulfonamide (pK_a = ~16.1) should be the leaving group forming the cyanamide.[7]



Scheme 46. Possible equilibria on reaction of 1,2,3,4-tetrahydroisoquinoline and NCTS

However, attack at carbon and the cyanamide are never observed. It could be proposed that the nitrogen nucleophile never attacks at the carbon centre, computational research would provide greater insight regarding this process.

When benzyl mercaptan is employed as a nucleophile and reacted with NCTS **101** in the presence of LHMDS the product of the reaction is dibenzyldisulfide **153**. Similarly, with 1,2,3,4-tetrahydroisoquinoline **57** attack at carbon was never observed. It could be proposed that if attack at carbon did occur and subsequent elimination with base, the best leaving group would be the anion of benzyl mercaptan reforming the starting reagents. The pK_a of benzyl mercaptan is 10.1 versus 16.1 for the sulfonamide.[7] In the case of attack at sulfur, the formation of dibenzyldisulfide is likely irreversible due to the strength of the disulfide bond.[37]



Scheme 47. Possible equilibria in a reaction between benzyl mercaptan and NCTS

3.11 Conclusion and outlook

An operationally simple one-pot protocol for the deoxycyanamidation of primary and secondary alcohols using *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS), accessing a diverse range of tertiary cyanamide products in excellent yield has been developed. The reaction also provides complementary reactivity to cyanation using trichloroacetonitrile providing aniline type cyanamide products. The mechanistic investigations show that the technique also exploits the underdeveloped desulfonylative reactivity pathway of NCTS. The role of the additive was also probed and was shown to have a dual role as a phase transfer catalysts and formation of a more reactive alkyl iodide. The stereospecificity of the reaction was determined to be poor, however it could be established that the reaction proceeds predominantly *via* an S_N2 pathway, with the S_N1 pathway also accessible.

The reactivity of NCTS was further probed and it has been established that oxygen nucleophiles with NCTS undergo a deoxycyanamidation process. Nitrogen and sulfur nucleophiles react with NCTS *via* a desulfonylative process. *N*-Cyano-*N*,4-dimethylbenzenesulfonamide **156** provides different reactivity with oxygen nucleophiles however formation of cyanates with benzylic type alcohols is problematic. Future work could include investigating alcohols without α-protons such as phenol, however pKa values for the elimination step (pKa phenol = 10.0, pKa sulfonamide is 16.1) do not favour cyanate formation.[7] Phenol type cyanates however have much greater precedent in chemical literature however decreased nucleophilicity may need to be overcome. Further modification of NCTS to make the sulfonamide a better leaving group could be developed, for example exchanging the tosyl group for a triflyl group.

3.12 References

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Chapter 4: Synthesis and Reactivity of *N*-Allenyl Cyanamides

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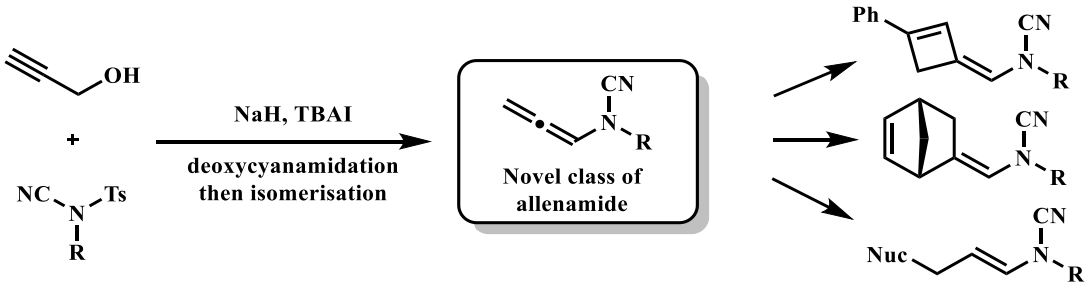
4.1 Preface

This chapter describes the discovery of *N*-allenyl cyanamides. *N*-Allenyl cyanamides have been accessed *via* a one-pot deoxycyanamidation-isomerisation approach using propargyl alcohols and *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide. The utility of this novel class of allenamides was explored through derivatisation, with cycloaddition, hydroarylation and hydroamination protocols to access an array of cyanamide containing products.



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4.1.1 Acknowledgements

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K. B. Ling: Syngenta, Jealott's Hill International Research Centre

L. C. Morrill: Supervisor, Cardiff University

4.2 Introduction

Allenes have become a versatile building block in synthetic organic chemistry over the last half century.[1] They are characterised by their central sp hybridised carbon atom to which are immediately connected two perpendicular π bonds (Figure 4.1). Due to their interesting structure there is little surprise that the reactivity of allenes is equally interesting – with rearrangement, addition, elimination and substitution reactions being developed.[2] Moreover the scope of allene chemistry has been extended to asymmetric synthesis and exploited in natural product synthesis.[3]

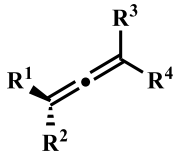


Figure 4.1. The structure of an allene

Heteroatom substituted allenes such as allenol ethers, allenyl sulfides and allenamines have also been discovered (Figure 4.2). Viehe was the first to report the formation of allenamines in 1968 in an effort to synthesise ynamides (Scheme 4.1).[4]

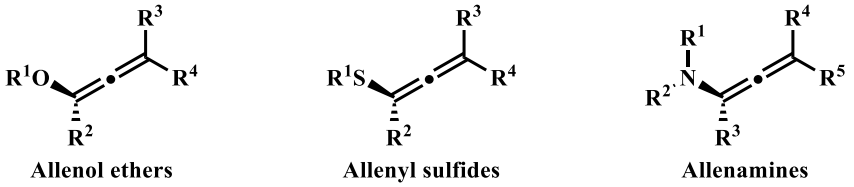
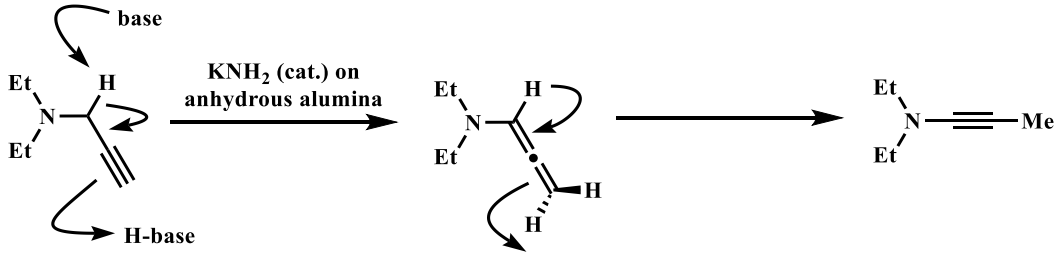


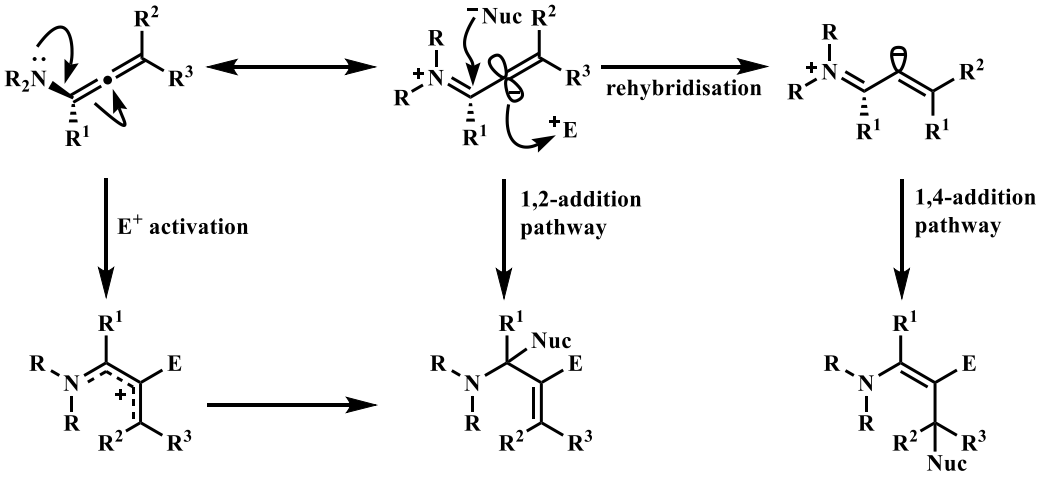
Figure 4.2. The structures of heteroatom substituted allenes



Scheme 4.1. Viehe's pioneering synthesis of allenamines

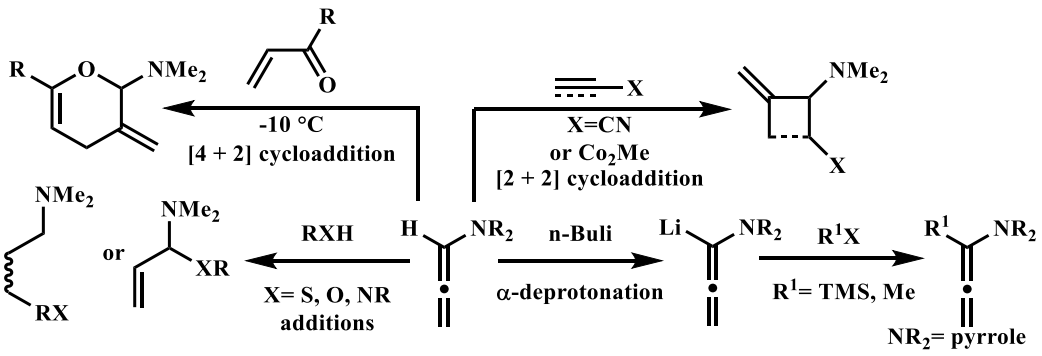
The chemistry of allenamines is distinct when compared to allenes. The potential for lone pair donation from the nitrogen heteroatom into the π-system means that allenamines are more electron rich. This means that allenamines are more suitable for electrophilic activations. Due to the delocalisation of the nitrogen lone pair into the allenic moiety regioselective reactions with successive additions of nucleophiles and electrophiles can

be achieved (Scheme 4.2). Additionally, products of allenamine chemistry possess a nitrogen functionality which are abundant in natural and unnatural products of medicinal interest.[5,6]



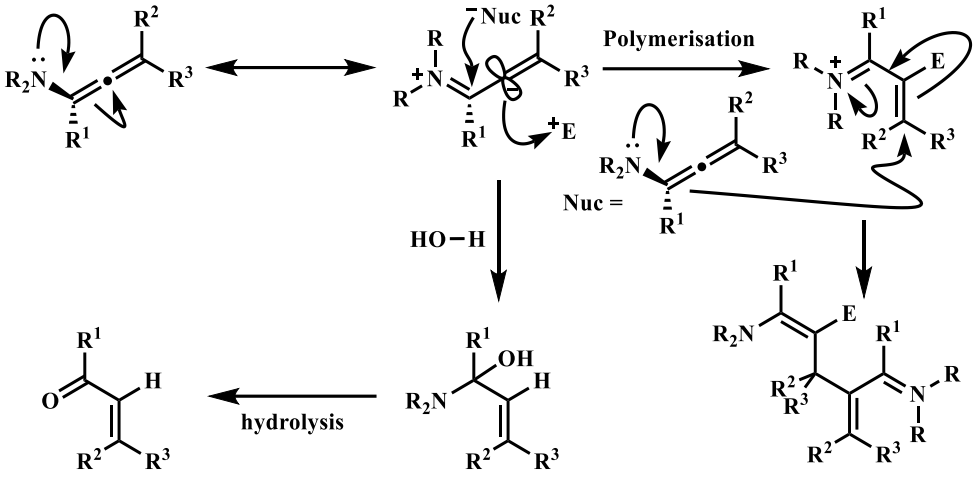
Scheme 4.2. Resonance structure of allenamines and their reactivity

A range of chemical transformations involving allenamines have been developed demonstrating they are useful in organic chemistry. Examples are shown (Scheme 4.3), such as α-depronation with butyl lithium and trapping with trimethysilyl chloride or methyl iodide. Addition reactions have also been established with sulfur, nitrogen and oxygen nucleophiles *via* 1,2- or 1,4- pathways.[7,8] Cycloaddition reactions have also been developed with [2 + 2] and [4 + 2] cycloadditions shown.[7,9]



Scheme 4.3. Overview of the chemistry of allenamines

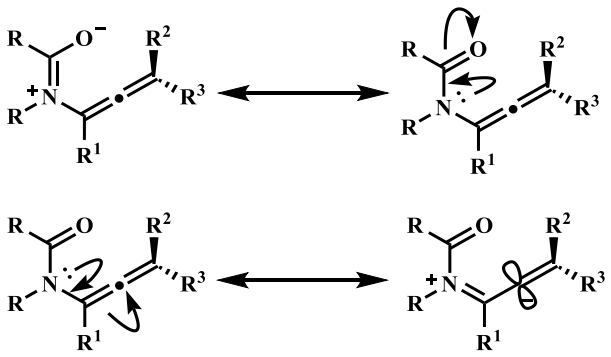
However, the chemistry of allenamines has significant challenges. Allenamines are generally prone to hydrolysis and polymerisation reactions, making their synthesis and isolation a challenge (Scheme 4.4).[10,11] Therefore the identification of allenamine equivalents that balance reactivity and stability is important. To this end, allenamides have been identified as potentially ideal candidates as allenamine equivalents.



Scheme 4.4. Polymerisation and hydrolysis routes of allenamines

4.2.1 Allenamides

Allenamides are electron deficient allenamines characterised by an electron withdrawing group bonded to the nitrogen. The electron withdrawing group makes the nitrogen lone pair of electrons less able to donate into the π-system of the allenic moiety and therefore enhances the stability of the molecule. The additional resonance form localising a negative charge on the oxygen diverts the electrons from the allenic moiety, allowing for the enhanced stability (Scheme 4.5). Therefore, allenamides have been proposed as suitable allenamine equivalents.

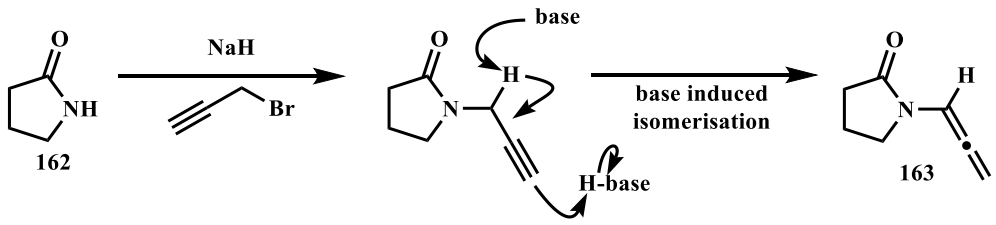


Scheme 4.5. Resonance structures of allenamides

4.2.2 Synthesis of allenamides

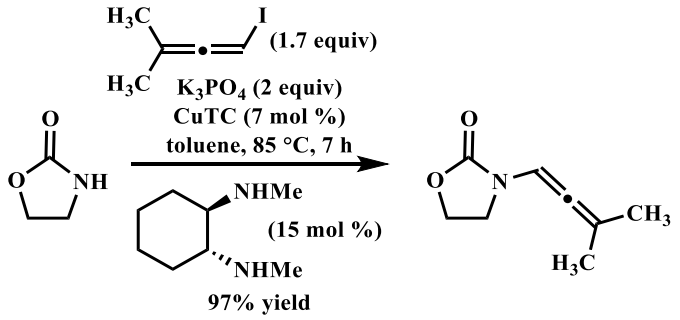
The synthesis of allenamides is often achieved by base induced isomerisation reactions. The first reported synthesis was by Dickinson in 1967.[12] In this work Dickinson demonstrated that 2-pyrrolidinone **162** on treatment with sodium hydride and propargyl bromide yielded 1-(propa-1,2-dien-1-yl)pyrrolidin-2-one **163** as a major and stable

product (Scheme 4.6). Unlike Viehe's work, further isomerisation to the ynamide was not observed.[4]

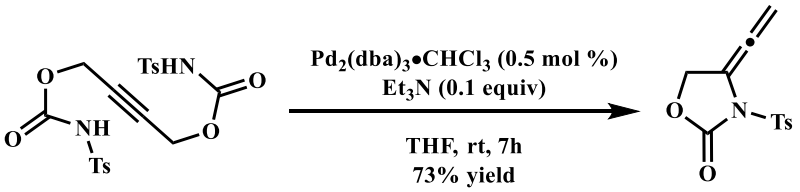


Scheme 4.6. Dickinson's synthesis of 1-(propa-1,2-dien-1-yl)pyrrolidin-2-one

The formation of allenamides with propargyl bromides followed by base induced isomerisation has been well established to date and is used frequently to form a range of allenamides.[13] Subsequently techniques including sigmatropic rearrangements, Hsung-Trost *N*-allenylations (Scheme 4.7), aminocylisation (Scheme 4.8), and Suzuki-Miyaura cross couplings have been developed to access a wide variety of allenamides.[14,15,24,16–23]



Scheme 4.7. Trost and co-worker's copper catalysed allenic coupling

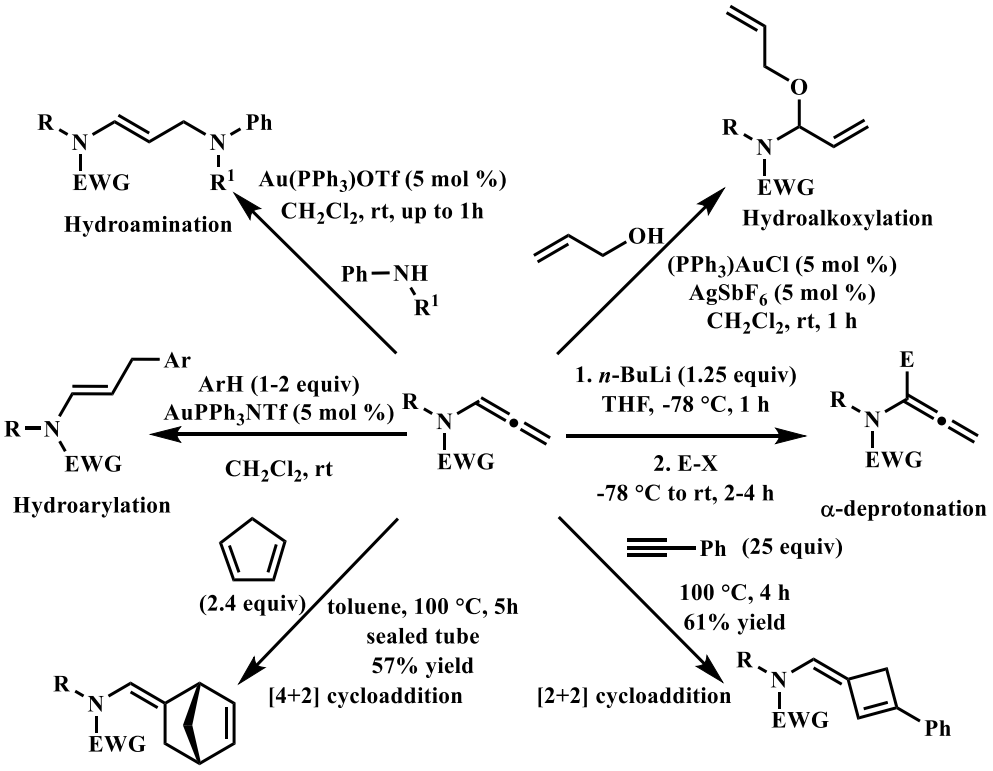


Scheme 4.8. Amino cyclisation developed by Tamura et al.

4.2.3 Reactivity of allenamides

The enhanced stability of allenamides due to their electron deficient nature compared to allenamines has opened a vast array of fascinating chemical transformations. Allenamides have been found suitable to undergo a range of reactions (Scheme 4.9).[13,15] Treatment of an allenamide with *n*-BuLi deprotonates at the α- position with regards to nitrogen, an electrophile can then be attacked forming a wide variety of α-substituted allenamides.[25–28] Allenamides also undergo addition reactions such as hydroalkoxylation,

hydroamination, and hydroarylation.[29–31] Moreover allenamides have been found suitable for a range of cycloadditions, such as a [2+2] with phenylacetylene developed by Tamaru *et al.* and a [4+2] with cyclopentadiene developed by Van Vranken *et al.*.[20,32,33] Allenamides have become a valuable resource in synthetic chemistry to access a wide variety of interesting and potentially otherwise difficult to synthesise molecules.

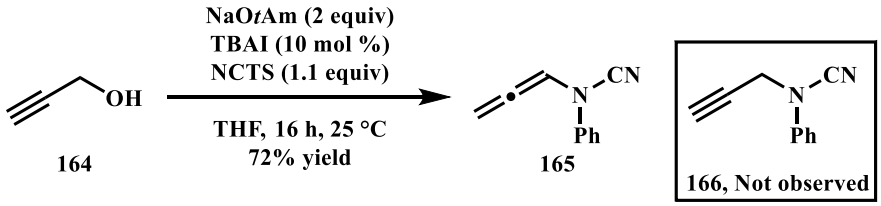


Scheme 4.9. Reactivity of allenamides

4.3 Results and discussion

4.3.1 Introduction

It has been discovered that when propargyl alcohol **164** is subjected to deoxycyanamidation under the standard conditions as discussed in chapter 3 a novel type of allenamide was formed. When propargyl alcohol **164** and NCTS **101** are reacted under the standard procedure *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** was isolated not the expected *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **166** (Scheme 4.10). This was confirmed by NMR, with characteristic peaks in both the ^{1}H spectrum – 5.60 (2H, d, *J* 6.1) and 6.38 (1H, t, *J* 6.1) and the ^{13}C spectrum at 203.2 for the sp hybridised allene carbon.

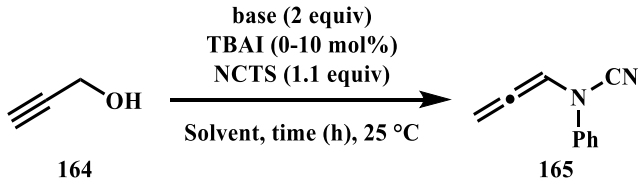


Scheme 4.10. Initial discovery of the formation of an N-allenyl cyanamide via deoxycyanamidation

It was envisaged that this unusual molecule could be of interest as a chemical building block with similar properties to an allenamide. An investigation into the formation, mechanism, substrate scope and derivatisation of this new class of allenamide was proposed.

4.4 Optimisation

The optimisation of this reaction was achieved using propargyl alcohol and NCTS as the standard reagents. To a reaction vial was added propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv) followed by THF ([**164**] = 0.2 mol dm^{-3}) base (1.5-2 equiv). 1,3,5-trimethylbenzene (139 µL, 1 mmol, 1 equiv) as internal standard, NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) and TBAI (0-10 mol %) as an additive, the reactions were stirred at constant temperature (Scheme 4.11). The reaction was monitored *via* ^{1}H NMR taking aliquots at specified times (T1= 1 h, T2= 3 h, T3= 6 h, T4 = 23 h). Each ^{1}H NMR was analysed to determine the amount of product **165** present within the reaction mixture.



164 **165**

Scheme 4.11. Optimisation of the formation of N-allenyl cyanamides

Entry	Base (eq.)	Solvent	Additive (mol %)	**T1 = 1 h 165/ %**	**T2 = 3 h 165/ %**	**T3 = 6 h 165/ %**	**T4 = 23 h 165t/ %**
1	NaH (2)	THF	TBAI (10)	30	74	76	56
2	NaO*t*Am (2)	THF	TBAI (10)	35	63	61	58
3	KO*t*Bu (2)	THF	TBAI (10)	7	17	18	19
4	DBU (2)	THF	TBAI (10)	0	0	0	5
5	LHMDS (2)	THF	TBAI (10)	0	0	0	0
6	DBN (2)	THF	TBAI (10)	0	0	0	0
7	NaH (2)	THF	-	8	26	36	40
8	NaO*t*Am (2)	THF	-	20	30	33	40
9	NaO*t*Am (2)	DME	TBAI (10)	47	59	73	73

Table 4.1. Optimisation of the formation of N-allenyl cyanamides base added first

Initial testing began varying the base. Utilising NaH (Table 4.1, entry 1) in the presence of 10 mol % TBAI yielded a maximum of 76% NMR yield to the allenamide after 6 h. A significant drop of 20% was observed when the reaction was left for 23 h. This indicated decomposition of the allenamide in the reaction conditions which will be discussed in section 4.5. This trend was also observed when NaO*t*Am was used (Table 4.1, entry 2). A maximum of 63% was achieved followed by some degradation to 58% NMR yield after 23 h. KO*t*Bu was also tested however this resulted in low NMR yield (Table 4.1, entry 3). DBU, DBN and LHMDS all failed to provide conversion to the product. The lack of reactivity with the use of DBU and DBN can be rationalised by considering the relative pK_as of the compounds. Amidine bases have pK_aH values of 12-14 and propargyl alcohol of 15-16. Therefore, DBU and DBN are not significantly basic enough to form the alkoxide required to facilitate nucleophilic attack. The NMR spectra when using LHMDS suggests that product formation is possible, as the propargyl alcohol is consumed. However, the allenamide peaks are never observed. This could be due to severe decomposition of the allenamide to unidentifiable compounds.

Entries 7 and 8 (Table 4.1) were then run to test the necessity for the addition of TBAI (10 mol %) to the reaction. The role of TBAI had already been investigated under the deoxycyanamidation protocol and was found to work as both a phase transfer catalyst (cation exchange) and *in situ* conversion of the alkyl tosylate to the more reactive alkyl

iodide. In this work it was also found to have a significant effect upon the yield of the reaction. With both NaH and NaO*t*Am the reactions only reached 40% NMR yield after 23 h (Table 4.1, entries 7 and 8). To avoid NaH due to safety reasons the reaction using NaO*t*Am was tested in DME, and it was found that the reaction reached a higher maximum of 75% NMR yield after 23 h. In addition, degradation between 6 and 23 h was not observed.[34] With this result a series of reactions were run to isolate *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** using the conditions found in Table 4.1, entry 9. This proved to be problematic with highly irreproducible results. The reaction was run by several people with isolated yields ranging from 19-52%.

At this point several alternative work-up and purification techniques were tested. For example, acidic (Sat. Aq. NH_4Cl, HCl 1 M, HCl 2 M) neutral (H_2O) and basic (Sat. Aq. $NaHCO_3$, NaOH 1 M, NaOH 2 M) work-up procedures were tested. No discernible difference in isolated yield could was achieved by varying the work-up procedure. Purification techniques were scrutinised to try and obtain the allenamide in better isolated yield. Concern that the silica gel was degrading the allenamide was investigated using 2D TLC with pure isolated allenamide **165**. After several tests and varying residence times on a silica TLC plate, no new components with different R_f values were visualised. Flash column chromatography with alumina and triethylamine treated silica gel were also tested and provided generally irreproducible yields.

A further series of tests were run (Table 4.2) where the base was added last. To a reaction vial was added propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv) followed by THF ([**164**] = 0.2 mol dm^{-3}), 1,3,5-trimethylbenzene (139 µL, 1 mmol, 1 equiv) as internal standard, NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) and TBAI (0-10 mol %) as an additive and stirred for 5 min. Base (1.5-2 equiv) is then added and the reactions were stirred at constant temperature. The reaction was monitored taking aliquots at specified times (T1= 1 h, T2= 3 h, T3= 6 h, T4 = 23 h) *via* ^{1}H NMR analysis. Each ^{1}H NMR was analysed to determine the amount of product present within the reaction mixture.

Entry	Base (eq.)	Solvent	Additive (mol %)	**T1 = 1h 165/ %**	**T2 = 3 h 165/ %**	**T3 = 6 h 165/ %**	**T4 = 23 h 165/ %**
1	NaO*t*Am (2)	DME	TBAI (10)	55	61	73	75
2	**NaH (2)**	**THF**	**TBAI (10)**	**38**	**73**	**73**	**76**
3	NaH (2)	DME	TBAI (10)	40	75	75	74
4	NaO*t*Am (1.5)	THF	TBAI (10)	24	27	46	42
5	NaH (1.5)	THF	TBAI (10)	31	44	52	56

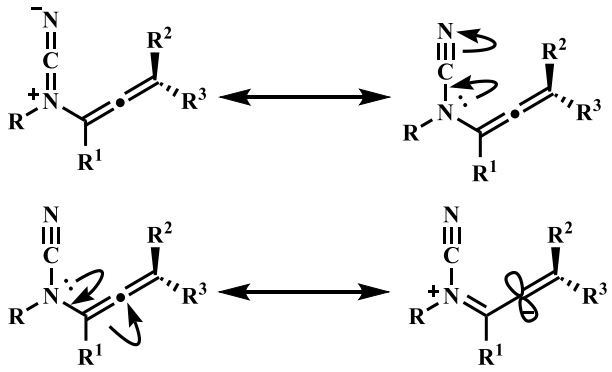
Table 4.2. Optimisation of the formation of N-Cyano allenamides base added last

Gratifyingly it was observed that good NMR yields could be achieved after 6h. Entries 1,2 and 3 providing 73, 73 and 75% NMR yield respectively. Moreover, the addition of base last to the reaction mixture appeared to suppress decomposition of the allenamide. Lowering the amount of base to 1.5 equivalents (Table 4.2, entries 4 and 5) was tested however conversion after 23 h dropped showing that 2 equivalents were required.

With this second series of optimisation experiments, reactions were then run to confirm isolated yields. It was found that utilising NaO*t*Am would still give irreproducible results. However, NaH as base in THF gave highly reproducible isolated yields between 50-60%, this observation will be discussed in section 4.5. The conditions in entry 2, table 4.2 were chosen as the optimal conditions. Despite avoiding NaH where possible it was found most suitable for this transformation. For purposes of assessing the scope of this protocol the reaction time was set at 16 h, so the reaction could be run overnight, and ensure full conversion across a range of substrates. No drop in NMR yield occurred between 6 and 23 h, so this was determined suitable.

4.5 Stability investigations

The stability of allenamides as mentioned in section 4.4 can be attributed to the electron withdrawing group making the allenic moiety of an allenamide less electron rich. In the case of *N*-allenyl cyanamides the electron withdrawing group is a cyanamide. The resonance structures of *N*-allenyl cyanamides are shown (Scheme 4.12).



Scheme 4.12. Resonance structures of N-allenyl cyanamides

Despite the increased stability due to the electron withdrawing cyanamide, throughout the optimisation process it became clear that the allenamide product *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **165** was not stable under the reaction conditions. To investigate the decomposition, a series of bases were tested where the isolated allenamide *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** was stirred in THF with the corresponding base at 25 °C. The reactions were monitored for remaining *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** by ^{1}H NMR with mesitylene as internal standard over time. (T1=1 h, T2= 3 h, T3= 6 h and T4= 23 h)

Sodium hydride (Table 4.3, entry 1) was tested first and showed decomposition of the allenamide. After 23 h the amount of allenamide present in the reaction mixture had dropped to 60% of the original amount. With NaO*t*Am 57% of the allenamide had decomposed over 23 h (Table 4.3, entry 2). KO*t*Bu (Table 4.3, entries 4 and 4) decomposed 100% of the allenamide after 1 h – indicating why it was deemed inappropriate during the reaction optimisation.

Subsequently carbonate bases were tested (Table 4.3, entries 5 and 6) and no decomposition of the allenamide was observed over 23 h. Diisopropyl amine (Table 4.3, entry 7) also showed no decomposition of the allenamide over 23 h. In the presence of KOH the amount of allenamide remaining dropped to 97% after 23 h (Table 4.3, entry 8). A control test without the presence of base was also completed (Table 4.3, entry 9) and the allenamide was found to be highly stable in solution at 25 °C over 23h.

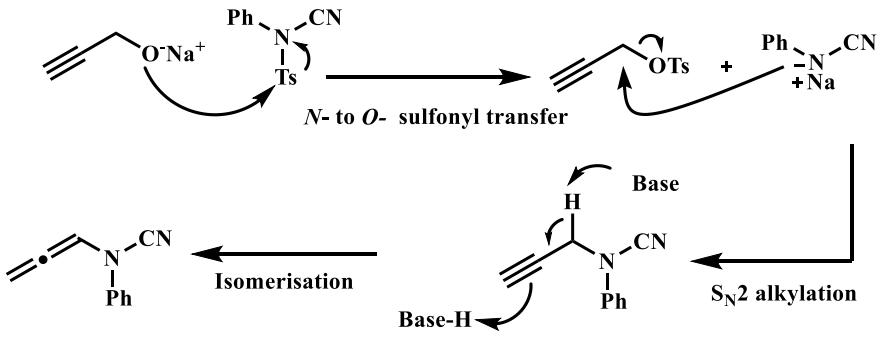
		% Allenamide remaining			
Entry	Base	T= 1 h	T= 3 h	T= 6 h	T= 23 h
1	NaH	87	81	82	60
2	NaOtAm	68	62	52	43
3	KOtBu	0	0	0	0
4	KOtBu (THF 1M)	0	0	0	0
5	Cs_2CO_3	100	100	100	100
6	K_2CO_3	100	100	100	100
7	DIPEA	100	100	100	100
8	KOH	100	100	98	97
9	No Base	100	100	100	100

Table 4.3. Percentage of alleneamide decomposition over time in the presence of base

This data shows that bases able to facilitate the formation of the allenamide are also able to decompose the allenamide. To understand this, reaction conditions of entry 2 were repeated to isolate any decomposition products. Unfortunately, after isolation of several components visualised by TLC no conclusion could be drawn as to what decomposition pathway is occurring. A potential route for decomposition could be through polymerisation similarly to allenamines as discussed in section 4.2. This could also account for the messy ^{1}H NMR spectra of the isolated compounds with no distinguishable peaks. Alternatively, the alkoxides can behave as nucleophiles and add to the allenamide. In the optimised reaction conditions, it was determined that the addition of base last to the reaction mixture decreased the decomposition of the allenamide. By adding the base last the concentration of propargyl alkoxide at any time point should be lower. As produced, the propargyl alkoxide should react with NCTS already in solution. With addition of base to the alcohol to pre-form the alkoxide, addition of NCTS occurs with a high concentration of the alkoxide leading to decomposition of the newly formed product. However, the product of this decomposition could not be identified.

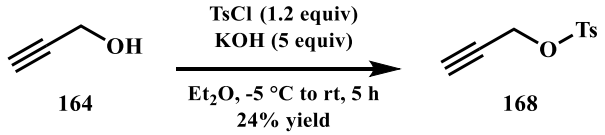
4.6 Mechanistic investigations

The mechanism of this reaction in accordance with the previous deoxycyanamidation work initiates with *N*- to *O*- sulfonyl transfer between NCTS and the sodium alkoxide giving a propargyl tosylate. Subsequent S_N2-type alkylation of the cyanamide ion with propargyl tosylate affords *N*-propargyl cyanamide which the undergoes base induced isomerisation to give the *N*-allenyl cyanamide (Scheme 4.13).



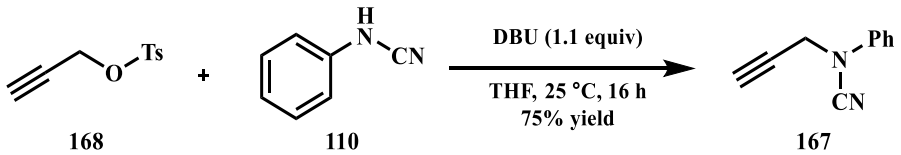
Scheme 4.13. Proposed reaction mechanism for formation of N-cyano allenamide

The validity of *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167** as an intermediate was investigated. First prop-2-yn-1-yl 4-methylbenzenesulfonate **168** was synthesised (Scheme 4.14) by reaction of propargyl alcohol **164** with tosyl chloride and KOH as a base.



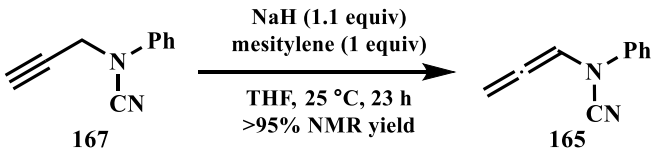
Scheme 4.14. Synthesis of prop-2-yn-1-yl 4-methylbenzenesulfonate

Next, the reaction of prop-2-yn-1-yl 4-methylbenzenesulfonate **168** and phenyl cyanamide **110** was run with a base screen in order to isolate the desired *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167**. The reactions were run with 1.1 equivalents of K_2CO_3, DBU, NaO*t*Am or NaH respectively and monitored by TLC and ^{1}H NMR over time. A control with no base was run and no conversion was observed. It was found that the reaction utilising DBU as base provided excellent conversion to *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167** in 16 h. K_2CO_3 gave no conversion and both NaO*t*Am and NaH had >50% starting material remaining. The reaction with NaH showed the presence of the allenamide and therefore over reaction. The reaction with DBU was then repeated on a larger scale to isolate 320 mg of the desired product **167** in 75% yield (Scheme 4.15).



Scheme 4.15. Synthesis of N-phenyl-N-(prop-2-yn-1-yl)cyanamide

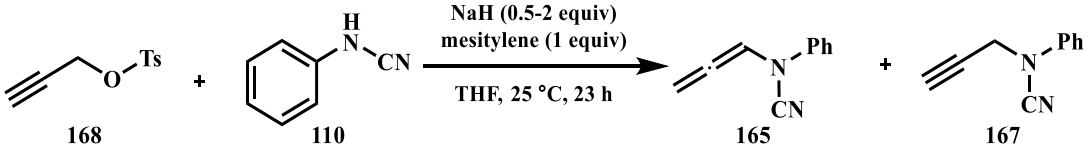
With *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167** isolated it was then treated with NaH in order to promote the base induced isomerisation and confirm the *N*-allenyl cyanamide can be isolated from this proposed intermediate (Scheme 4.16).



Scheme 4.16. Base induced isomerisation to form N-cyano allenamide

To a reaction vial was added 31 mg of *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167** (0.2 mmol) followed by THF (1 mL) and mesitylene as internal standard (28 µl, 0.2 mmol). NaH (8.8 mg, 0.22 mmol, 1.1 equiv) was then added and the reaction stirred at 25 °C. The reaction was monitored by taking an aliquot at 23 h and dissolving in $CDCl_3$ in a standard borosilicate NMR tube. The ^1H NMR was analysed to see the composition of the reaction. It was determined that >95% NMR yield to *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** occurred validating *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167** as an intermediate in the reaction mechanism. Interestingly in this isomerisation step the NMR yield was remarkably high. The allenamide was observed in >95% NMR yield suggesting that after it had formed no degradation had taken place. This could occur as the NaH is consumed and the concentration of base becomes significantly low enough for the allenamide to be stable.

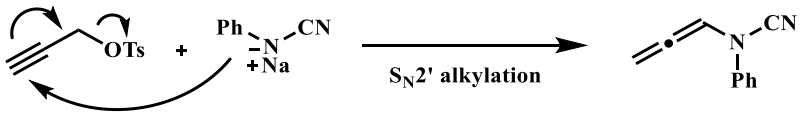
An S_N2 alkylation was favoured over the alternative S_N2' pathway (Scheme 4.18) due to studies involving the reaction of propargyl tosylate **168** with phenyl cyanamide **110** (Scheme 4.17). With 0.5 equivalents of NaH, 49% conversion to *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **168** was observed, with no *N*-allenyl cyanamide **165** (Table 4.4). Upon increasing the equivalents of NaH (1.1, 1.5, 2 equiv) increasing conversion to the *N*-allenyl cyanamide **165** was observed, providing evidence for an initial S_N2-type alkylation followed by a base induced isomerisation. With 0.5 equivalents of base, the theoretical maximum amount of nucleophile (deprotonated phenyl cyanamide) is 50%. In this case a 49% NMR yield of 167 was observed. It is clear from this experiment that the reaction proceeds *via* an S_N2 pathway, because no allenamide **165** is formed, which without base induced isomerisation can only be accessed *via* and S_N2' mechanism. In conclusion the proposed reaction mechanism starting with *N*- to *O*- sulfonyl transfer followed by S_N2 alkylation and a base induced isomerisation has been confirmed.



Scheme 4.17. Investigation of S_N2 over S_N2'

NaH used (equiv)	0.5	1	1.5	2
Propargyl tosylate **168** remaining (%)	51	27	25	<5
Conversion to propargylamide **167** (%)	49	30	19	<5
Conversion to *N*-allenyl cyanamide **165** (%)	0	31	46	90

Table 4.4. NMR yield of propargylamide and N-cyanoallenamide varying the equivalents of base

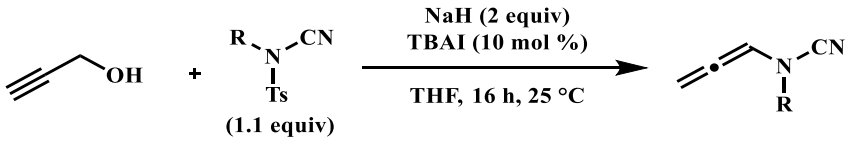


Scheme 4.18. Alternative S_N2' reaction pathway

4.7 Substrate scope

4.7.1 Sulfonamide scope

With optimised reaction conditions the generality of this process was examined. Initially propargyl alcohol **164** and a series of sulfonamide derivatives were tested (Scheme 4.19).



Scheme 4.19. Substrate scope conditions

Under the optimised reaction conditions, it was found that a range of *N*-aryl substituents within the sulfonamide could be incorporated giving *N*-allenyl cyanamides in synthetically useful yields (51-73%, Figure 4.3). *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** was accessed with NCTS **101** in 57% yield. Pleasingly, the allenamide *N*-(propa-1,2-dien-1-yl)-*N*-(p-tolyl)cyanamide **169** could obtained in 73% yield on a large scale (1.69 g, 14 mmol). Reaction of sulfonamides with substitution at the 2- and 3-position of the phenyl ring yielded *N*-(propa-1,2-dien-1-yl)-*N*-(*m*-tolyl)cyanamide **170** and *N*-(propa-1,2-dien-1-yl)-*N*-(*o*-tolyl)cyanamide **171** in 53 and 51% yield respectively. A sulfonamide featuring an electron donating methoxy group, *N*-cyano-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide was incorporated into the protocol effectively to form *N*-(4-methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide **172** in 54% yield. An electron withdrawing group (CF_3) was incorporated into sulfonamide *N*-cyano-

4-methyl-*N*-(4-(trifluoromethyl)phenyl)benzenesulfonamide and gave *N*-(4-fluorophenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide **173** in 53% yield. Therefore, it can be noted that the presence of an electron donating group or electron withdrawing group does not affect the progress of the reaction. Further examples include allenamides with halogen substituents incorporated into the phenyl ring. *N*-(4-Bromophenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide **174** was obtained in 53% yield. *N*-(4-Chlorophenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide **175** was obtained in 51% yield. Each of these molecules contain a functional handle that could be used for further functionalisation, for example cross coupling. *N*-(4-fluorophenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide **176** bearing a fluorine atom could be obtained in 53% yield.

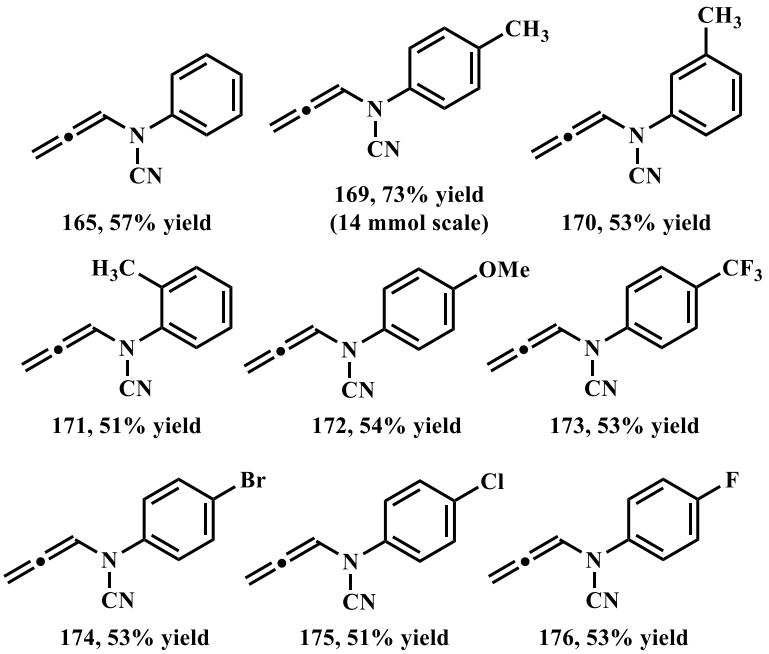
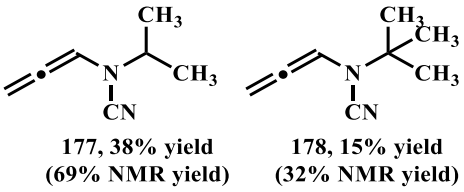


Figure 4.3. N-cyano allenamide substrate scope

N-Isopropyl-*N*-(propa-1,2-dien-1-yl)cyanamide **177** and *N*-(tert-butyl)-N-(propa-1,2-dien-1-yl)cyanamide **178** were isolated in significantly lower yields of 38 and 15% respectively (Figure 4.4). These examples required more careful handling, especially with regards to their volatility. In general, the allenamides accessed could be placed under the strong vacuum of a Schlenk line to remove all solvent. In the case of **177** and **178**, this resulted in the total loss of the compound. A solution to this issue was to run the purification in lower boiling solvents. Et_2O was used instead of EtOAc for **178**. Also, solvents were removed more gently on a rotary evaporator at 30 °C bath temperature and 50 mbar minimum pressure. None the less solvent free pure isolation resulted in a poor yield. In addition, *in situ* NMR yields were obtained with ^{1}H NMR where mesitylene was

added as an internal standard and yields of 69% for **177** and 32% for **178** were obtained. It could be proposed that in the mechanism initial attack at sulfur is less favoured with the alkyl sulfonamides. This is because the subsequent sulfonamide anion has inductively donating alkyl groups, which cannot stabilise the nitrogen anion as effectively as phenyl rings in the aryl examples.



177, 38% yield (69% NMR yield) **178, 15% yield (32% NMR yield)**

Figure 4.4. Volatile allenamides were obtained in lower yields

In addition to spectroscopic data for the allenes, the structures above were also ratified by X-ray diffraction of *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** via recrystallisation from hexane (Figure 4.5).

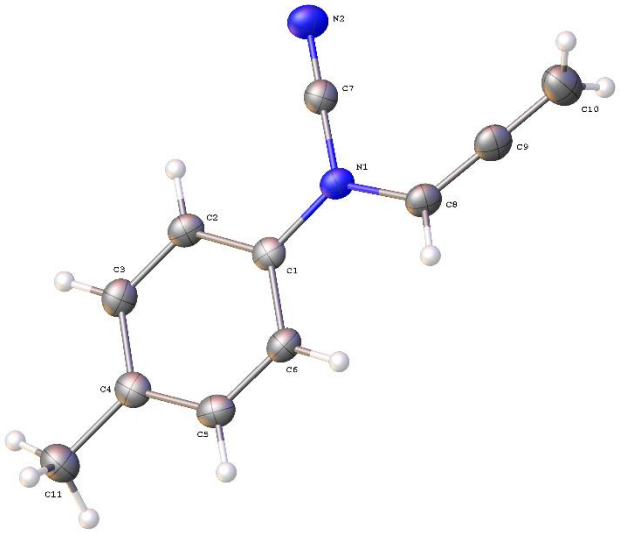
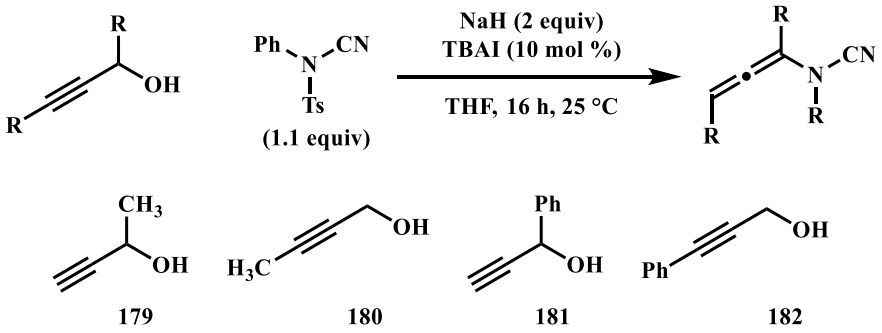


Figure 4.5. Crystal structure of N-*(propa-1,2-dien-1-yl)*-N-(p-*tolyl)cyanamide* ***169***

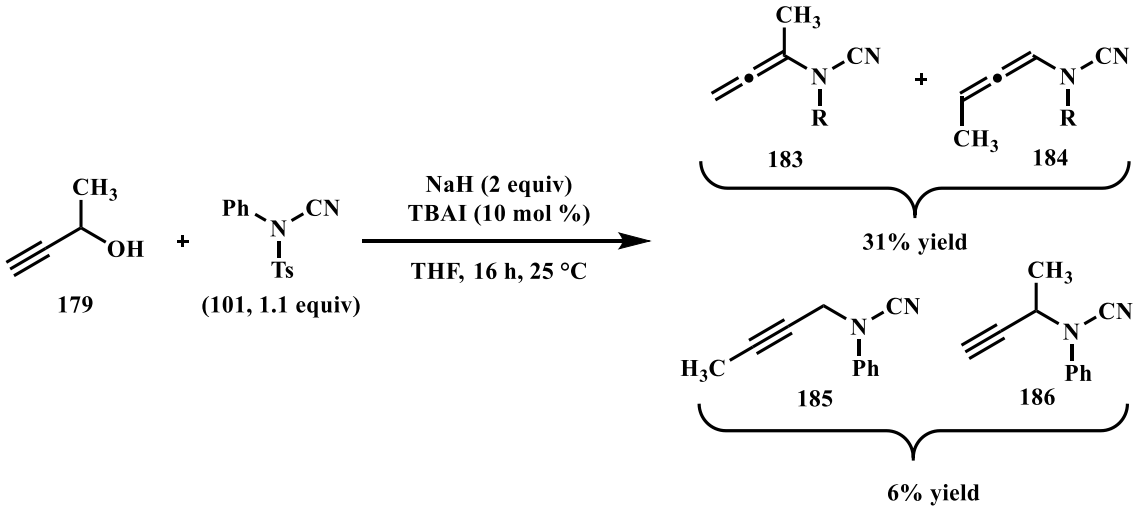
4.7.2 Propargyl alcohol scope

Having investigated the scope for sulfonamides attention turned to modification of the alcohol. For this a series of commercially available substituted propargyl alcohols were chosen (Scheme 4.20).



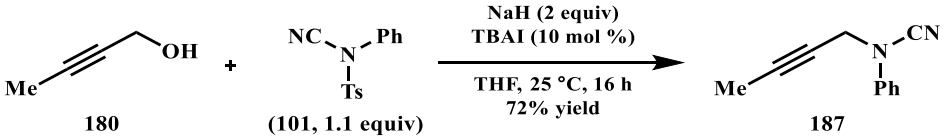
Scheme 4.20. Propargyl alcohol substrate scope

But-3-yn-2-ol **179** was subjected to the optimised reaction conditions and yielded a complex mixture of products (Scheme 4.21). Compounds **183** and **184** were isolated in 31% yield in a 2:1 ratio and were inseparable by flash silica gel column chromatography. Compounds **185** and **186** were also isolated as in inseparable mixture in 6% yield with a ratio of 3:1. This complex mixture is indicative of several reaction mechanisms taking place. The presence of both allenamide isomers suggests that both S_N2 followed by base induced isomerisation and S_N2' mechanisms are occurring when but-3-yn-2-ol is reacted. Alkynyl product **185** can be accessed via S_N2 alkylation without subsequent base induced isomerisation. The second alkynyl product **186** can be formed via S_N2' followed by base induced isomerisation converting an allenic moiety to an alkyne.



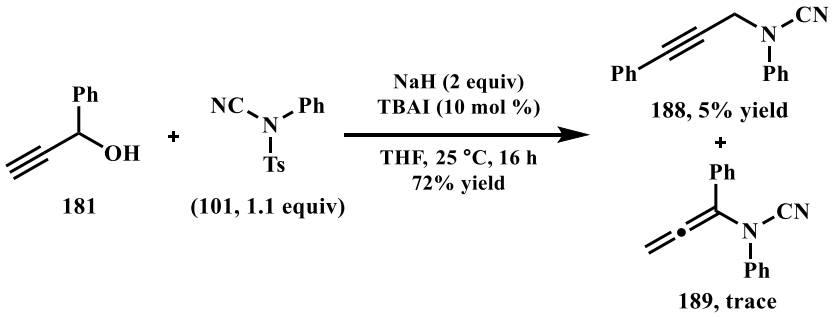
Scheme 4.21. The reaction of but-3-yn-2-ol under optimised conditions

Next but-2-yn-1-ol **180** was subjected to the standard reaction conditions and *N*-(but-2-yn-1-yl)-*N*-phenylcyanamide **187** was isolated as the only product in 72% yield (Scheme 4.22). With regards to the mechanism, S_N2 alkylation has occurred however the subsequent base induced isomerisation has not. An explanation for this is, that due to the presence of the methyl group the carbanion formed during the base induced isomerisation would be less stabilised and therefore less favoured.



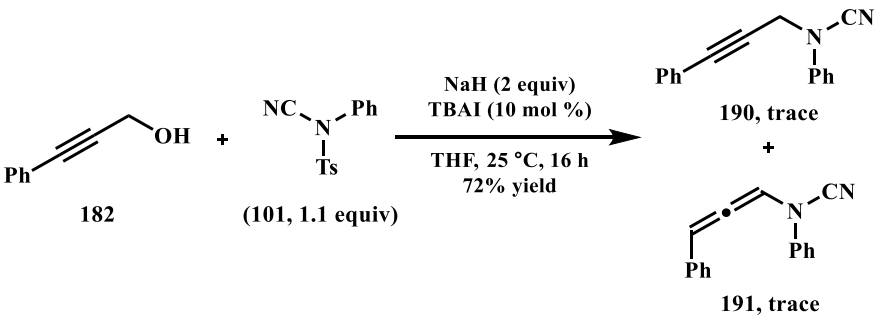
Scheme 4.22. Reaction of but-2-yn-1-ol under standard conditions

Two propargyl alcohols with phenyl substitution were then tested under the standard conditions. 1-phenylprop-2-yn-1-ol **181** was tested and yielded two products in very low yield (Scheme 4.23). Alkyne **188** is a product of *N*- to *O*- sulfonyl transfer followed by S_N2 alkylation without subsequent base induced isomerisation. Trace amounts of the allenamide **189** were detected in the crude ^{1}H NMR however this product was not stable enough to isolate.



Scheme 4.23. Reaction of 1-phenylprop-2-yn-1-ol under standard conditions

In the reaction with 3-phenylprop-2-yn-1-ol **182** a mixture was observed (Scheme 4.24). The alkyne **190** can be accessed via *N*- to *O*- sulfonyl transfer and S_N2 alkylation. The allenamide **191** was also observed in trace quantities which suggests that a base induced isomerisation has occurred. This contrasts with the instance when but-2-yn-1-ol **180** was reacted and no base induced isomerisation was observed (Scheme 21). In this case the phenyl group can provide enough stabilisation to the carbanion for the base induced isomerisation to occur, where the methyl group destabilised it. Nonetheless the reaction only showed trace quantities of the product compounds with predominantly starting materials remaining.



Scheme 4.24. Reaction of 3-phenylprop-2-yn-1-ol under standard conditions

Overall the applicability of substituted propargyl alcohols is limited. Multiple alkyne and allenamide containing compounds are produced. This is indicative of competing S_N2 and S_N2' type cyanamide alkylation reactions involving an alkyl tosylate intermediate. Moreover, the stability of the carbanion could determine whether a base induced isomerisation is favourable stopping the reaction at the alkyne in some cases.

4.8 Derivatisation of *N*-allenyl cyanamides

Considering that *N*-allenyl cyanamides are a novel structural motif the derivatisation of these compounds was then explored. This was done with the aim to generate a series of bespoke cyanamides that would otherwise be difficult to access using existing methodologies. For this study *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** was chosen as the model substrate because it is a bench stable solid (Figure 4.6).

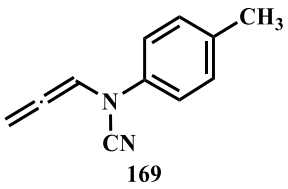


Figure 4.6. N-(propa-1,2-dien-1-yl)-N-(p-tolyl)cyanamide was the model derivatisation substrate

4.8.1 Hydroarylation and hydroamination

Based upon the work by Kimber *et al.*, it was sought to subject the *N*-cyano allenamide **169** to a hydroarylation protocol.[35] The protocol developed by Kimber *et al*. utilised gold (I) catalysis to activate allenamides to 1,4-addition and form enamides **192**. In recent years enamides have become an increasingly valuable functional group in synthetic chemistry. They have interesting reactivity due to the enamine character yet the nucleophilicity is lessened by electron withdrawing group on the nitrogen providing

chemical stability.[36] Utilising *N*-allenyl cyanamides will provide access to a series *N*-alkenylcyanamides **193** (Figure 4.8).

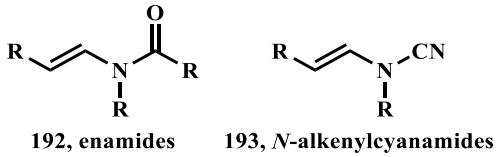
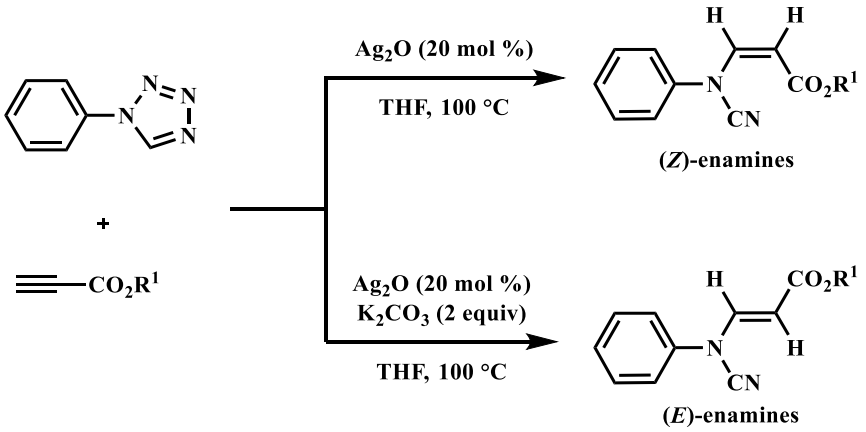


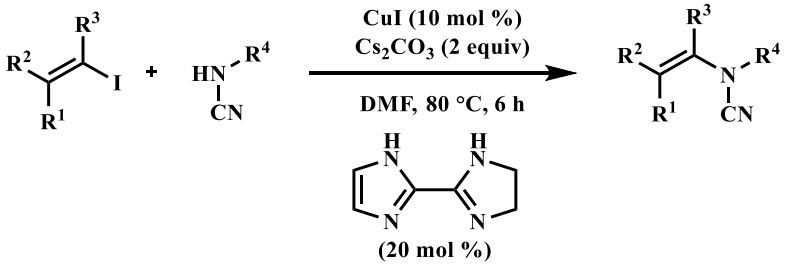
Figure 4.7. General structure of enamides and the N-cyanoenamines

Recent developments in the synthesis of *N*-alkenylcyanamides include the work by Wang and Zhang *et al.* in 2012 where they developed a stereocontrolled 1,2 addition reaction of 1-aryl-1H-tetrazoles with alkyl propiolates to form *N*-alkenylcyanamides (Scheme 4.25).[37] They found that they could control the *E/Z* isomerism of the reaction. In the presence of silver oxide (Ag_2O), the 1,2-addition reaction generated (*Z*)-*N*-alkenylcyanamides. The 1,2- addition reaction generated (*E*)-*N*-alkenylcyanamides in the presence of Ag_2O and potassium carbonate.



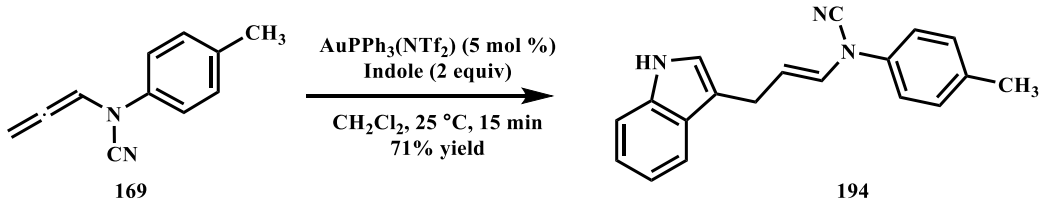
Scheme 4.25. Stereocontrolled synthesis of Z or E N-cyanoenamines

In 2017 Evano and coworkers developed a copper catalysed cross coupling between cyanamides and iodoalkanes (Scheme 4.26).[38] The reaction required catalytic amounts of copper(I) iodide and 2,2'-bisimidazole in the presence of caesium carbonate in DMF at 80 °C to form *N*-alkenylcyanamides.



Scheme 4.26. Copper catalysed synthesis of N-cyanoenamines

A hydroarylation reaction was run with an *N*-allenyl cyamide **169** to form an *N*-alkenyl cyanamide. To a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (54 mg, 0.32 mmol, 1 equiv) followed by CH_2Cl_2 (1 mL) as solvent and indole (75 mg, 0.64 mmol, 2 equiv). The solution was stirred before $AuPPh_3(NTf_2)$ (25 mg, 0.016 mmol, 0.05 equiv) was added as catalyst. The reaction was stirred at 25 °C and monitored by TLC. After 15 minutes the reaction had gone to full conversion as visualised by TLC and was filtered through celite and purified by flash column silica chromatography to yield the product **194** (Scheme 4.27) in 71% yield. A doublet of triplets at 6.15 (J = 13.6) and at 5.99 (J 13.6) is indicative of the *E* isomer. It was found important to keep a high concentration of indole present to limit formation of the diaddition product (Figure 4.9). As the reaction proceeds the concentration of unreacted indole decreases. Keeping the concentration of indole high with 2 equivalents, makes it more likely that unreacted indole will be available for nucleophilic attack.



Scheme 4.27. Gold (I) catalysed hydroarylation with indole

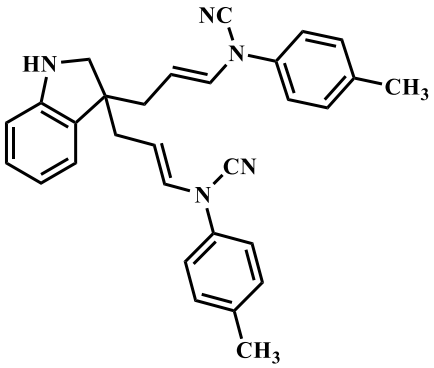
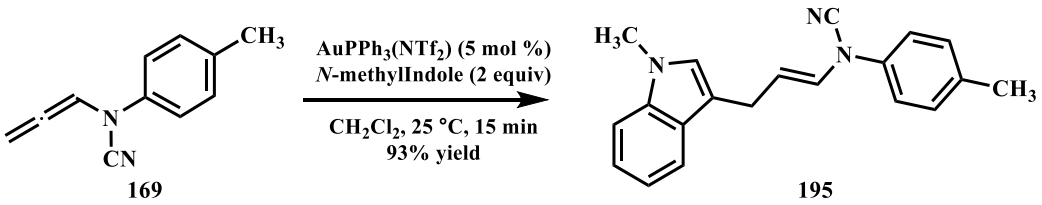
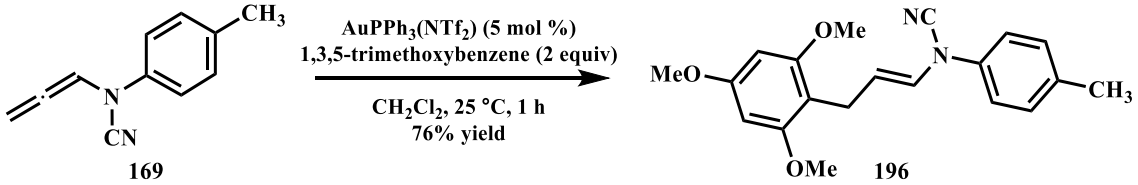


Figure 4.8. The di-addition product formed when 1 equivalent of indole was used

Subsequently *N*-methyl indole was tested as the nucleophile and the product (*E*)-*N*-(3-(1-methyl-1H-indol-3-yl)prop-1-en-1-yl)-*N*-(*p*-tolyl)cyanamide **195** was isolated in an excellent 93% yield (Scheme 4.28). The use of 1,3,5-trimethoxybenzene as nucleophile was also successful yielding (*E*)-*N*-(*p*-tolyl)-*N*-(3-(2,4,6-trimethoxyphenyl)prop-1-en-1-yl)cyanamide **196** in 76% yield after 1 h (Scheme 4.29).

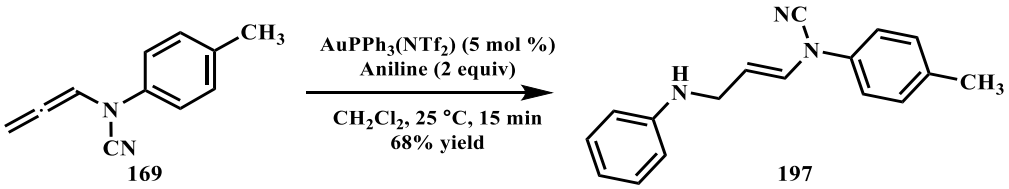


Scheme 4.28. Gold (I) catalysed hydroarylation with N-methylindole



Scheme 4.29. Gold (I) catalysed hydroarylation with 1,3,5-trimethoxybenzene

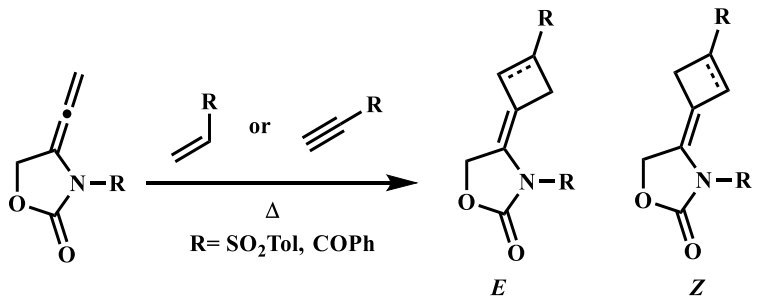
The scope of this reactivity was further tested in a hydroamination reaction also reported by Kimber *et al.* utilising the same conditions as discussed with hydroarylations above.[35] When aniline was employed as the nucleophile it was found that the corresponding product (*E*)-*N*-(3-(phenylamino)prop-1-en-1-yl)-*N*-(*p*-tolyl)cyanamide **197** could be accessed in 68% yield (Scheme 4.30).[31]



Scheme 4.30. Gold (I) catalysed hydroamination with aniline

4.8.2 [2+2] cycloaddition

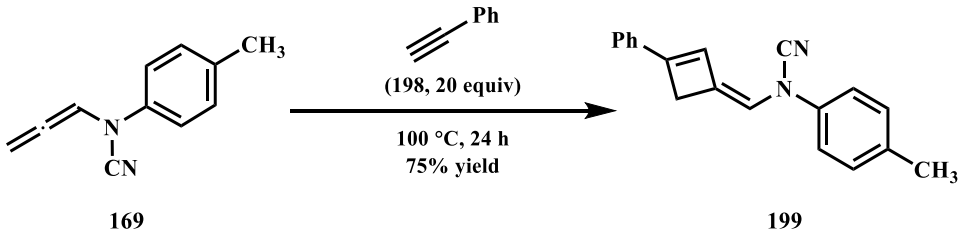
As discussed in section 4.2**,** allenamides can participate in thermal [2+2] cycloadditions. A [2+2] cycloaddition with *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** and an appropriate partner would be tested. Inspiration was taken from the work of Tamaru and co-workers (Scheme 4.31).[33] In their work 4-ethenylidene-1,3-oxazolidin-2-ones were reacted with a series of suitable [2+2] partners to provide the requisite cyclobutane or cyclobutene product.



Scheme 4.31. [2+2] cycloadditions developed by Tamaru et al.

The investigation with *N*-allenyl cyanamides started with using phenylstyrene as the [2+2] partner. Following an adapted literature procedure *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (50 mg, 0.32 mmol, 1 equiv) was added to a reaction vial with styrene (2.3 mL, 20 mmol, 62 equiv) and stirred at 100 °C for 22 h. The [2+2] cycloaddition was successful giving a 72% isolated yield. However, the reaction was not regioselective and the two isomers were not separable by silica gel flash column chromatography or recrystallisation. Further reactions were performed with methyl vinyl ketone and acrylonitrile however in both cases only starting material remained after significant time and heating.

In the work by Tamaru *et al.* it was reported that the reaction of the allenamide with phenylacetylene provided only one regioisomer. With the previous difficulty in separating regioisomers the reaction with phenylacetylene was run with *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (Scheme 4.32). To a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (50 mg, 0.29 mmol, 1 equiv) and phenylacetylene **198** (640 µl, 5.8 mmol, 20 equiv) and the reaction was stirred for 24 h at 100 °C obtaining (*Z*)-*N*-((3-phenylcyclobut-2-en-1-ylidene)methyl)-*N*-(*p*-tolyl)cyanamide **199** in a regioselective reaction in 75% isolated yield.

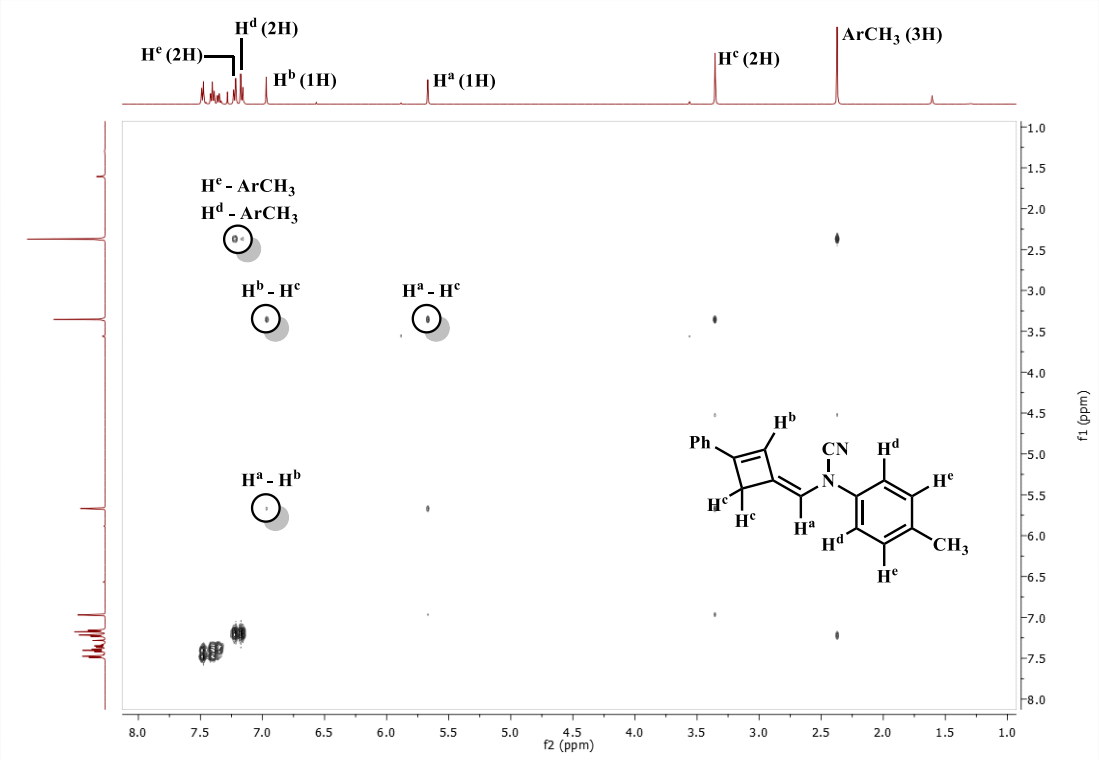


169 199

Scheme 4.32. [2+2] cycloaddition with phenylacetylene

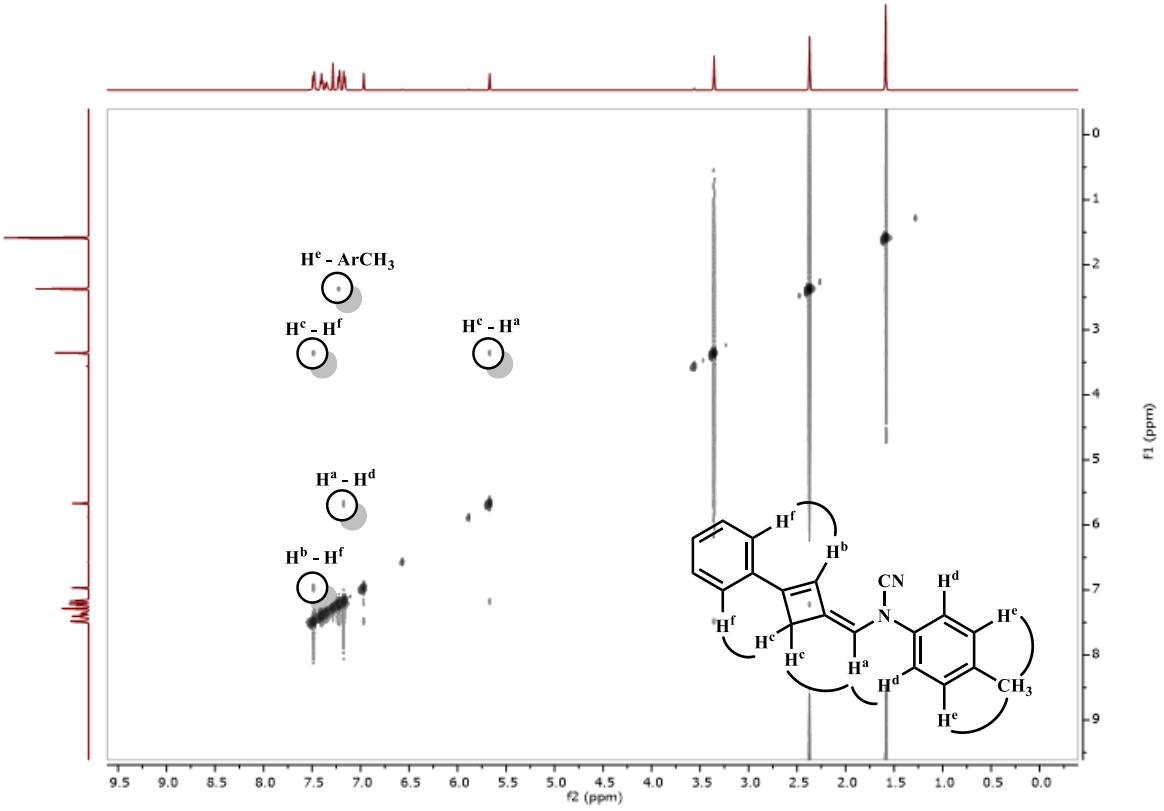
The relative configuration of the molecule was determined using NOESY ^{1}H NMR studies.[17,39] First all peaks were assigned using ^{1}H NMR and COSY experiments (Spectrum 4.1). The peaks for the cyclobutene product could be assigned using integrals,

chemical shift and coupling which is important for determining the through space interactions in the NOESY spectrum.



Spectrum 4.1. COSY data for [2+2] cycloaddition with phenylacetylene

The NOESY spectrum for (*Z*)-*N*-((3-phenylcyclobut-2-en-1-ylidene)methyl)-*N*-(*p*-tolyl)cyanamide could be used to for confirmation of the structure by the presence of interactions between H^a and H^c and no interactions between H^a and H^b (Spectrum 4.2). In the alternative regioisomer (Figure 4.9) an interaction between the H^b and H^c would be expected.



Spectrum 4.2. NOESY data for [2+2] cycloaddition with phenylacetylene

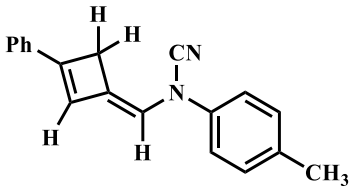
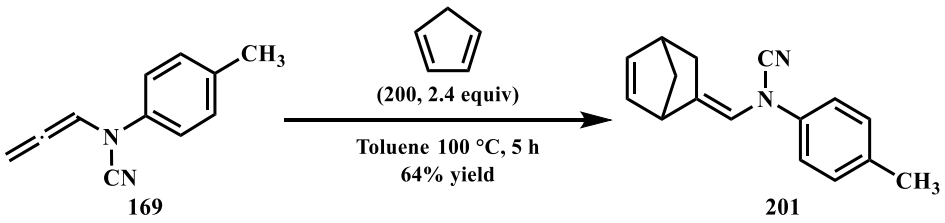


Figure 4.9. Alternative unobserved regioisomer in [2+2] formation with phenylacetylene

4.8.3 [4+2] cycloaddition

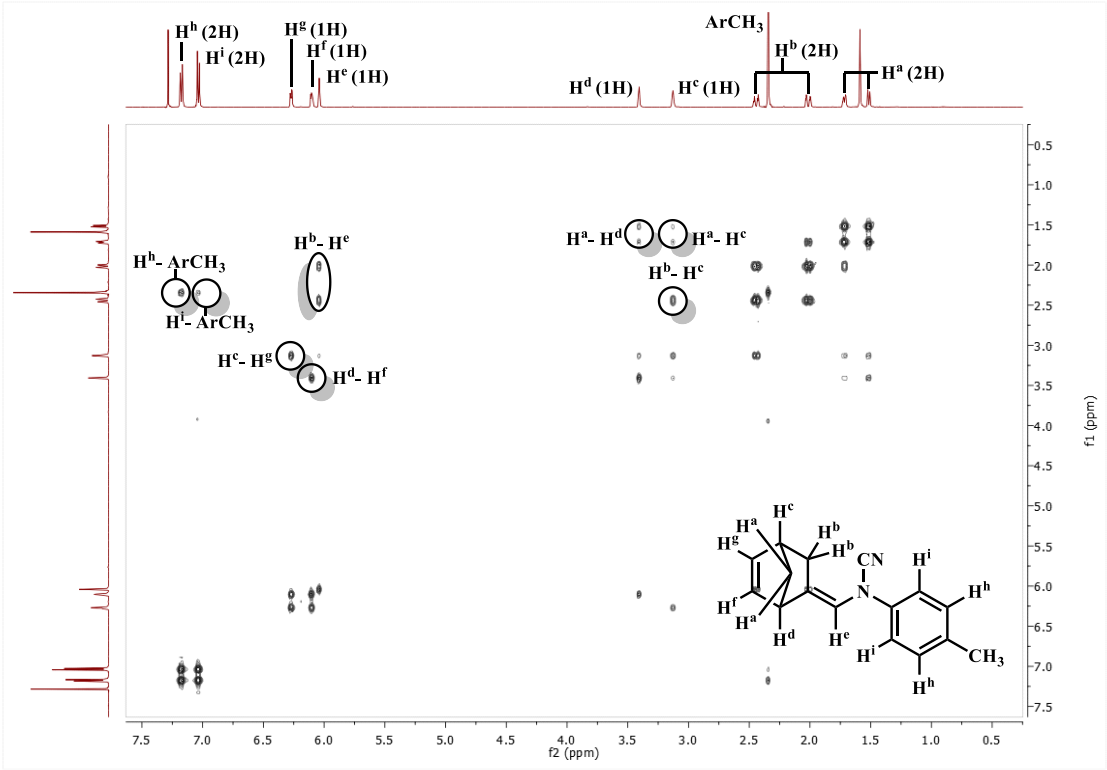
Allenamides can also participate in [4+2] cycloadditions, rapidly increasing the complexity of the molecule. Based upon chemistry developed by Van Vranken *et al*. with allenamides cyclopentadiene **200** was chosen as an appropriate reagent for this reaction (Scheme 4.33).[20]

N-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (50 mg, 0.29 mmol, 1 equiv) in toluene (0.5 mL) was added freshly distilled cyclopentadiene **200** (59 µL, 0.70 mmol, 2.4 equiv) and heated to 100 °C in a sealed vial. After 5 h the reaction was complete after analysis by TLC. After purification (*E*)-*N*-(bicyclo[2.2.1]hept-5-en-2-ylidenemethyl)-*N*-(*p*-tolyl)cyanamide **201** was isolated in 64% yield (Scheme 4.33).



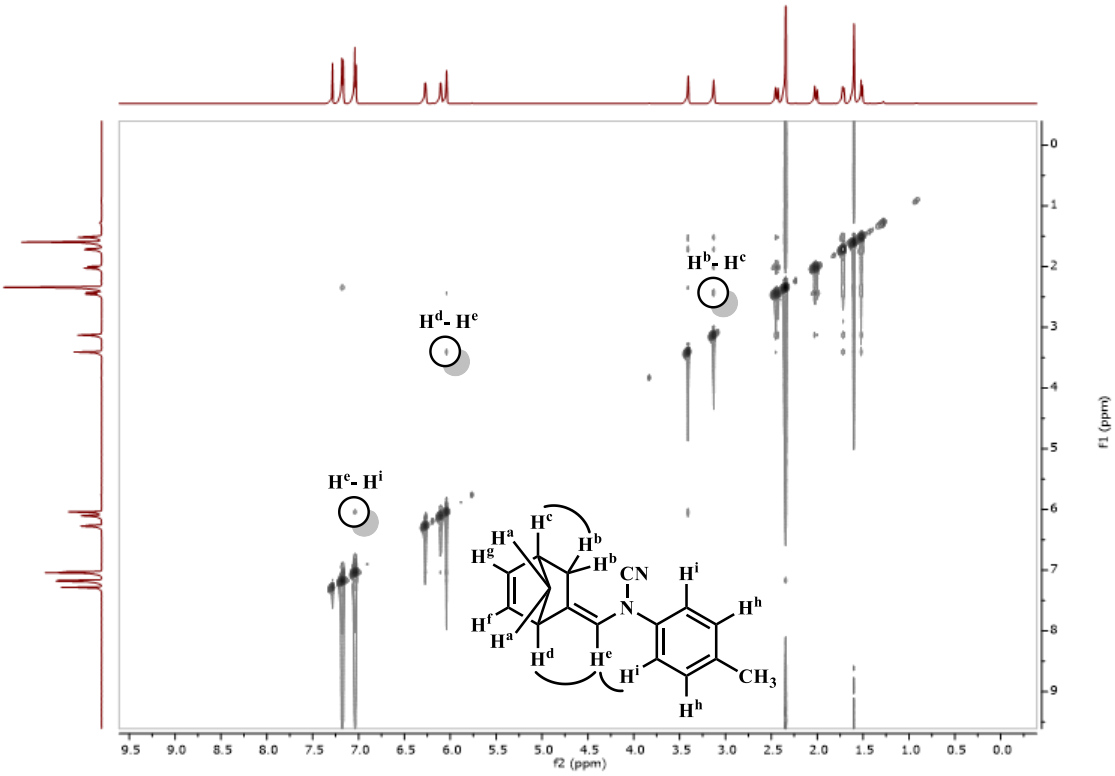
Scheme 4.33. [4+2] cycloaddition with cyclopentadiene

The relative configuration of the molecule could be determined using NOESY ^{1}H NMR studies as shown in the spectra below. Firstly, as with the [2+2] example the ^{1}H NMR spectrum was assigned, using a COSY experiment (Spectrum 4.3). Utilising the coupling, integrals and chemical shifts the peaks could be assigned to the compound. Using this the NOESY could be interpreted to determine the relative configuration of the molecule.



Spectrum 4.3. COSY spectrum for [4+2] with cyclopentadiene

The key through space interaction to confirm relative configuration of the molecule was between H^{d} and H^{e} (Spectrum 4.4) and no through space interaction between H^{b} and H^{e} which would be expected in the spectrum of an alternative regioisomer (Figure 4.10).



Spectrum 4.4. NOESY spectrum for [4+2] with cyclopentadiene

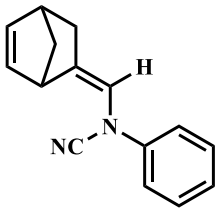


Figure 4.10. Alternative unobserved regioisomer in [4+2] with cyclopentadiene

4.9 Conclusion

A protocol for the preparation of a new class of allenamide and cyanamide has been developed – *N*-allenyl cyanamides. The operationally simple one-pot deoxycyanamidation-isomerisation protocol with propargyl alcohol proceeds *via N*- to *O*-sulfonyl transfer, followed by *N*-alkylation and base induced isomerisation. A wide variety of sulfonamides can be incorporated giving a range of aryl substituted *N*-allenyl cyanamides in good yield. The applicability of substituted propargyl alcohols was tested, however these can proceed *via* different mechanisms providing a mixture of products. The utility of *N*-allenyl cyanamides was explored through derivatisations. Hydroarylation, hydroamination and cycloaddition reactions gave access to an array of synthetically interesting compounds which may otherwise be difficult to synthesise.

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Chapter 5. Experimental and characterisation data

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5.1 General information

Unless stated otherwise, all reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with teflon-coated magnetic stirrer bars. Dry tetrahydrofuran (THF), acetonitrile, toluene, hexanes and diethyl ether were obtained after passing these previously degassed solvents through activated alumina columns (Mbraun, SPS-800). All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and -77 °C were obtained using ice/water and CO_2(s)/acetone baths respectively. Temperatures of 0 °C to -50 °C for overnight reactions were obtained using an immersion cooler. All reactions involving heating were carried out using DrySyn blocks and a contact thermometer. *In vacuo* refers to the use of a rotary evaporator under reduced pressure.

Analytical thin layer chromatography was carried out using aluminium plates coated with silica (Kieselgel 60 F_{254} silica) and visualization was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. Flash chromatography used Kieselgel 60 silica in the solvent system stated.

Melting points were recorded on an Electrothermal 100 apparatus and are corrected using benzophenone and benzoic acid as calibration standards. Dec refers to decomposition.
Infra red spectra were recorded on a Shimadzu IRAffinity-1 Fourier Transform ATIR spectrometer as thin films using a pike miracle ATR accessory. Characteristic peaks are quoted (ν_{max} / cm^{-1}).

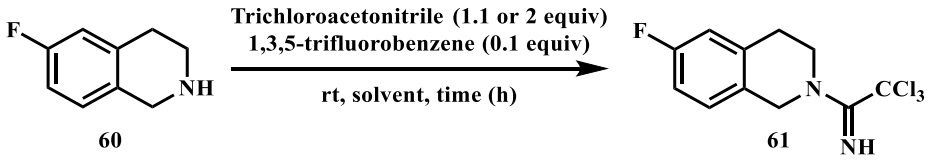
^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$ NMR spectra were obtained on either a Bruker Avance 300 (300 MHz ^{1}H, 76 MHz ^{13}C, 282 MHz ^{19}F), Bruker Avance 400 (400 MHz ^{1}H, 101 MHz ^{13}C, 377 MHz ^{19}F) or a Bruker Avance 500 (500 MHz ^{1}H, 126 MHz ^{13}C, 471 MHz ^{19}F) spectrometer at 25 °C in the solvent stated. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent signal. All coupling constants, *J*, are quoted in Hz. Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and multiples thereof. The abbreviation Ar is used to

denote aromatic, Ph to denote phenyl, Bn to denote benzyl, br to denote broad and app to denote apparent.

High resolution mass spectrometry (HRMS, *m/z*) data was acquired either at Cardiff University on a Micromass LCT spectrometer or at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

5.2 Experimental and characterisation data for chapter 2

5.2.1 Optimisation of 1st Step

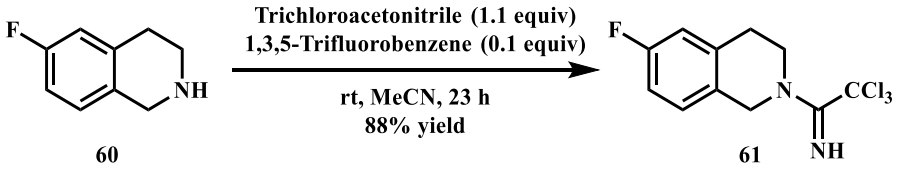


General procedure 1

To a standard borosilicate glass 178 mm length, 4.97 mm O.D. x 4.20 mm I.D. NMR tube was charged in order 6-fluoro-1,2-3,4-tetrahydroisoquinoline **60** (81.9 µL, 0.60 mmol, 1 equiv.), the required volume of the requisite non-deuterated solvent to provide the desired concentration ([**60**] = 1 mol dm^{-3}, total reaction volume = 0.60 mL), 1,3,5-trifluorobenzene (6.21 µL, 0.06 mmol, 0.1 equiv.) as internal standard and trichloroacetonitrile **56** (1.1 or 2 equiv.). The contents of NMR tube were thoroughly mixed and analysed by *in situ* $^{19}F\{^{1}H\}$ NMR at three time points (T1 ≈ 30 minutes, T2 = 5 h, T3 = 23 h). Each $^{19}F\{^{1}H\}$ NMR was analysed to determine the composition of the reaction mixture, quoted as a ratio of starting material **1** to product **2** to other products, i.e. **60**:**61**:Other. The results are shown in the table below. For entry 14, the crude product was purified by flash silica column chromatography (eluent = 15% EtOAc in hexanes) to give the recorded yield.

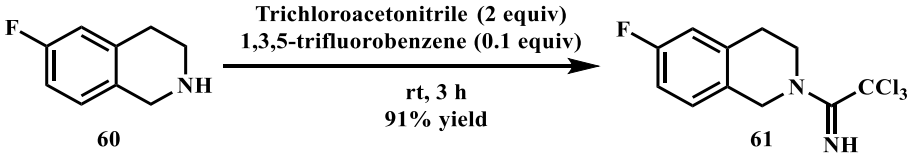
			Reaction composition/ %		
Entry	TCAN	Solvent	T= 30 min	T= 5 h	T= 23 h
	/ eq.		**60** : **61** : Other	**60** : **61** : Other	**60** : **61** : Other
1	2	Dioxane	94:03:03	69:27:04	18:78:4
2	2	Tol	92:05:03	48:48:04	0:96:4
3	2	TBME	91:06:03	48:48:04	7:90:3
4	2	MCPE	91:05:04	48:48:04	9:87:4
5	2	$CHCl_3$	95:02:03	75:21:04	36:61:3
6	2	EtOAc	94:03:03	59:38:03	12:83:5
7	2	DME	93:03:04	64:32:04	12:84:4
8	2	THF	88:07:05	40:56:04	9:87:4
9	2	CH_2Cl_2	95:02:03	47:50:03	0:96:4
10	2	*t*-BuOH	97:00:03	85:12:03	51:46:3
11	2	Acetone	67:26:07	0:47:63	0:66:34
12	2	MeOH	75:22:03	72:22:06	66:22:12
13	2	MeCN	68:28:04	0:97:3	0:96:4
14	**1.1**	**MeCN**	**80:17:03**	**18:79:3**	**0:97:3**
15	2	DMF	69:27:04	0:95:5	0:95:5
16	2	DMSO	59:37:04	0:94:6	0:95:5

2,2,2-trichloro-1-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-imine (Entry 14)



To a standard borosilicate glass 178 mm length, 4.97 mm O.D. x 4.20 mm I.D. NMR tube was charged in order 6-fluoro-1,2-3,4-tetrahydroisoquinoline **60** (81.9 µL, 0.60 mmol, 1 equiv.), MeCN (446 µL), 1,3,5-trifluorobenzene (6.21 µL, 0.06 mmol, 0.1 equiv.) as internal standard and trichloroacetonitrile **56** (66.2 µL, 0.66 mmol, 1.1 equiv.). After 23 h at rt the reaction was complete as determined by *in situ* $^{19}F\{^{1}H\}$ NMR analysis. Purification by flash silica column chromatography (eluent = 15% EtOAc in hexanes, 30 x 120 mm silica), gave the title compound **62** (156 mg, 0.53 mmol, 88% yield) as a light yellow oil. R_f = 0.41 (eluent = 20% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2839 (C-H), 1601 (C≡N), 1501, 1398, 1260, 1132; ^{1}H NMR (300 MHz, $CDCl_3$) σ_H: 2.97 (2H, t, *J* 5.6, C*H*$_2$), 3.92 (2H, t, *J* 5.6, C*H*$_2$), 4.74 (2H, s, C*H*$_2$), 6.93-6.84 (2H, m, Ar*H*), 7.10 (1H, t, *J* 7.0, Ar*H*), 7.91 (1H, br s, N*H*); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) σ_F: -116.2 ; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) σ_c: 28.6 (d, *J* 1.5, *C*H$_2$), 45.9 (*C*H$_2$), 50.0 (NH*C*), 94.3 (*C*Cl$_3$), 113.6 (d, ^{2}J 21.6, Ar*C*), 115.1 (d, ^{2}J 21.0, Ar*C*), 128.0 (d, ^{3}J 8.2, Ar*C*), 129.1 (d, ^{4}J 3.0, Ar*C*), 136.3 (d, ^{3}J 7.6, Ar*C*), 159.8, 161.5 (d, ^{1}J 243.4, Ar*C*); HRMS (NSI+) calculated for $[C_{11}H_{11}Cl_3{}^{19}FN_2]^+$ $(M+H)^+$: *m/z* 294.9966, found 294.9967 (+0.1 ppm).

2,2,2-trichloro-1-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-imine

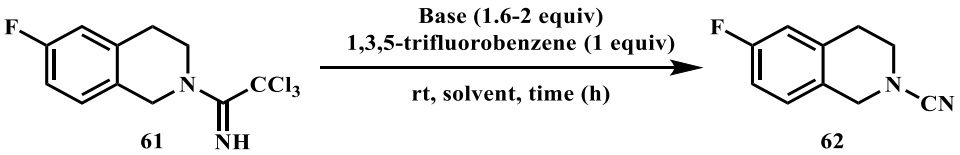


To a small glass vial containing a magnetic follower was charged in order 6-fluoro-1,2-3,4-tetrahydroisoquinoline **60** (81.9 µL, 0.60 mmol, 1 equiv), 1,3,5-trifluorobenzene (6.21 µL, 0.06 mmol, 0.1 equiv) as internal standard and trichloroacetonitrile **56** (120 µL, 1.20 mmol, 2 equiv). The reaction mixture was stirred and analysed by $^{19}F\{^{1}H\}$ NMR, taking aliquots at three time points (T1 = 30 minutes, T2 = 2 h, T3 = 3 h). Each $^{19}F\{^{1}H\}$ NMR was analysed to determine the composition of the reaction mixture, quoted as a ratio of starting material **60** to product **61** to other products, i.e. **60**:**61**:Other. The results are shown in the table below.

Entry	TCAN / eq.	T= 30 min **60** : **61** : Other	T= 2 h **60** : **61** : Other	T= 3 h **60** : **61** : Other	Yield/ %
1	2	39:60:1	3:96:1	0:99:1	91

After stirring for 3 h at rt, purification by flash silica column chromatography (eluent = 15% EtOAc in hexanes, 30 x 120 mm silica), gave the title compound **2** (161 mg, 0.54 mmol, 91% yield) as a light yellow oil with physical properties and spectroscopic data identical to those obtained previously.

5.2.2 Optimisation of 2nd Step

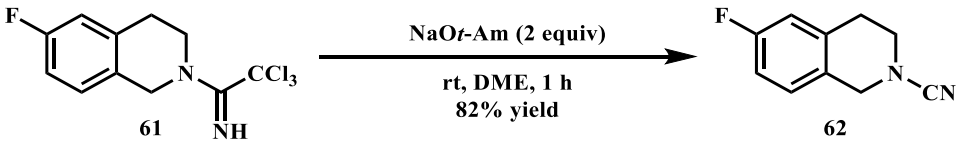


General Procedure 2

To a glass vial containing a magnetic follower was charged in order 2,2,2-trichloro-1-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-imine **61** (29.6 mg, 0.10 mmol, 1 equiv.), the required volume of the requisite solvent to provide the desired concentration ([**2**] = 0.20 mol dm^{-3}, total reaction volume = 0.50 mL), 1,3,5-trifluorobenzene (10.3 µL, 0.10 mmol, 1 equiv.) as internal standard and the requisite base (1.6 or 2 equiv.). The reaction mixture was stirred at rt and monitored by taking aliquots at specified times (T1 = 5 or 30 minutes, T2 = 5 h, T3 = 23 h) *via* $^{19}F\{^{1}H\}$ NMR analysis. Each $^{19}F\{^{1}H\}$ NMR was analysed to determine the composition of the reaction mixture, quoted as a ratio of starting material **61** to product **62** to other products, i.e. **61**:**62**:Other. The results are shown in the table below. For entry 6 the crude product was purified by flash silica column chromatography (eluent = 25% EtOAc in hexanes) to give the recorded yield.

Entry	Base (equiv)	Solvent	T1 / min	**61** : **62** : O /%	T= 5 h **61** : **62** : O /%	T= 23 h **61** : **62** : O /%
1	DBN (2)	THF	30	99 : 0 : 1	99 : 0 : 1	97 : 0 : 3
2	DBU (2)	THF	30	98 : 0 : 2	98 : 0 : 2	98 : 0 : 2
3	TBD (2)	THF	30	100 : 0 : 0	100 : 0 : 0	95 : 5 : 0
4	KO*t*-Bu (2)	THF	30	11 : 89 : 0	10 : 90 : 0	7 : 93 : 0
5	NaOAm (2)	THF	30	5 : 95 : 0	4 : 96 : 0	3 : 97 : 0
6	**NaOAm (2)**	**DME**	**30**	**0 : 100 : 0**	**0 : 100 : 0**	**0 : 100 : 0**
7	NaH (2)	THF	30	8 : 91 : 1	40 : 60 : 0	0 : 100 : 0
8	LHMDS (2)	THF	5	Complex mixture		
9	KHMDS (2)	Tol	5	Complex mixture		
10	KHMDS (1.6)	Tol	5	3 : 84 : 13	-	-

6-fluoro-3,4-dihydroisoquinoline-2(1*H*)-carbonitrile (Entry 6)



To a 10 mL microwave vial containing a magnetic follower was charged in order 2,2,2-trichloro-1-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)ethan-1-imine **61** (177 µL, 0.60 mmol, 1 equiv), DME (3 mL), 1,3,5-trifluorobenzene (62.1 µL, 0.60 mmol, 1 equiv) as internal standard and NaO*t*-Am (132 mg, 1.20 mmol, 2 equiv). The reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched by drop-wise addition of sat. aq. $NaHCO_3$ and the product extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash silica column chromatography (eluent = 25% EtOAc in hexanes, 22 x 120 mm silica), gave the title compound **62** (86.6 mg, 0.50 mmol, 82% yield) as a yellow solid; mp 45-47 °C; R_f = 0.19 (eluent = 20% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2930 (C-H), 2212 (C≡N), 1616, 1503, 1387, 1236, 1144; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 2.96 (2H, t, *J* 5.9, C*H*$_2$), 3.48 (2H, t, *J* 5.9, C*H*$_2$), 4.39 (2H, s, C*H*$_2$), 6.86 (1H, dd, *J* 9.2, 2.6, Ar*H*), 6.92 (1H, td, *J* 8.4, 2.6,Ar*H*), 7.02 (1H, dd, *J* 8.4, 5.6, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) σ_F: -114.9; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) σ_c: 27.9 (d, ^{4}*J* 1.5, *C*H$_2$), 46.5 (*C*H$_2$), 49.8 (*C*H$_2$), 114.2 (d, ^{2}*J* 21.7, Ar*C*), 115.8 (d, ^{2}*J* 21.2, Ar*C*), 117.9 (*C*≡N), 126.5 (d, ^{4}*J* 3.1, ArC), 127.8 (d, ^{3}*J* 8.3, Ar*C*), 134.9 (d, ^{3}*J* 7.6, Ar*C*), 161.7 (d, ^{1}*J* 244.8, Ar*C*); HRMS (ASAP+) calculated for $[C_{10}H_{10}FN_2]^+$ $(M+H)^+$: *m/z* 177.0828, found 177.0833 (+2.8 ppm).

5.2.3 Substrate scope

General procedure 3

To an appropriate reaction vessel containing a magnetic follower was charged the requisite amine (1 equiv), MeCN ([amine] = 1 mol dm^{-3}) and trichloroacetonitrile (1.1 equiv). The reaction mixture was stirred at rt until the reaction was complete by TLC analysis (typically 16-24 h). The reaction mixture was concentrated *in vacuo* ensuring that all MeCN and remaining trichloroacetonitrile is removed. The reaction mixture was diluted with DME ([intermediate amidine] = 0.2 M) and NaO*t*-Am (2 equiv) was added in a single portion followed by stirring at rt for 1 h. Mesitylene (1 equiv) was added as internal standard and an aliquot of the reaction mixture was analysed by ^{1}H NMR to determine the NMR yield. The reaction mixture was quenched by drop-wise addition of sat. aq. $NaHCO_3$ and the product extracted with EtOAc (× 3). The combined organic fraction was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

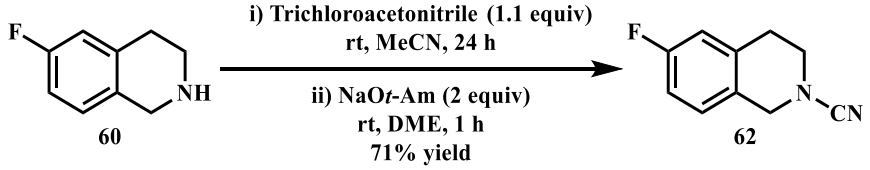
General procedure 4

To an appropriate reaction vessel containing a magnetic follower was charged the requisite amine (1 equiv), MeCN ([amine] = 1 mol dm^{-3}) and trichloroacetonitrile (1.1 equiv). The reaction mixture was stirred at rt until the reaction was complete by TLC analysis (typically 16-24 h). The reaction mixture was concentrated *in vacuo* ensuring that all MeCN and remaining trichloroacetonitrile is removed. The reaction mixture was diluted with DME ([intermediate amidine] = 0.2 M) and 4-methylstyrene (1 equiv.) was added as a dichlorocarbene scavenger. NaO*t*-Am (2 equiv) was added in a single portion followed by stirring at rt for 1 h. Mesitylene (1 equiv) was added as internal standard and an aliquot of the reaction mixture was analysed by ^{1}H NMR to determine the NMR yield. The reaction mixture was quenched by drop-wise addition of sat. aq.. $NaHCO_3$ and the product extracted with EtOAc (× 3). The combined organic fraction was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

General procedure 5

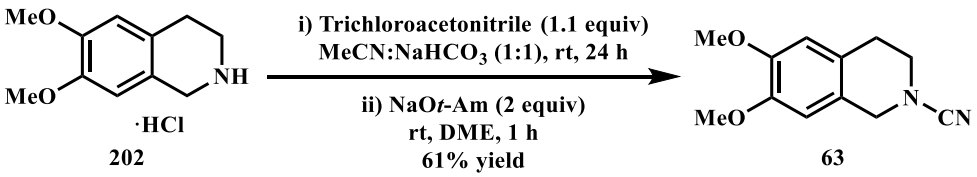
To an appropriate reaction vessel containing a magnetic follower was charged the requisite amine (1 equiv.), MeCN ([amine] = 1 mol dm^{-3}), trichloroacetonitrile (1.1 equiv) and imidazole (10 mol%). The reaction mixture was stirred at 80 °C until the reaction was complete by TLC analysis (typically 16-24 h). The reaction mixture was concentrated *in vacuo* ensuring that all MeCN and remaining trichloroacetonitrile is removed. The reaction mixture was diluted with DME ([intermediate amidine] = 0.2 M) and NaO*t*-Am (2 equiv) was added in a single portion followed by stirring at rt for 1 h. Mesitylene (1 equiv) was added as internal standard and an aliquot of the reaction mixture was analysed by ^{1}H NMR to determine the NMR yield. The reaction mixture was quenched by drop-wise addition of sat. aq. $NaHCO_3$ and the product extracted with EtOAc (× 3). The combined organic fraction was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

6-fluoro-3,4-dihydroisoquinoline-2(1*H*)-carbonitrile



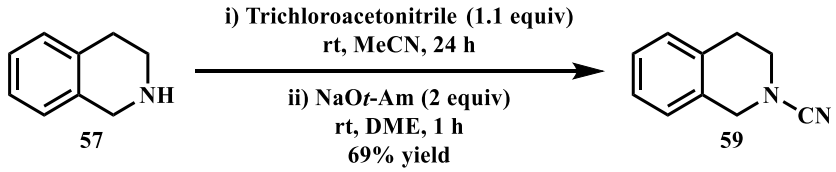
Following general procedure 3, 6-fluoro-1,2,3,4-tetrahydroisoquinoline **60** (137 µL, 1.00 mmol, 1 equiv.), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 79% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **62** (125 mg, 0.71 mmol, 71% yield) as a yellow solid with physical properties and spectroscopic data identical to those obtained previously.

6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carbonitrile



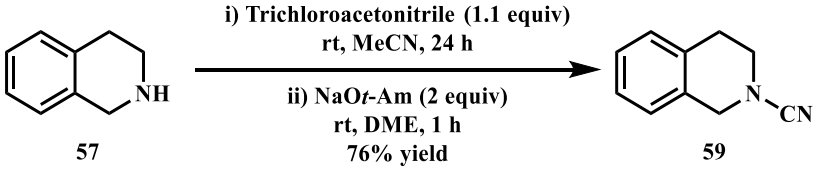
Following modified general procedure 3, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride **202** (229 mg, 1 mmol, 1 equiv), MeCN (1 mL) sat. aq. $NaHCO_3$ (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) were stirred for 24 h at rt. The reaction was then diluted with H_2O (15 mL) and extracted in EtOAc (3 × 10 mL). Combined organics washed with brine and dried over $MgSO_4$ and filtered before concentration *in vacuo*. The resultant concentrate was dissolved in DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) was added followed by stirring for 1 h at rt. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted into EtOAc (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* After flash silica column chromatography (eluent = 15 % EtOAc in hexanes, 30 x 120 mm silica) the title compound **63** (133 mg, 0.61 mmol, 61% yield) as a white solid; mp 124-126 °C; R_f = 0.1 (eluent = 15% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2958 (C-H), 2201 (C≡N),1616, 1517, 1463, 1381, 1228, 1111; ^1H NMR (400 MHz, $CDCl_3$) σ_H: 2.89 (2H, t, *J* 5.8, C*H*$_2$) 3.47 (2H, t, *J* 5.8, C*H*$_2$), 3.85 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 4.36 (2H, s, C*H*$_2$), 6.51 (1H, s, Ar*H*), 6.61 (1H, s, Ar*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) σ_c: 27.2 (*C*H$_2$), 46.9 (*C*H$_2$), 49.8 (*C*H$_2$), 56.0 (O*C*H$_3$), 56.0 (O*C*H$_3$), 108.5 (*C*≡N), 111.7 (Ar*C*), 118.0 (Ar*C*), 122.5 (Ar*C*), 124.5 (Ar*C*), 148.0 (Ar*C*), 148.2 (Ar*C*); HRMS (EI+) calculated for $[C_{12}H_{14}O_2N_2]^+$ $(M)^+$: *m/z* 218.1050, found 218.1054 (+0.4 ppm).

3,4-dihydroisoquinoline-2(1*H*)-carbonitrile



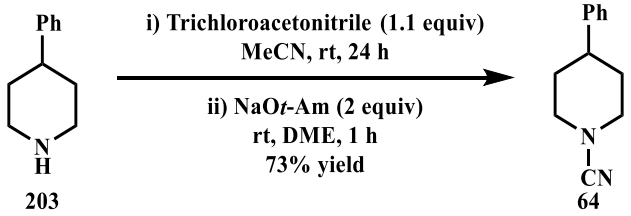
Following General procedure 3, 1,2,3,4-tetrahydroisoquinoline **57** (120 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 75% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **59** (109 mg, 0.69 mmol, 69% yield) as a white solid with physical properties and spectroscopic data in accordance with the literature.[1] mp 42-44 °C; {lit.[1] mp 68-70 °C}; R_f = 0.25 (eluent = 15% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) σ_H: 2.97 (2H, t, *J* 5.9, C*H*$_2$), 3.50 (2H, t, *J* 5.9, C*H*$_2$), 4.43 (2H, s, C*H*$_2$), 7.03-7.08 (1H, m, Ar*H*), 7.13-7.17 (1H, m, Ar*H*), 7.19-7.25 (2H, m, Ar*H*).

3,4-dihydroisoquinoline-2(1*H*)-carbonitrile (Scale-up Reaction)



Following general procedure 3, 1,2,3,4-tetrahydroisoquinoline **57** (2.50 mL, 20.0 mmol, 1 equiv), MeCN (20 mL) and trichloroacetonitrile **56** (2.21 mL, 22.0 mmol, 1.1 equiv) for 24 h at rt followed by DME (100 mL) and NaO*t*Am (4.41 g, 40.0 mmol, 2 equiv) for 1 h at rt gave 78% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 50 x 120 mm silica), the title compound **59** (2.42 g, 15.3 mmol, 76% yield) as a white solid with physical properties and spectroscopic data identical to those obtained previously.

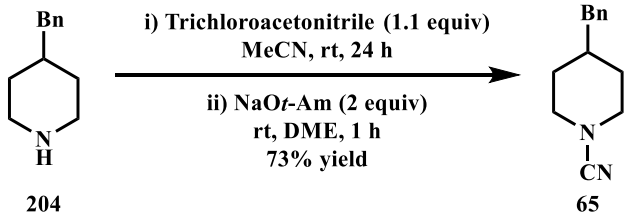
4-phenylpiperidine-1-carbonitrile



203 64

Following general procedure 3, 4-phenylpiperidine **203** (161 mg, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 89% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 20% EtOAc in hexanes, 30 x 120 mm silica), the title compound **64** (136 mg, 0.73 mmol, 73% yield) as an off-white solid with physical properties and spectroscopic data in accordance with the literature.[1] mp 76-78 °C; {lit.[1] mp 69-71 °C}; R_f = 0.3 (eluent = 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.85-1.89 (4H, m, 2×C*H*$_2$), 2.58-2.60 (1H, m, C*H*), 3.12-3.19 (2H, m, C*H*$_2$), 3.52-3.57 (2H, m, C*H*$_2$), 7.19-7.26 (3H, m, Ar*H*), 7.31-7.35 (2H, m, Ar*H*).

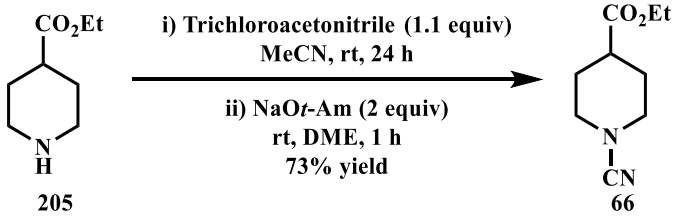
4-benzylpiperidine-1-carbonitrile



204 65

Following general procedure 3, 4-benzylpiperidine **204** (175 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 79% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **65** (146 mg, 0.73 mmol, 73% yield) as a yellow oil with physical properties and spectroscopic data in accordance with the literature.[1] ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.34-1.42 (2H, m, C*H*$_2$), 1.59-1.68 (3H, m, C*H*$_2$, C*H*), 2.55 (2H, d, *J* 6.9, C*H*$_2$), 2.91-2.95 (2H, m, C*H*$_2$), 3.38 (2H, d, *J* 10.21, C*H*$_2$), 7.12 (2H, d, *J* 6.9, PhC*H*$_2$), 7.21-7.23 (1H, m, Ar*H*), 7.27-7.31(2H, m, Ar*H*).

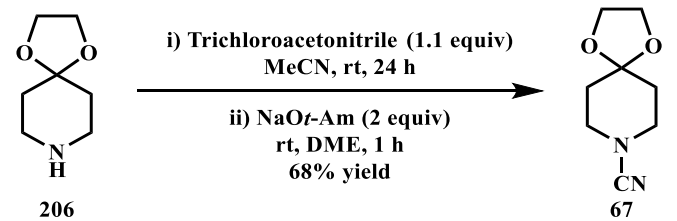
ethyl 1-cyanopiperidine-4-carboxylate



205 **66**

Following general procedure 3, ethyl piperidine-4-carboxylate **205** (154 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 79% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **66** (135 mg, 0.73 mmol, 73% yield) as a yellow oil with physical properties and spectroscopic data in accordance with the literature.[1] ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.26 (3H, t, *J* 7.2, CH_2CH_3), 1.81-1.88 (2H, m, CH_2), 1.95-1.99 (2H, m, CH_2), 2.39-2.46 (1H, m, C*H*), 3.03-3.10 (2 H, m, CH_2), 3.41-3.45 (2H, m, CH_2), 4.15 (2 H, q, *J* 7.2, CH_2CH_3).

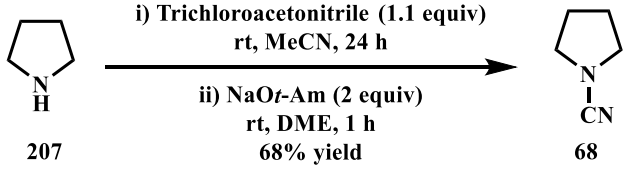
1,4-dioxa-8-azaspiro[4.5]decane-8-carbonitrile



206 **67**

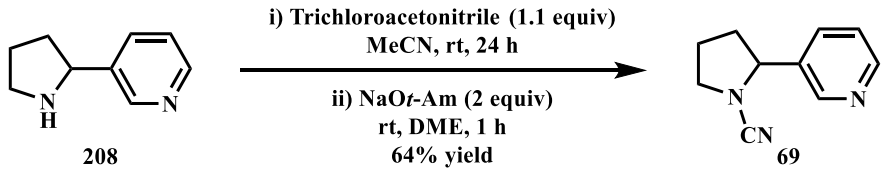
Following general procedure 4, 1,4-dioxa-8-azaspiro[4.5]decane **206** (126 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 89% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **67** (151 mg, 0.68 mmol, 68% yield) as a white solid; mp 68-71 °C; R_f = 0.16 (eluent = 25% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2956 (C-H), 2208 (C≡N), 1134, 1093 ; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.77-1.80 (4H, m, CH_2), 3.32-3.35 (4H, m CH_2), 3.97 (4H, s, 2×OCH_2); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) σ_c: 34.2 (CH_2), 48.0 (CH_2), 64.6 (CH_2), 105.5 (*C*), 118.1 (*C*≡N); HRMS (NSI+) calculated for $[C_8H_{13}N_2O_2]^+$ $(M+H)^+$: *m/z* 169.0977, found 169.0981 (+2.4 ppm).

pyrrolidine-1-carbonitrile



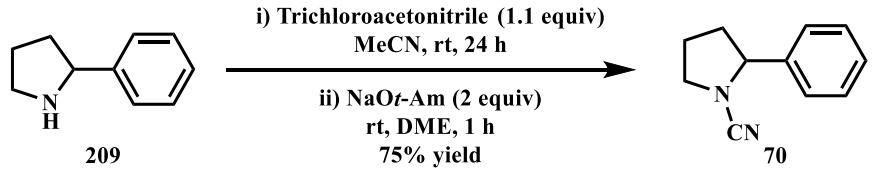
Following general procedure 3, pyrrolidine **207** (83.5 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 78% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 60% Et_2O in hexanes, 30 x 120 mm silica), the title compound **68** (65.6 mg, 0.68 mmol, 68% yield) as a light brown oil; R_f = 0.40 (eluent = 40% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2959 (C-H), 2208 (C≡N), 1458, 1532, 1282, 1123; ^1H NMR (400 MHz, $CDCl_3$) σ_H: 1.88-1.91 (4H, m, 2×C*H*(3)$_2$), 3.37-3.40 (4H, m, 2×C*H*(2)$_2$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) σ_c: 25.7 (*C*H_2), 50.5 (*C*H_2), 118.0 (*C*≡N); (HRMS (EI+) calculated for $[C_5H_8N_2]^+$ $(M)^+$: *m/z* 96.0687, found 96.0682 (-5.2 ppm)

2-(pyridin-3-yl)pyrrolidine-1-carbonitrile



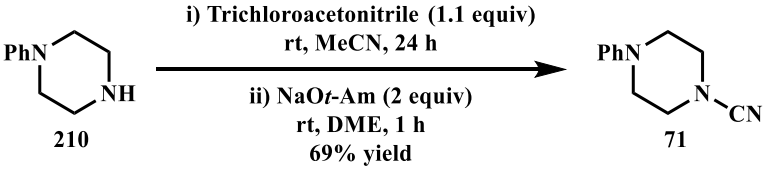
Following general procedure 3, 3-(pyrrolidin-2-yl)pyridine **208** (148 mg, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt after flash silica column chromatography (eluent = EtOAc, 30 x 120 mm silica), the title compound **69** (111 mg, 0.64 mmol, 64% yield) as a yellow oil; R_f = 0.3 (eluent = EtOAc); ν_{max} cm^{-1} (film) 2937 (C-H), 2205 (C≡N), 1577. 1427, 1242, 1103; ^1H NMR (400 MHz, $CDCl_3$) σ_H: 1.83-1.92 (1H, m, C*H*), 2.05-2.10 (2H, m, C*H*$_2$), 2.41 (1H, dq, *J* 12.8, 6.4, C*H*), 3.60 (1H, q, *J* 7.4, C*H*), 3.73 (1H, q, *J* 7.8, C*H*), 4.70 (1H, t, *J* 7.2, C*H*), 7.32-7.35 (1H, m, Ar*H*), 7.64 (1H, d, *J* 7.8, Ar*H*), 8.58 (2H, br. s., Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) σ_c 24.8 (*C*H_2), 35.5 (*C*H_2), 51.6 (*C*H_2), 63.7 (*C*H), 116.4 (*C*≡N), 123.8 (Ar*C)*, 134.1 (Ar*C)*, 135.4 (Ar*C)*, 148.1 (Ar*C)*, 149.6 (Ar*C)*; HRMS (FTMS) calculated for $[C_{10}H_{12}N_3]^+$ $(M + H)^+$: *m/z* 174.1026, found 174.1022 (-2.1 ppm).

2-phenylpyrrolidine-1-carbonitrile



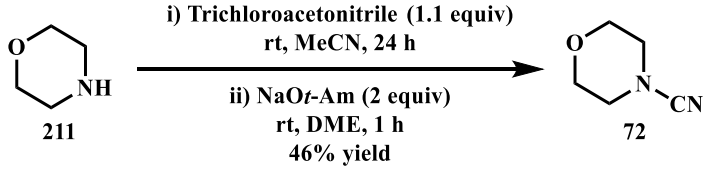
Following general procedure 3, 2-phenylpyrrolidine **209** (147 mg, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt after flash column chromatography (eluent = 30% EtOAc in hexanes, 30 x 120 mm silica), the title compound **70** (130 mg, 0.75 mmol, 75% yield) as an orange oil with physical properties and spectroscopic data in accordance with the literature.[1] R_f = 0.35 (eluent = 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.78-1.90 (1H, m, C*H*), 1.92-2.04 (2H, m, CH_2), 2.25-2.33 (1H, m, C*H*), 3.52-3.57 (1H, m, C*H*), 3.67 (1H, q, *J* 7.8, C*H*), 4.62 (1H, t, *J* 7.0, C*H*), 7.22-7.24 (3H, m, Ar*H*), 7.28-7.35 (2H, m, Ar*H*); HRMS (FTMS) calculated for $[C_{11}H_{13}N_2]^+$ $(M + H)^+$: *m/z* 173.1073, found 173.1070 (+0.3 ppm).

4-phenylpiperazine-1-carbonitrile



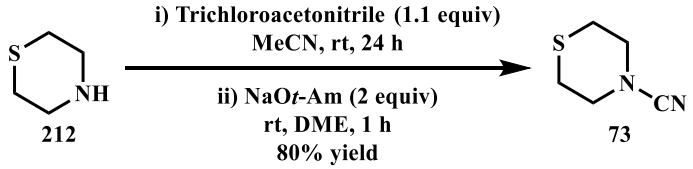
Following general procedure 3, 1-phenylpiperazine **210** (153 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 83% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **71** (130 mg, 0.69 mmol, 69% yield) as a light brown solid with physical properties and spectroscopic data in accordance with the literature.[2] mp 50-52 °C; {lit.[2] mp 51-52 °C}; R_f = 0.38 (eluent = 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 3.23-3.25 (4H, m, 2×CH_2), 3.39-3.41 (4H, m, 2×CH_2), 6.90-6.97 (3H, m, Ar*H*) 7.27-7.32 (2H, m, Ar*H*).

morpholine-4-carbonitrile



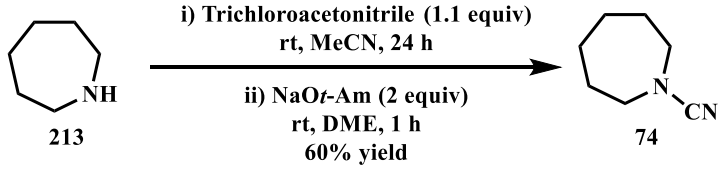
Following general procedure 3, morpholine **211** (87.5 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 75% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 40% EtOAc in hexanes, 30 x 120 mm silica), the title compound **72** (51.3 mg, 0.46 mmol, 46% yield) as a light brown oil with physical properties and spectroscopic data in accordance with the literature.[3] R_f = 0.31 (eluent = 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 3.24-3.26 (4H, m, 2×C*H*$_2$N), 3.74-3.76 (4H, m, 2×C*H*$_2$O).

Thiomorpholine-4-carbonitrile



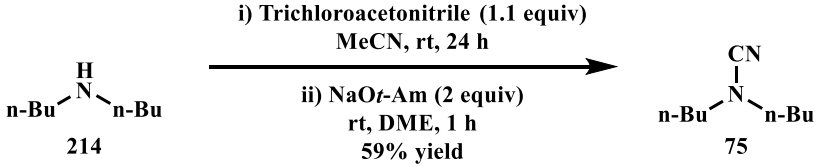
Following general procedure 3, thiomorpholine **212** (101 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **73** (104 mg, 0.80 mmol, 80% yield) as an off-white solid with physical properties and spectroscopic data in accordance with the literature.[4] mp 41-43 °C; {lit.[1] mp 41-43 °C}; R_f = 0.2 (eluent = 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 2.70-2.72 (4H, m, 2×C*H*$_2$), 3.46-3.48 (4H, m, 2×C*H*$_2$).

azepane-1-carbonitrile



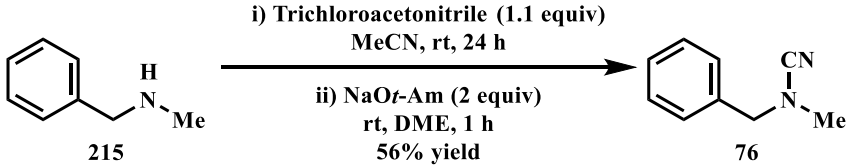
Following general procedure 3, azepane **213** (123 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 65% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 30% EtOAc in hexanes, 30 x 120 mm silica), the title compound **74** (74.1 mg, 0.60 mmol, 60% yield) as a light brown oil; R_f = 0.48 (eluent = 30% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2924 (C-H), 2859, 2197 (C≡N), 1451, 1389, 1163, 1130, 1092; ^{1}H NMR (500 MHz, $CDCl_3$) σ_H: 1.61-1.66 (4H, m, 2×C*H*$_2$), 1.73-1.79 (4H, m, 2×C*H*$_2$), 3.25 (4H, t, *J* 5.9, 2×C*H*$_2$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) σ_c: 27.3, 28.6, 51.3, 119.5 (*C*≡N); HRMS (EI+) calculated for $[C_7H_{12}N_2]^+$ $(M)^+$: *m/z* 124.1000, found 124.1000 (±0.0 ppm).

***N,N*-dibutylcyanamide**



Following general procedure 3, dibutylamine **214** (168 mg, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 60% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 20% EtOAc in hexanes, 30 x 120 mm silica), the title compound **75** (92.6mg, 0.59 mmol, 59% yield) as a red oil with physical properties and spectroscopic data in accordance with the literature.[1] ; R_f = 0.69 (eluent = 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 0.94 (6H, t, *J* 7.3, 2×C*H*$_3$), 1.38 (4H, dq, *J* 15.0, 7.3, 2×CH_3C*H*$_2$), 1.58-1.65 (4H, m, 2×CH_3CH_2C*H*$_2$), 2.97 (4H, t, *J* 7.3, 2×NC*H*$_2$).

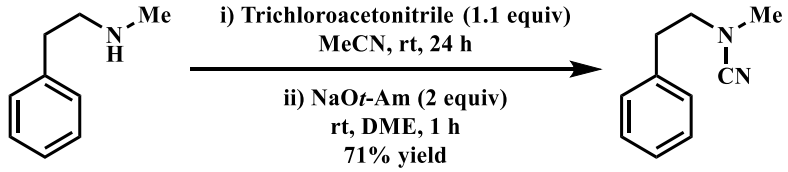
_N_-benzyl-_N_-methylcyanamide



215 76

Following general procedure 3, N-benzylmethylamine **215** (129 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 63% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 25% EtOAc in hexanes, 30 x 120 mm silica), the title compound **76** (82 mg, 0.56 mmol, 56% yield) as a yellow oil with physical properties and spectroscopic data in accordance with the literature.[1] R_f = 0.25 (eluent = 25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 2.78 (3H, s, C*H*$_3$), 4.16 (2H, s, PhC*H*$_2$), 7.34-7.40 (5H, m, Ar*H*).

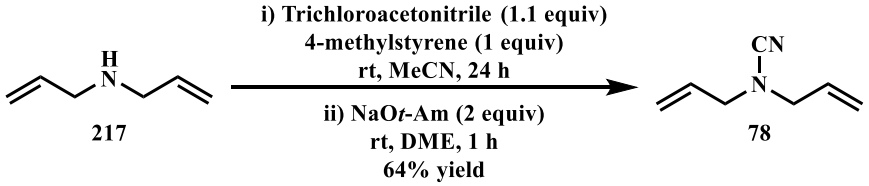
_N_-methyl-_N_-phenethylcyanamide



216 77

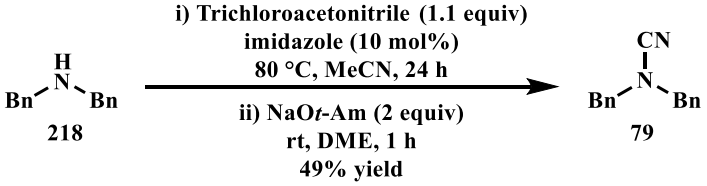
Following general procedure 3, N-methyl-2-phenylethan-1-amine **216** (145 mg, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 79% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 15 - 30% EtOAc in hexanes, 30 x 120 mm silica), the title compound **77** (114 mg, 0.71 mmol, 71% yield) as a yellow oil with physical properties and spectroscopic data in accordance with the literature.[1] R_f = 0.3 (eluent = 15% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 2.85 (3H, s, C*H*$_3$), 2.95-2.99 (2H, m, C*H*$_2$), 3.24 (2H, t, *J* 7.50, C*H*$_2$), 7.24-7.28 (3H, m, Ar*H*), 7.29-7.37 (2H, m, Ar*H*).

N,N-diallylcyanamide



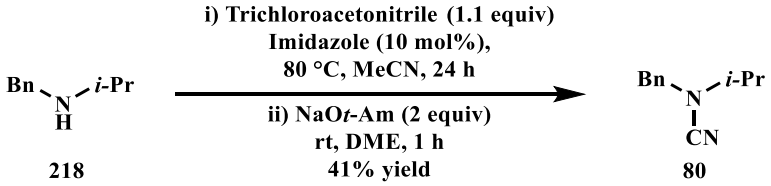
Following general procedure 4, diallylamine **48** (123 µL, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) for 24 h at rt followed by DME (5 mL), 4-methylstyrene **83** (132 µL, 1.00 mmol, 1 equiv) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 69% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 15% EtOAc in hexanes, 30 x 120 mm silica), the title compound **78** (77.9 mg, 0.64 mmol, 64% yield) as a light yellow oil with physical properties and spectroscopic data in accordance with the literature.[1] R_f = 0.25 (eluent = 10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 3.62 (4H, dt, *J* 6.4, 1.2, 2×C*H*$_2$), 5.31 (2H, dd, *J* 7.8, 1.2, 2×C*H*), 5.34 (2H, app. s, 2×C*H*), 5.79-5.89 (2H, m, 2×C*H*).

N,N-dibenzylcyanamide



Following General procedure 5, dibenzylamine **218** (192 µL, 1.00 mmol, 1 equiv), MeCN (1 mL), trichloroacetonitrile **56** (110 µL, 1.10 mmol, 1.1 equiv) and imidazole (6.81 mg, 0.10 mmol, 10 mol %) for 24 h at 80 °C followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 50% NMR yield (mesitylene internal standard) and, after flash silica column chromatography (eluent = 12.5% EtOAc in hexanes, 30 x 120 mm silica), the title compound **79** (110 mg, 0.49 mmol, 49% yield) as a light brown solid with physical properties and spectroscopic data in accordance with the literature.[1] mp 45-46 °C; {lit.[1] mp 51-53 °C}; R_f = 0.62 (eluent = 20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) σ_H: 4.12 (4H, s, 2×PhC*H*$_2$), 7.30-7.32 (4H, m, Ar*H*), 7.34-7.41 (6H, m, Ar*H*).

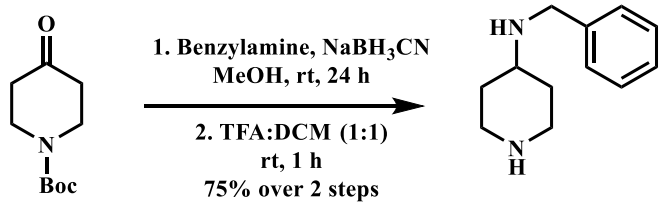
N-benzyl-*N*-isopropylcyanamide



Following modified general procedure 5, *N*-benzylpropan-2-amine **218** (149 mg, 1 mmol, 1 equiv), MeCN (1 mL) trichloroacetonitrile **56** (110 µL, 1.1 mmol, 1.1 equiv) and (6.81 mg, 0.10 mmol, 10 mol %) for 24 h at 80 °C followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave 49% NMR yield (mesitylene internal standard) and after flash silica column chromatography (eluent = 20% EtOAc in hexanes, 30 x 120 mm silica), the title compound **80** (72.1 mg, 0.41 mmol, 41% yield) as a yellow oil with physical properties and spectroscopic data in accordance with the literature.[2] ; R_f = 0.27 (eluent = 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.25 (6H, d, *J* 6.5, 2×C*H*$_3$), 3.12 (1H, dt, *J* 13.0, 6.5, C*H*), 4.22 (2H, s, PhC*H*$_2$), 7.32-7.39 (5H, m, Ar*H*).

5.2.4 Selectivity studies

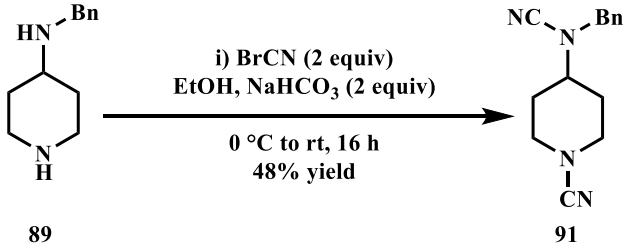
tert-butyl 4-(benzylamino)piperidine-1-carboxylate



90 **89**

To a flame dried 250 mL round bottomed flask was added tert-butyl 4-oxopiperidine-1-carboxylate **90** (2.00 g, 10.0 mmol, 1 equiv), MeOH (50 mL) followed by benzylamine (1.21 mL, 11 mmol, 1.1 eq) and acetic acid (1.5 mL). $NaBH_3CN$ (1.26 g, 20.o mmol, 2 equiv) was then added portionwise. The vessel was purged with nitrogen and allowed to stir at rt overnight. After 24 h the reaction was concentrated *in vacuo* and the residue taken up in NaOH (2 M) and extracted into CH_2Cl_2. The combined organics were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude colourless oil. The oil was taken crude and added to a flame dried 50 mL round bottomed flask with CH_2Cl_2 (7 mL). The solution was cooled to 0 °C and TFA (7 mL, 92 mmol, 10 equiv) was added dropwise and the reaction stirred for 1 h. After 1 h the reaction was then concentrated *in vacuo* and then diluted with NaOH (2 M) and extracted into EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a crude white solid. To the solid was then added hexanes (50 mL) and the mixture stirred for 30 minutes. The solution was then filtered to yield the pure title compound **89** (1.43 g, 7.50 mmol, 75% yield over 2 steps) as a white solid. mp 62-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.44-1.53 (2H, m, C*H*$_2$), 2.01 (2H, d, *J* 10.9, C*H*$_2$), 2.72-2.78 (3H, m), 3.22-3.26 (3H, m), 3.82 (2H, s, PhC*H*$_2$), 7.27 (2H, br. s., Ar*H*), 7.30-7.35 (4H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) σ_c: 30.1, 42.8, 50.8, 51.8, 127.3 (Ar*C)*, 128.2 (Ar*C)*, 128.7 (Ar*C)*, 139.9 (Ar*C)*; HRMS (EI+ calculated for $[C_{12}H_{18}N_2]^+$ $(M)^+$: *m/z* 190.1470, found 190.1473 (+1.6 ppm).

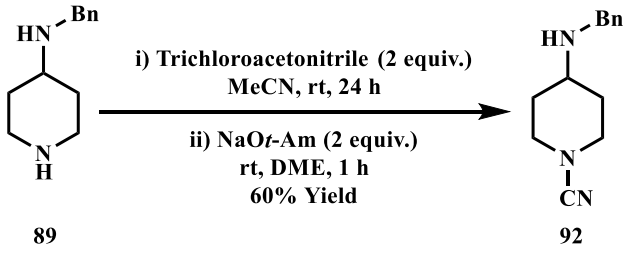
_N_-benzyl-_N_-(1-cyanopiperidin-4-yl)cyanamide



89 **91**

To a reaction vial was added N-benzylpiperidin-4-amine **89** (190 mg, 1.00 mmol, 1 equiv), EtOH (2 mL, 0.2 M) and $NaHCO_3$ (168 mg, 2.00 mmol, 2 equiv). The slurry was cooled to 0 °C before BrCN **30** (212 mg, 2.00 mmol, 2 equiv) was added. The reaction is allowed to warm to rt and stirred overnight. The slurry was then filtered and the filter cake washed with EtOH before the filtrate is concentrated *in vacuo*. The residue was then purified by flash silica column chromatography (eluent = EtOAc 40-60% in hexanes, 30 x 120 mm silica), to yield the pure title compound **91** (115.4 mg, 0.48 mmol, 48% yield) as a white solid. mp 40-42 °C; R_f = 0.32 (eluent = EtOAc 40% in hexanes); ν_{max} cm^{-1} (film) 2927 (C-H), 2200 (C≡N), 1456, 1384, 1361, 1145, 1068, 702; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.74-1.95 (4H, m, 2×CH_2), 2.80-2.87 (1H, m, C*H*), 2.88-3.02 (2H, m, CH_2), 3.50 (2H, d, *J* 13.33, CH_2), 4.25 (2H, s, PhCH_2), 7.29 - 7.42 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) σ_c: 29.0, 48.1, 54.3, 54.3, 115.8 (*C*≡N), 117.2 (*C*≡N), 128.2 (Ar*C)*, 128.9 (Ar*C)*, 129.1 (Ar*C)*, 134.6 (Ar*C)*; HRMS (EI+ calculated for $[C_{14}H_{17}N_4]^+$ $(M)^+$: *m/z* 241.1453, found 241.1446 (-2.9 ppm).

4-(benzylamino)piperidine-1-carbonitrile



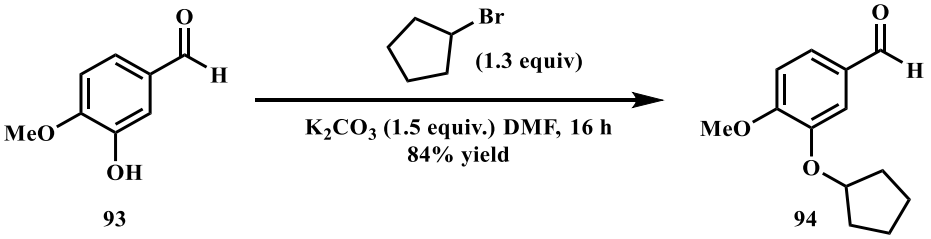
89 **92**

Following General procedure 3, N-benzylpiperidin-4-amine **89** (190 mg, 1.00 mmol, 1 equiv), MeCN (1 mL) and trichloroacetonitrile (200 µL, 2 mmol, 2 equiv) for 24 h at rt followed by DME (5 mL) and NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) for 1 h at rt gave after flash silica column chromatography (eluent = 1% Et_3N in EtOAc, 30 x 120 mm silica), the title compound **92** (130 mg, 0.60 mmol, 60% yield) as a brown solid. mp 56-60 °C; R_f = 0.4 (eluent = 1% Et_3N in EtOAc); ν_{max} cm^{-1} (film) 2924 (C-H), 2204 (C≡N),

1688, 1456, 1386, 1214, 704; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.48-1.57 (2H, m, C*H*$_2$), 1.93 (2H, dd, *J* 13.2, 3.3, C*H*$_2$), 2.65-2.70 (1H, m, C*H*), 2.99-3.05 (2H, m, C*H*$_2$), 3.43-3.49 (2H, m, C*H*$_2$), 3.81 (2H, s, PhC*H*$_2$), 7.28-7.35 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) σ_c: 31.3, 48.1, 50.8, 52.4, 118.4 (C≡N), 127.3 (Ar*C*), 128.2 (Ar*C*), 128.7 (Ar*C*), 140.0 (Ar*C*); HRMS (EI+ calculated for $[C_{13}H_{17}N_3]^+$ $(M)^+$: *m/z* 215.1422, found 215.1432 (+4.6 ppm)

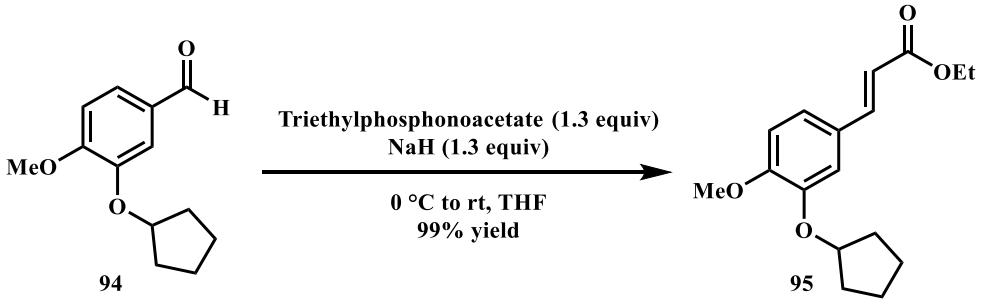
5.2.5 Synthesis of Rolipram derived cyanamide

3-(cyclopentyloxy)-4-methoxybenzaldehyde



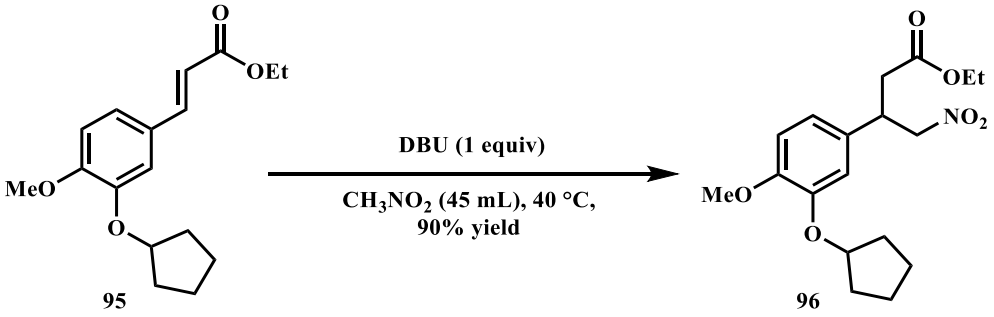
Following a modified procedure,[5] to a flame dried 500 mL round bottomed flask was added sequentially 3-hydroxy-4-methoxybenzaldehyde **93** (25 g, 164 mmol, 1 equiv), K-$_2$CO$_3$ (34 g, 246 mmol, 1.5 equiv) and cyclopentyl bromide (22 mL, 213 mmol, 1.3 equiv) in DMF (150 mL). The mixture was stirred at 65 °C for 16 h. The solution was then allowed to cool before filtering. The filter cake was washed with EtOAc. The filtrate was then diluted with 1:1 EtOAc:hexanes and washed with water. The organic layer was then separated, washed with brine and dried over $MgSO_4$, filtered and concentrated to yield the title compound **94** (30 g, 136 mmol, 84% yield) as an orange oil; R_f = 0.70 (eluent = 40% EtOAc in hexanes) ν_{max} cm^{-1} (film) 2958, 2358, 1681, 1581, 1506, 1431, 1236, 1130, 805, 640; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.61-1.63 (2H, m, C*H*$_2$), 1.81-1.88 (4H, m, 2×C*H*$_2$), 1.98-2.03 (2H, m, C*H*$_2$), 3.92 (3H, s, OC*H*$_3$), 4.83 (1H, br. s, C*H*), 6.95 (1H, d, *J* 8.2, Ar*H*), 7.38-7.42 (2H, m, Ar*H*), 9.83 (1H, s, C*H*O); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) σ_c: 24.2 (*C*H$_2$), 32.8 (*C*H$_2$), 56.3 (O*C*H$_3$), 80.6 (O*C*CH$_2$), 110.9 (Ar*C*), 112.2 (Ar*C*), 126.4 (Ar*C*), 130.1 (Ar*C*), 148.4 (Ar*C*), 155.5 (Ar*C*), 191.1 (*C*=O); HRMS (ASAP+) calculated for $[C_{13}H_{17}O_3]^+$ $(M)^+$: *m/z* 221.1178, found 221.1177 (-0.5 ppm).

ethyl (*E*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)acrylate



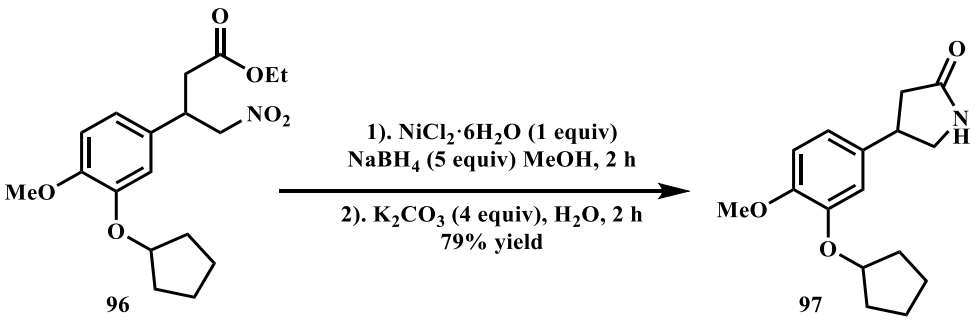
Following a modified procedure,[6] to a flame dried 1 L round bottomed flask was added THF (350 mL) followed by 60% NaH in paraffin oil (3.54 g, 89 mmol, 1.3 equiv). The solution was cooled to 0 °C in an ice water bath. Triethylphosphonacetate (17.56 mL, 88.53 mmol, 1.3 equiv) was then added dropwise. After full addition the solution was allowed to stir for 30 minutes before a solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde **94** (15 g, 68 mmol, 1 equiv) in THF (150 mL) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and was stirred until complete by TLC. Once complete the reaction was concentrated *in vacuo* and dissolved in H_2O. Extracted into Et_2O × 3 and washed with brine before drying over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to yield a yellow oil. The oil was purified by flash column chromatography (eluent = 40% EtOAc in hexanes) to yield the title compound **95** (19.7 g, 67.9 mmol, 99% yield) as a clear oil; R_f = 0.75 (eluent = 40% EtOAc in hexanes); ν_{max} cm^{-1} (film) 1958, 1703, 1631, 1508, 1249, 1026, 804; ^1H NMR (400 MHz, $CDCl_3$) σ_H: 1.33 (3H, t, *J* 7.1, CH_2CH_3), 1.61-1.63 (2H, m, CH_2), 1.81-2.04 (6H, m), 3.87 (3H, s, OCH_3), 4.25 (2H, q, *J* 7.1, CH_2), 4.77 (1H, br. s., C*H*), 6.27 (1H, d, *J* 15.9, C*H*), 6.84 (1H, d, *J* 8.25, C*H*), 7.05-7.09 (2H, m, Ar*H*), 7.61(1H, d, *J* 15.9, Ar*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) σ_c: 14.5 (CH_2CH_3), 24.2 (CH_2), 32.9 (CH_2), 56.2 (OCH_3), 60.5 (CH_2CH_3), 80.6 ($OCCH_2$), 111.7 (Ar*C*), 113.4 (Ar*C*), 115.8 (*C*HCHC=O), 122.4 (Ar*C*), 127.4 (Ar*C*), 144.8 (*C*HC=O), 148.0 (Ar*C*), 152.2 (Ar*C*), 167.4 (*C*=O); HRMS (ASAP+) calculated for $[C_{17}H_{23}O_4]^+$ $(M)^+$: *m/z* 291.1596, found 291.1594 (-0.7 ppm).

ethyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate



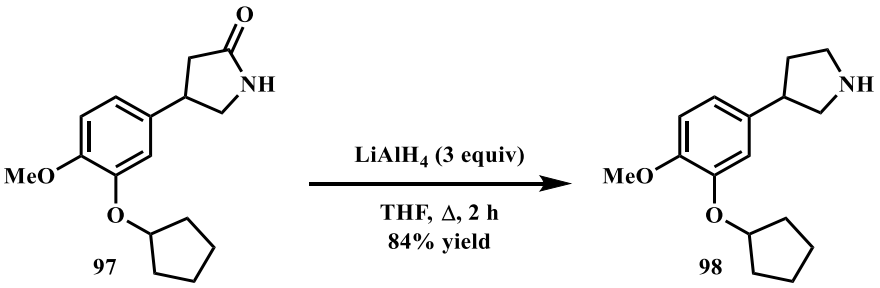
Following a modified procedure,[7] to a flamed dried 250 mL round bottomed flask was added ethyl (E)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)acrylate **95** (15.0 g, 51.7 mmol, 1 equiv) followed by CH_3NO_2 (45 mL). DBU (7.86 g, 51.7 mmol, 1 equiv) was then added and the reaction warmed to 40 °C and monitored by TLC. On completion the reaction was poured onto H_2O before extracting with Et_2O × 3. The combined organic phases were washed with brine, dried over $MgSO_4$ and filtered before concentrating *in vacuo* to yield the title compound **96** (16.4 g, 46.5 mmol, 90% yield) as a yellow solid; mp 68-70 °C; R_f = 0.61 (eluent = 20% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2957, 1732, 1514, 1431, 1255, 1234, 1138, 852, 642; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.18 (3H, t, *J* 7.1, CH_2CH_3), 1.58 - 1.61 (2H, m, C*H*$_2$), 1.80-1.95 (6H, m), 2.72 (2H, d, *J* 7.5, C*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 3.91 (1H, quin, *J* 7.5, C*H*), 4.09 (2 H, q, *J* 7.1. C*H*$_2$), 4.56-4.61 (1H, m, C*H*), 4.66-4.71, (1H, m, C*H*), 4.74 (1H, br. s., C*H*), 6.72-6.74 (2H, m, Ar*H*), 6.79-6.82 (1H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) σ_c: 14.2 (CH_2CH_3), 24.2 (CH_2), 32.9 (CH_2), 38.1 (CH_2), 40.0 (*C*H), 56.1 (OCH_3), 61.0 (CH_2), 79.9 (CH_2NO_2), 80.6 (O*C*CH_2), 112.4 (Ar*C*), 114.5 (Ar*C*), 119.4 (Ar*C*), 130.7 (Ar*C*), 148.0 (Ar*C*), 149.9 (Ar*C*), 170.8 (*C*=O); HRMS (ASAP+) calculated for $[C_{18}H_{25}NO_6]^+$ $(M)^+$: *m/z* 351.1682, found 351.1673 (-2.8 ppm).

Rolipram



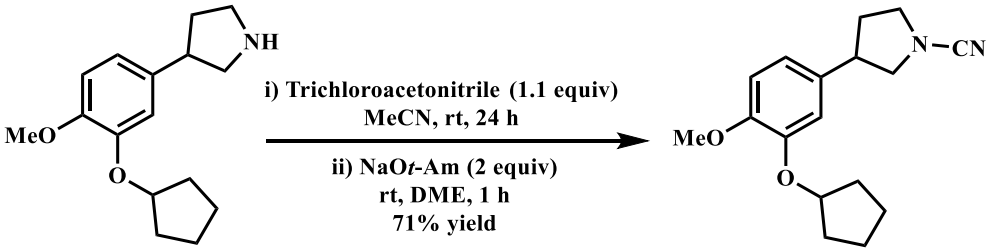
Following a modified procedure,[8] to a flame dried 1 L round bottomed flask was added ethyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate **96** (12.0 g, 34.1 mmol, 1 equiv) and $NiCl_2{\cdot}6H_2O$ (8.12 g, 34.2 mmol, 1 equiv) in MeOH at 0 °C. To this solution was added $NaBH_4$ (6.46 g, 171 mmol, 5 equiv) portionwise. The resultant mixture was stirred allowing to warm to room temperature for 2 h. The reaction was then quenched with K_2CO_3 (18.9 g, 137 mmol, 4 equiv) in H_2O (150 mL). The reaction was stirred for a further 2 h. After 2 h the mixture was extracted with EtOAc and the combined organics washed with brine and dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to yield an off-white solid. The solid was recrystallised from EtOAc and the pure title compound **97** (7.47 g, 27.1 mmol, 79% yield) was isolated as a white solid; mp 122-124 °C (EtOAc); $R_f = 0.80$ (eluent = 40% EtOAc in hexanes); ν_{max} cm^{-1} (film) 3194, 3093, 2941, 1683, 1271, 1247, 1001, 815, 507; ^1H NMR (400 MHz, $CDCl_3$) σ_H: 1.60 (2H, m, C*H*$_2$), 1.78-1.93 (6H, m), 2.46 (1H, dd, *J* 16.8, 9), 2.70 (1H, dd, *J* 16.8, 9.0), 3.35-3.39 (1H, m), 3.58-3.67 (1H, m), 3.72-3.80 (1H, m), 3.83 (3H, s) 4.76 (1H, br. s., C*H*) 5.70 (1H, br. s., N*H*) 6.76-6.78 (2H, m, Ar*H*) 6.81-6.83 (1H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) σ_c: 24.2 (*C*H_2), 33.0 (*C*H_2), 38.1 (*C*H_2), 40.2 (*C*H), 49.8 (*C*H_2), 56.3 (O*C*H_3), 80.8 (O*C*CH_2), 112.4 (Ar*C*), 114.0 (Ar*C*), 119.0 (Ar*C*), 134.6 (Ar*C*), 148.0 (Ar*C*), 149.4 (Ar*C*), 177.5 (*C*=O); HRMS (ES+) calculated for $[C_{16}H_{22}NO_3]^+$ $(M)^+$: *m/z* 276.1600, found 276.1601 (+0.4 ppm).

3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine



To a flame dried 25 mL round bottomed flask was added 1 mL THF and cooled to 0 °C and purged with nitrogen. $LiAlH_4$ was then added portion wise. The solution was stirred for 10 minutes. Rolipram **97** (275 mg, 1 mmol, 1 equiv) was dissolved in 4 mL THF and added dropwise to the $LiAlH_4$ slurry. The mixture was then heated to reflux for 2 h. After 2 h the reaction was allowed to cool to room temperature before sat. aq. $NaHCO_3$ was added. Extracted into EtOAc, the combined organics were washed with brine, dried over $MgSO_4$ filtered and concentrated *in vacuo* to yield the pure title compound **98** (220 mg, 0.84 mmol, 84% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.58-1.61 (2H, m, C*H*$_2$), 1.81-1.93 (6H, m), 2.21-2.29 (1H, m, C*H*), 2.89 (1H, t, *J* 9.9, C*H*), 3.11-3.27 (3H, m), 3.42 (1H, dd, *J* 10.6, 7.8), 3.82 (3H, s, OC*H*$_3$), 4.46-4.47 (1H, m, C*H*), 4.74-4.79 (1H, m, C*H*) 6.74-6.81 (3H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) σ_c: 24.2 (*C*H$_2$), 33.0 (*C*H$_2$), 34.5 (*C*H$_2$), 45.1 (*C*H), 47.2 (N*C*H$_2$), 54.8 (N*C*H$_2$), 56.3 (O*C*H$_3$), 80.6 (O*C*CH$_2$), 112.2 (Ar*C*), 114.6 (Ar*C*), 119.2 (Ar*C*), 136.0 (Ar*C*), 147.8 (Ar*C*), 148.8 (Ar*C*); HRMS (ES+) calculated for $[C_{16}H_{24}NO_2]^+$ $(M)^+$: *m/z* 262.1807, found 262.1809 (+0.8 ppm).

3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine-1-carbonitrile

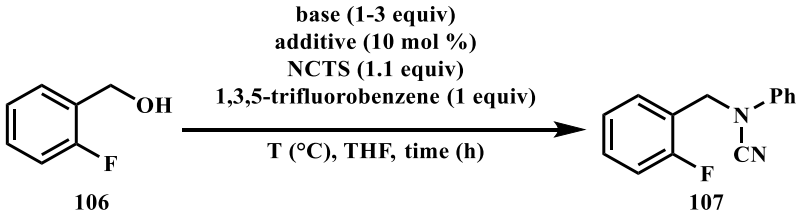


98 **8**

Following General procedure 3, 3-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidine **98** (213 mg, 0.8 mmol, 1 equiv), MeCN (0.8 mL) and trichloroacetonitrile (90 µL, 0.88 mmol, 1.1 equiv) for 24 h at rt followed by DME (4 mL) and NaO*t*Am (176 mg, 1.6 mmol, 2 equiv) for 1 h at rt, gave after flash column chromatography (eluent = 30% EtOAc in hexanes, 30 x 120 mm silica), the title compound **8** (164 mg, 0.57 mmol, 71% yield) as an off-white solid; mp 38-40 °C; R_f = 0.26 (eluent = 30% EtOAc in hexanes); ν_{max} cm^{-1} (film) 2954 (C-H), 2868, 2210 (C≡N), 1589, 1516, 1444, 1138, 1002, 800; ^{1}H NMR (400 MHz, $CDCl_3$) σ_H: 1.58-1.62 (2H, m, C*H*$_2$), 1.79- 2.04 (6H, m), 2.27 (1H, ddt, *J* 9.5, 6.3, 3.2, 3.2), 3.33-3.40 (2H, m, C*H*$_2$), 3.53 (1H, td, *J* 9.2, 6.9, C*H*) 3.63 (1H, td, *J* 8.7, 3.2, C*H*), 3.73-3.81 (1H, m, C*H*), 3.82 (3H, s, OC*H*$_3$), 4.74-4.77 (1H, m, C*H*), 6.72-6.74 (2H, m, Ar*H*), 6.81-6.83 (1H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) σ_c: 24.2 (*C*H$_2$), 33.0 (*C*H$_2$), 33.6 (*C*H$_2$), 44.0 (*C*H), 50.6 (*C*H$_2$), 56.3 (*C*H$_2$), 56.7 (O*C*H$_3$), 80.8 (O*C*CH$_2$), 112.3 (Ar*C*), 114.2 (Ar*C*), 117.6 (*C*≡N), 119.1 (Ar*C*), 132.3 (Ar*C*), 148.0 (Ar*C*), 149.5 (Ar*C*); HRMS (EI+ calculated for $[C_{17}H_{22}N_2O_2]^+$ $(M)^+$: *m/z* 286.1681, found 286.1685 (+1.4 ppm).

5.3 Experimental and characterisation data for chapter 3

5.3.1 Reaction optimisation



106 **107**

General procedure 6

To a flame dried reaction vial was added 2-fluorobenzyl alcohol **106** (110 µL, 1 mmol, 1 equiv) followed by THF (5 mL), base (1.1, 2 or 3 equiv) and additive as required (10 mol %) and stirred for 15 minutes at the desired temperature. NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) and 1,3,5-trifluorobenzene (104 µL, 1 mmol, 1 equiv) as internal standard were added and the reaction stirred at a constant temperature. The reaction was monitored taking aliquots at specified times (T1 = 30 minutes, T2 = 1 h, T3 = 3 h, T4 = 6 h, T5 = 23 h) *via* $^{19}F\{^{1}H\}$ NMR analysis. Each $^{19}F\{^{1}H\}$ NMR was analysed to determine the composition of the reaction mixture quoted as a mixture of product **107** to other (where other = SM, alkoxide or tosylate intermediates)

Entry	Base (eq.)	Additive (mol %)	T / °C	**T1 = 30 min 107:Other /%**	**T2 = 1 h 107:Other /%**	**T3 = 3 h 107:Other /%**	**T4 = 6 h 107:Other /%**	**T5 = 23 h 107:Other /%**
1	NaH (3)	-	50	84 : 0	84 : 0	84 : 0	84 : 0	84 : 0
2	NaH (3)	-	rt	71 : 18	76 : 12	81 : 0	81 : 0	81 : 0
3	NaH (2)	-	rt	44 : 32	50 : 33	72 : 11	80 : 0	80 : 0
4	NaOtAm (2)	-	rt	42 : 30	42 : 23	67 : 12	78 : 0	78 : 0
5	KOtBu (2)	-	rt	39 : 41	52 : 30	65 :20	85 : 0	85 : 0
6	LHMDS (2)	-	rt	44 : 40	55 : 17	75 : 0	75 :0	75 : 0
7	KHMDS (2)	-	rt	0 : 100	0 :100	0 : 100	0 : 100	0 : 100
8	DBU (2)	-	rt	11 : 82	33 : 63	54 : 46	60 : 40	86 : 14
9	DBN (2)	-	rt	0 : 100	0 : 100	0 : 100	0 : 100	0 : 100
10	TBD (2)	-	rt	19 : 81	20 : 80	20 : 80	30 : 68	47 : 53
11	NaH (1.1)	-	rt	34 : 53	43 : 46	52 : 36	56 : 32	62 : 35
12	NaOtAm (1.1)	-	rt	33 : 53	39 : 43	50 : 36	55 : 32	59 : 34
13	NaH (1.1)	-	50	65 : 26	66 : 25	67 : 24	68 : 21	71 : 19
14	NaOtAm (1.1)	-	50	58 : 30	60 : 29	59 : 33	61 : 28	66 : 28
15	NaH (1.5)	-	rt	64 : 23	75 : 18	89 : 9	89 : 9	89 : 9
16	NaOtAm (1.5)	-	rt	63 : 33	68 : 24	88 : 10	88 : 10	88 : 10
17	DBU (2)	-	rt	67 : 33	69 : 31	77 : 23	77 : 23	77 : 23
18	NaOtAm (2)	TBAB (10)	rt	89 : 11	99 : 1	100 : 0	100 : 0	100 : 0
19	**NaOtAm (2)**	**TBAI (10)**	**rt**	**99 : 1**	**100 : 0**	**100 : 0**	**100 :0**	**100 : 0**
20	NaOtAm (1.1)	TBAB (10)	rt	46 : 54	57 : 43	61 : 39	63 : 37	63 : 37
21	NaOtAm (1.1)	TBAI (10)	rt	52 : 48	62 : 38	68 : 32	70 : 30	70 : 30
22	NaOtAm (2)	TBA BF4 (10)	rt	92 : 8	100 : 0	100 : 0	100 : 0	100 : 0
23	NaOtAm (2)	TBA PF6 (10)	rt	90 : 10	100 : 0	100 : 0	100 : 0	100 : 0
24	NaOtAm (2)	NaI (10)	rt	90 : 10	100 : 0	100 : 0	100 : 0	100 : 0

5.3.2 Substrate scope - alcohols

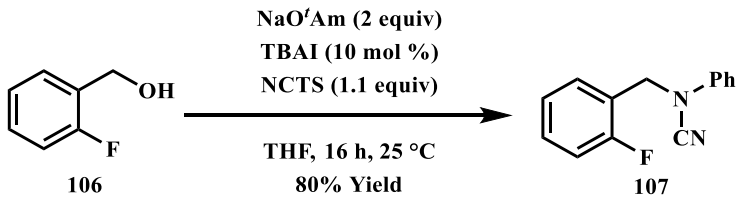
General procedure 7

To a flame dried reaction vial was added the requisite alcohol (1 equiv) followed by THF ([alcohol] = 0.2 mol dm^{-3}), NaO*t*Am (2 equiv) and TBAI (10 mol %) and stirred for 15-20 minutes at 25 °C. NCTS (1.1 equiv) was then added and the reaction stirred for 16 h at 25 °C. The reaction was then quenched with sat. aq. NH_4Cl and diluted with H_2O, the product was extracted with EtOAc (× 3). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography or recrystallisation.

General procedure 8

To a flame dried reaction vial was added the requisite alcohol (1 equiv) followed by 1,4-dioxane ([alcohol] = 0.2 mol dm^{-3}), NaO*t*Am (2 equiv) and TBAI (10 mol %) and stirred for 15-20 minutes at 80 °C. NCTS (2 equiv) was then added and the vessel sealed, reaction stirred for 16 or 48 h at 100 °C. The reaction was then cooled and quenched with sat. aq. NH_4Cl and diluted with H_2O, the product was extracted with EtOAc (× 3). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography or recrystallisation.

***N*-(2-fluorobenzyl)-*N*-phenylcyanamide**

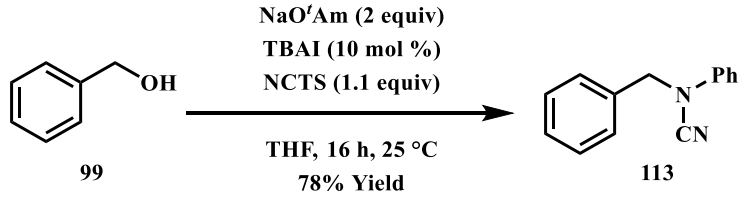


106 107

Following general procedure 7, 2-fluorobenzyl alcohol **106** (110 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 130 mm silica) the title compound **3** (181 mg, 0.80 mmol, 80% yield) as a white solid; mp 74-76 °C; R_f = 0.45

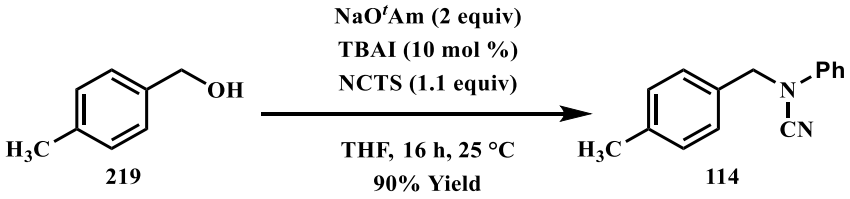
(eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2990, 2216 (C≡N), 1490, 1454, 1365, 1186, 1039, 738; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.86 (2H, s, PhC*H*$_2$), 7.09-7.18 (5H, m, CH_2Ar*H*), 7.34-7.42 (3H, m, Ar*H*), 7.42 (1H, t, *J* 7.5, Ar*H*); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ_F: -117.5; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 47.6 (d, *J* 4.5, *C*H_2), 113.7 (*C*≡N), 115.9 (Ar*C*), 116.1 (Ar*C*), 121.4 (d, *J* 14.3, Ar*C*), 124.0 (Ar*C*), 124.9 (d, *J* 3.4, Ar*C*), 129.7 (d, *J* 3.4, Ar*C*), 129.7 (Ar*C*), 130.7 (d, *J* 8.8, Ar*C*) 139.7 (Ar*C*), 160.7 (d, *J* 248.2, Ar*C*); HRMS (EI^+) calculated for $[C_{14}H_{11}FN_2]^+$ $(M)^+$: m/z 227.0979, found 227.0980 (+0.4 ppm)

N-benzyl-*N*-phenylcyanamide



Following general procedure 7, benzyl alcohol **90** (2.07 mL, 20 mmol, 1 equiv), THF (100 mL), NaO*t*Am (4.41 g, 40 mmol, 2 equiv), TBAI (738.7 mg, 2 mmol, 0.1 equiv) and NCTS **101** (5.99 g, 22 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 80 × 110 mm silica) the title compound **113** (3.23 mg, 15.65 mmol, 78% yield) as a white solid; mp 56-59 °C; R_f = 0.43 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3015, 2212 (C≡N), 1597, 1492, 1359, 937, 744, 684, 650; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.81 (2H, s, C*H*$_2$), 7.07-7.14 (3H, m, Ar*H*), 7.32-7.39 (7H, m, Ar*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 53.9 (*C*H_2), 114.1 (*C*≡N), 116.2 (Ar*C*), 123.8 (Ar*C*), 126.5 (Ar*C*), 128.7 (Ar*C*), 129.2 (Ar*C*), 129.8 (Ar*C*), 134.4 (Ar*C*), 140.0 (Ar*C*); HRMS (NSI^+) calculated for $[C_{14}H_{12}N_2]^+$ $(M)^+$: m/z 209.1073, found 209.1073 (-0.1 ppm)

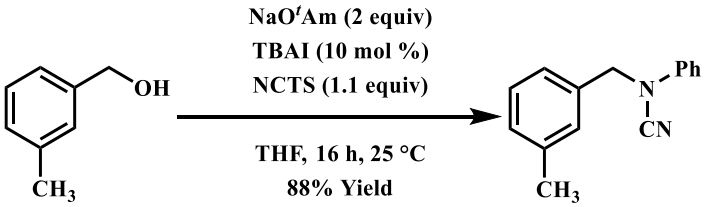
N-(4-methylbenzyl)-*N*-phenylcyanamide



Following general procedure 7, 4-methylbenzyl alcohol **219** (122 mg, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv)

and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 130 mm silica) the title compound **114** (201 mg, 0.90 mmol, 90% yield) as a white solid; mp 100-104 °C (Et_2O); R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2995, 2222 (C≡N), 1595, 1492, 1381. 1274, 1174, 1031, 756; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.34 (3H, s, C*H*$_3$), 4.75 (2H, s, C*H*$_2$), 7.07 (1H, t, *J* 7.4, Ar*H*), 7.13 (2H, d, *J* 8.0), 7.18 (2H, d, *J* 7.6, Ar*H*), 7.26 (2H, d, *J* 7.2, Ar*H*), 7.33 (2H, t, *J* 7.6, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 21.3 (*C*H$_3$), 53.7 (*C*H$_2$), 114.1 (*C*≡N), 116.2 (Ar*C*), 123.8 (Ar*C*), 127.6 (Ar*C*), 129.7 (Ar*C*), 129.9 (Ar*C*), 131.3 (Ar*C*), 138.5 (Ar*C*), 140.0 (Ar*C*); HRMS (NSI^+) calculated for $[C_{15}H_{14}N_2]^+$ $(M+H)^+$: m/z 223.1230, found 223.1230 (+0.1 ppm)

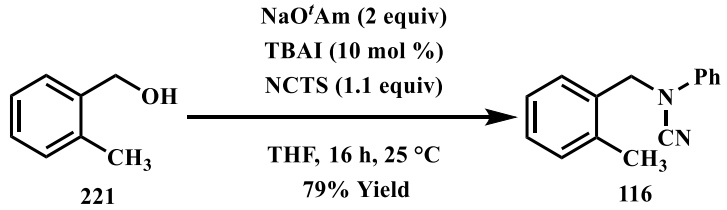
_N_-(3-methylbenzyl)-_N_-phenylcyanamide



220 **115**

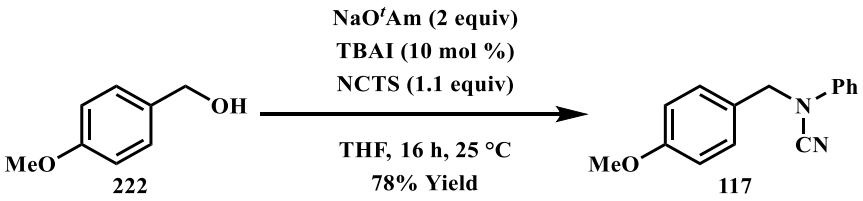
Following general procedure 7, 3-methylbenzyl alcohol **220** (122 mg, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after recrystallisation (Et_2O) the title compound **115** (196 mg, 0.88 mmol, 88% yield) as a white solid; mp 57-59 °C (Et_2O); R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2218 (C≡N), 1597, 1494, 1363, 1226, 1363, 1188, 885, 742; ^1H NMR (500 MHz, $CDCl_3$) δ_H; 2.35 (3H, s, C*H*$_3$), 4.76 (2H, s, C*H*$_2$), 7.08 (1H, t, *J* 7.4, Ar*H*), 7.10-7.20, (5H, m, Ar*H*), 7.26 (1H, dd, *J* 9.8, 5.2, Ar*H*), 7.33 (2H, t, *J* 7.8, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 21.6 (*C*H$_3$), 53.9 (*C*H$_2$), 114.1 (*C*≡N), 116,1 (Ar*C*), 123.8 (Ar*C*), 124.5 (Ar*C*), 128.1 (Ar*C*), 129.1 (Ar*C*), 129.4 (Ar*C*), 129.8 (Ar*C*), 134.4 (Ar*C*), 139.0 (Ar*C*), 140.0 (Ar*C*); HRMS (NSI^+) calculated for $[C_{15}H_{14}N_2]^+$ $(M)^+$: m/z 223.1230, found 223.1230 (+0.1 ppm)

N-(2-methylbenzyl)-*N*-phenylcyanamide



Following general procedure 7, 2-methylbenzyl alcohol **221**(122 mg, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after recrystallisation (Et_2O) the title compound **116** (176 mg, 0.79 mmol, 79% yield) as a white solid; mp 93-95 °C (Et_2O); R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2968, 2222 (C≡N), 1593, 1494, 1377, 1276, 1232, 1176, 744; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.38 (3H, s, C*H*$_3$), 4.75 (2H, s, C*H*$_2$), 7.11-7.16 (3H, m, Ar*H*), 7.21-7.31 (4H, m, Ar*H*), 7.37 (2H, t, *J* 7.6, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.3 (*C*H$_3$), 51.9 (*C*H$_2$), 113.5 (*C*≡N), 116.1 (Ar*C*), 123.9 (Ar*C*), 126.7 (Ar*C*), 128.4 (Ar*C*), 128.9 (Ar*C*), 129.8 (Ar*C*), 131.0 (Ar*C*), 131.8 (Ar*C*), 136.4 (Ar*C*), 140.3 (Ar*C*); HRMS (EI$^+$) calculated for $[C_{15}H_{14}N_2]^+$ $(M)^+$: m/z 223.1230, found 223.1229 (-0.3 ppm)

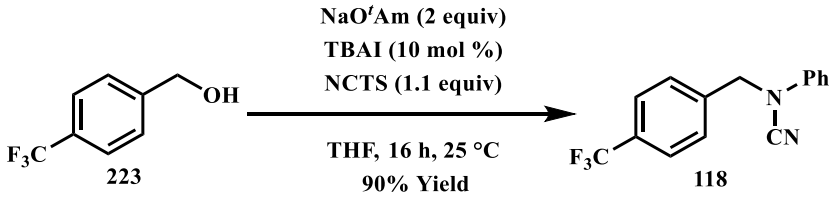
N-(4-methoxybenzyl)-*N*-phenylcyanamide



Following general procedure 7, 4-methoxybenzyl alcohol **222** (123 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 130 mm silica) the title compound **117** (187 mg, 0.78 mmol, 78% yield) as a white solid; mp 61-63 °C; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2218 (C≡N), 1595, 1512, 1494, 1382, 1247, 1172, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.80 (3H, s, OC*H*$_3$), 4.75 (2H, s, C*H*$_2$), 6.90 (2H, d, *J* 8.3, Ar*H*), 7.10 (1H, t, *J* 7.3, Ar*H*), 7.15 (2H, d, *J* 7.9, Ar*H*), 7.28-7.36 (4H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 53.4 (*C*H$_2$), 55.4 (O*C*H$_3$), 114.0 (Ar*C*), 114.6 (*C*≡N), 116.3 (Ar*C*), 123.8 (Ar*C*), 126.2 (Ar*C*), 129.3 (Ar*C*), 129.8 (Ar*C*),

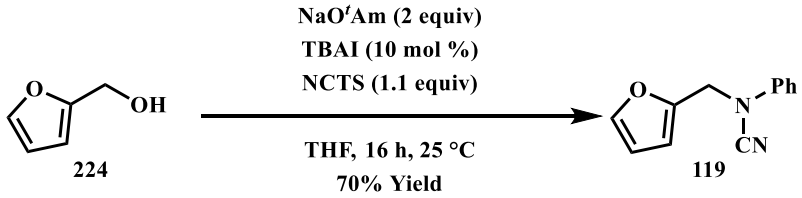
140.1 (Ar*C*), 159.9 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{15}H_{15}O_1N_2]^+$ (M+H)+: m/z 239.1179, found 239.1180 (+0.5 ppm).

_N_-phenyl-_N_-(4-(trifluoromethyl)benzyl)cyanamide



Following general procedure 7, 4-trifluoromethylbenzyl alcohol **223** (137 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 130 mm silica) the title compound **118** (199 mg, 0.90 mmol, 90% yield) as a white solid; mp 86-84 °C; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2222 (C≡N), 1498, 1375, 1321, 1163, 1062, 819; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.88 (2H, s, C*H*$_2$), 7.11 (3H, d, *J* 7.9, Ar*H*), 7.35 (2H, t, *J* 8.0, Ar*H*), 7.49 (2H, d, *J* 8.1, ArIH), 7.65 (2H, d, *J* 8.1, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: -62.7; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 53.4 (*C*H$_2$), 113.8 (*C*≡N), 116.1 (Ar*C*), 123.9 (q, ^{1}*J* 272.2, Ar*C*), 124.2 (Ar*C*), 126.2 (q, ^{3}*J* 3.7, Ar*C*), 127.6 (Ar*C*), 130.0 (Ar*C*), 131.45 (q, ^{2}*J* 65.5, Ar*C*), 138.5 (Ar*C*), 139.5 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{15}H_{12}F_3N_2]^+$ $(M+H)^+$: m/z 277.0947, found 277.0950 (+0.8 ppm)

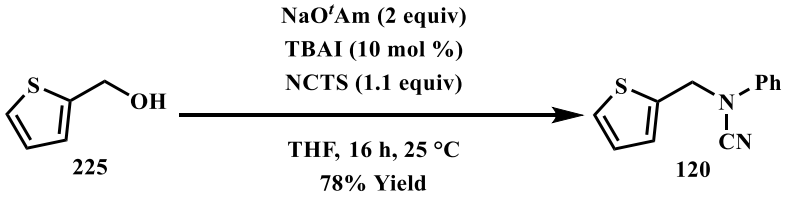
_N_-(furan-2-ylmethyl)-_N_-phenylcyanamide



Following general procedure 7, furfuryl alcohol **224** (86.4 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 130 mm silica) the title compound **119** (138 mg, 0.70 mmol, 70% yield) as a white solid; mp 60-62 °C; R_f = 0.29 (eluent = 20% EtOAc in hexane); ν_{max} / cm^{-1} (film): 2995, 2991, 2216 (C≡N), 1597, 1490, 1363, 1143, 1076, 945, 738, 682; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.75 (2H, s, C*H*$_2$), 6.37 (1H, s, C*H*), 6.45 (1H,

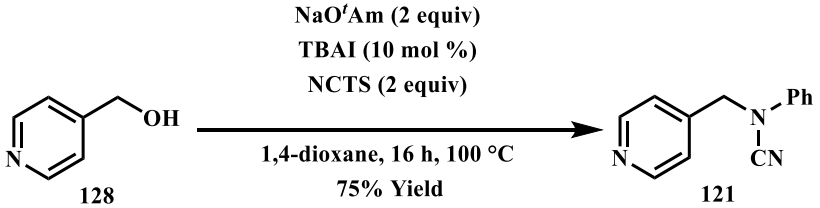
s, Ar*H*), 7.12 (1H, t, *J* 7.2, Ar*H*), 7.20 (2H, d, *J* 7.8, Ar*H*), 7.37 (2H, t, *J* 7.4, Ar*H*), 7.43 (1H, s, Ar*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 46.9 (*C*H_2), 110.6 (Ar*C*), 110.9 (Ar*C*), 113.5 (*C*≡N), 116.4 (Ar*C*), 124.1 (Ar*C*), 129.8 (Ar*C*), 139.8 (Ar*C*), 143.7 (Ar*C*), 147.8 (Ar*C*); HRMS (NSI^+) calculated for $[C_{12}H_{11}N_2O_1]^+$ $(M+H)^+$: m/z 199.0866, found 199.0866 (+0.1 ppm)

_N_-phenyl-_N_-(thiophen-2-ylmethyl)cyanamide



Following general procedure 7, 2-thiophene methanol **225** (94.8 µL, 1 mmol, 1 equiv), THF (5 mL) and NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 130 mm silica) the title compound **120** (167 mg, 0.78 mmol, 78% yield) as a white solid; mp 56-58 °C; R_f = 0.46 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3015, 2998, 2222 (C≡N), 1595, 1489, 1382, 1257, 1180, 1149, 1035, 725; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 4.95 (2H, s, CH_2), 7.01 (1H, s, Ar*H*), 7.08-7.24 (4H, m, Ar*H*), 7.29-7.38 (3H, m, Ar*H*); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 48.9 (*C*H_2), 113.4 (*C*≡N), 116.5 (Ar*C*), 124.2 (Ar*C*), 126.7 (Ar*C*), 127.4 (Ar*C*), 127.1 (Ar*C*), 128.0 (Ar*C*), 136.2 (Ar*C*), 139.6 (Ar*C*); HRMS (NSI^+) calculated for $[C_{12}H_{11}N_2S_1]^+$ $(M+H)^+$: m/z 215.0637, found 215.0638 (+0.3 ppm)

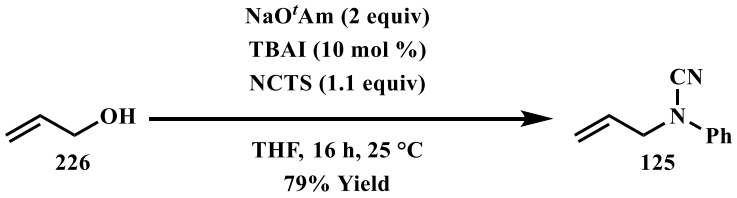
_N_-phenyl-_N_-(pyridin-4-ylmethyl)cyanamide



Following general procedure 8, 4-pyridine methanol **226** (109 mg, 1 mmol, 1 equiv), 1,4-dioxane (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv) and TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) stirred for 15-20 min at 80 °C followed by NCTS **101** (544 mg, 2 mmol, 2 equiv) at 100 °C for 16 h gave after flash silica column chromatography (eluent = 50-100% EtOAc in hexanes, 30 × 130 mm silica) the title compound **121** (158 mg, 0.75 mmol, 75%

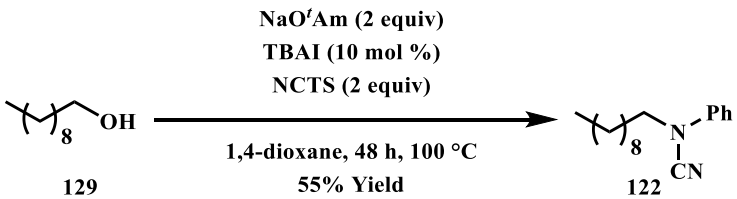
yield) as an orange solid; mp 79-81 °C; R_f = 0.3 (eluent = EtOAc); ν_{max} / cm^{-1} (film): 3000, 2222 (C≡N), 1587, 1494, 1421, 1367, 1190, 939, 740, 584; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.85 (2H, s, C*H*$_2$), 7.06-7.09 (2H, m, Ar*H*), 7.10-7.15 (1H, m, Ar*H*), 7.27-7.30 (2H, m, Ar*H*), 7.32-7.39 (2H, m, Ar*H*), 8.64 (2H, dd, *J* 4.4, 1.7, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 52.8 (*C*H$_2$), 113.6 (*C*≡N), 115.9 (Ar*C*), 121.7 (Ar*C*), 124.3 (Ar*C*), 130.0 (Ar*C*), 139.3 (Ar*C*), 143.6 (Ar*C*), 150.8 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{13}H_{12}N_3]^+$ $(M+H)^+$: m/z 210.1026, found 210.1026 (+0.1 ppm).

_N_-allyl-_N_-phenylcyanamide



Following general procedure 7, allyl alcohol **226** (68.0 µl, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 130 mm silica) the title compound **125** (125 mg, 0.79 mmol, 79% yield) as a colourless oil; R_f = 0.55 (eluent = 20% EtOAc in hexanes; ν_{max} / cm^{-1} (film): 2208 (C≡N), 1490, 1452, 1367, 1251, 1195, 738; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.22 (2H, dt, *J* 5.6, 1.5, C*H*$_2$N), 5.41 (2H, ddq, *J* 13.6, 10.4, 1.1, CHC*H*$_2$), 5.86-6.06 (1H, m, C*H*), 7.03-7.15 (3H, m, Ar*H*), 7.29-7.42 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 52.3 (*C*H$_2$), 113.6 (*C*≡N), 116.0, 120.2, 123.8, 129.8, 130.3, 139.9; HRMS (NSI$^+$) calculated for $[C_{10}H_{11}N_2]^+$ $(M+H)^+$: m/z 159.0917, found 159.0914 (-1.7 ppm)

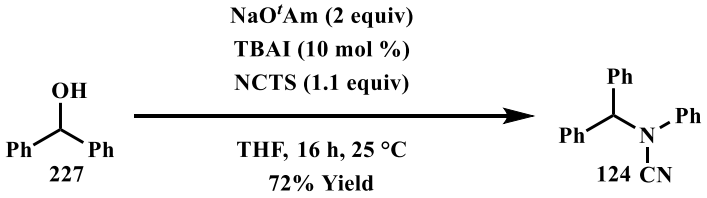
_N_-decyl-_N_-phenylcyanamide



Following general procedure 8, decan-1-ol **129** (191 µL, 1.00 mmol, 1 equiv), 1,4-dioxane (5 mL), NaO*t*Am (221 mg, 2.00 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) stirred for 15-20 min at 80 °C and NCTS **101** (544 mg, 2 mmol, 2 equiv) at 100 °C for 48 h gave after flash silica column chromatography (eluent = 5% EtOAc in

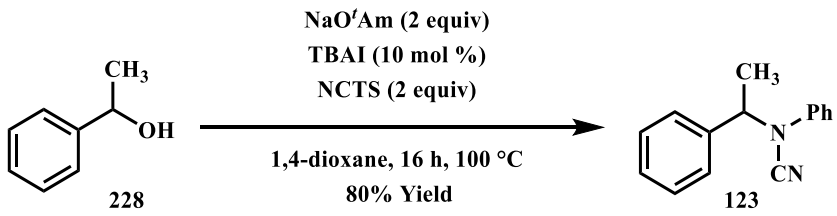
hexanes, 40 x 110 mm silica) the title compound **122** (141 mg, 0.55 mmol, 55%) as a colourless oil; R_f = 0.81 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2922, 2853, 2216 (C≡N), 1599, 1499, 1458, 750, 691; ^{1}H NMR (400 MHz $CDCl_3$) δ_H: 0.88 (3H, t, *J* 6.9, C*H*$_3$), 1.26-1.57 (14H, m, alkyl), 1.82 (2H, quintet, *J* 7.4, C*H*$_2$), 3.57 (2H, t, *J* 9.3, C*H*$_2$), 7.08-7.13 (3H, m, Ar*H*), 7.34-7.39 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz $CDCl_3$) δ_C: 14.3, 22.8, 26.7, 27.6, 29.3, 29.4, 29.6, 29.6, 32.0, 49.6, 113.8 (*C*≡N), 116.0 (Ar*C*), 123.6 (Ar*C*), 129.8 (Ar*C*), 140.2 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{17}H_{27}N_2]^+$ $(M+H)^+$: m/z 159.0917, found 159.0914 (-1.7 ppm

_N_-benzhydryl-_N_-phenylcyanamide



Following general procedure 8, benzhydrol **227** (184 mg, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) gave after recrystallisation (hexane) the title compound **124** (205 mg, 0.72 mmol, 72% yield) as colourless crystals; mp 95-98 °C; R_f = 0.64 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2996, 2208 (C≡N), 1490, 1452, 1367, 1251, 1195, 738 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.00 (1H, s, C*H*), 7.07-7.11 (1H, m, Ar*H*), 7.18 (2H, d, *J* 7.9, Ar*H*), 7.30-7.43 (12H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 66.7 (*C*H), 112.6 (*C*≡N), 116.9 (Ar*C*), 124.0 (Ar*C*), 128.6 (Ar*C*), 128.9 (Ar*C*), 129.1 (Ar*C*), 129.8 (Ar*C*), 137.6 (Ar*C*), 140.7; HRMS (NSI$^+$) calculated for $[C_{20}H_{17}N_2]^+$ $(M+H)^+$: m/z 285.1386, found 285.1390 (+0.5 ppm)

_N_-phenyl-_N_-(1-phenylethyl)cyanamide

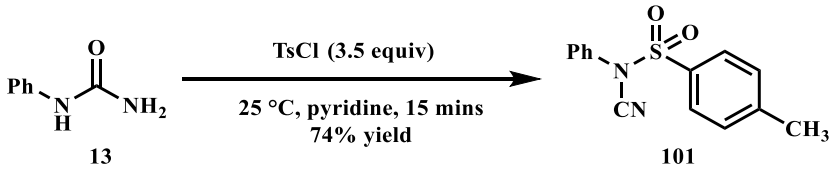


Following general procedure 8, 1-phenyl ethanol **228** (122 µL, 1 mmol, 1 equiv), 1,4-dioxane (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) stirred for 15-20 min at 80 °C and NCTS **101** (544 mg, 2 mmol, 2 equiv) at 100

°C gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 120 mm silica) the title compound **123** (158 mg, 0.80 mmol, 80% yield) as a white solid; mp 58-60 °C; R_f = 0.5 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2997, 2212 (C≡N), 1598, 1487, 1274, 1217, 1188, 1029, 749, 684, 489; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.84 (3H, d, *J* 7.0, C*H*$_3$), 4.87 (1H, q, *J* 7.0, CH_3C*H*), 7.05 (1H, t, *J* 7.3, Ar*H*), 7.11 (2H, d, *J* 8.7, Ar*H*), 7.29 (3H, t, *J* 7.7, Ar*H*), 7.33-7.40 (4H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 22.3 (*C*H$_3$), 57.9 (*C*H), 112.6 (*C*≡N), 117.1 (Ar*C*), 123.9 (Ar*C*), 125.9 (Ar*C*), 128.3 (Ar*C*), 129.2 (Ar*C*), 129.7 (Ar*C*), 140.2 (Ar*C*), 140.8 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{15}H_{15}N_2]^+$ $(M+H)^+$: m/z 223.1230, found 223.1231 (+0.6 ppm)

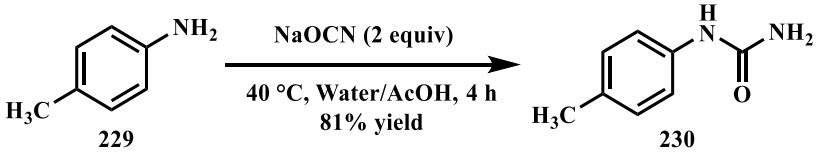
5.3.3 Sulfonamide synthesis

_N_-cyano-_N_-phenyl-4-methylbenzenesulfonamide



To a 1 L round-bottom flask containing a magnetic follower was charged phenylurea **13** (21.8 g, 160 mmol, 1 equiv) and pyridine (108 mL). The flask was immersed in a 25 °C water bath before *p*-toluenesulfonyl chloride (106 g, 554 mmol, 3.5 equiv) was added portion wise over 5 minutes. The reaction mixture was stirred at 25 °C for 15 min. The reaction was quenched with ice-cooled water (800 mL) and left to stir for an additional 15 min. The precipitate formed was filtered and washed with water. The crude product was recrystallised from ethanol and the pure title compound **101** (32.1 g, 118 mmol, 74%) was isolated as a white crystalline solid with physical properties and spectroscopic data in accordance with the literature;[9] mp 85-86 °C (EtOH); R_f = 0.55 (eluent = 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.47 (3H, s, C*H*$_3$), 7.19 (2H, d, *J* 7.7, Ar*H*), 7.33-7.44 (5H, m, Ar*H*), 7.64 (2H, d, *J* 8.3. Ar*H*).

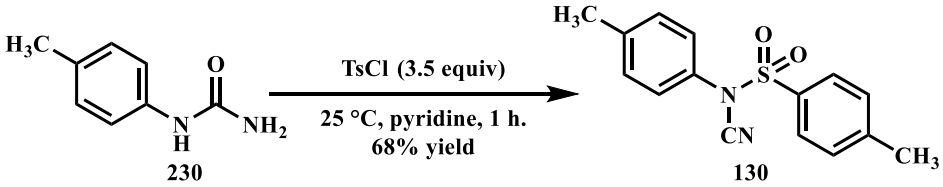
1-(*p*-tolyl)urea



229 230

To a 250 mL round-bottom flask containing a magnetic follower was charged in order *p*-toluidine **229** (4.61 g, 43 mmol, 1 equiv), acetic acid (12 mL), water (12 mL) and sodium cyanate (5.59 g, 86 mmol, 2 equiv). The reaction was stirred at 40 °C for 4 h. Water (50 mL) was added to the mixture and was stirred at 25 °C for an additional 30 min. The precipitate formed was filtered, washed with water and dried *in vacuo*. The crude product was recrystallised from Et_2O and gave the pure title compound **230** (5.21 g, 34.7 mmol, 81%) as a white crystalline solid with physical properties and spectroscopic data in accordance with the literature;[10] mp 176-178 °C (Et_2O); R_f = 0.10 (eluent = 50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H: 2.20 (3H, s, C*H*$_3$), 5.76 (2H, s, N*H*$_2$), 7.01 (2H, d, *J* 7.9, Ar*H*), 7.26 (2H, d, *J* 8.0, Ar*H*), 8.39 (1H, s, N*H*).

***N*-cyano-4-methyl-*N*-(*p*-tolyl)benzenesulfonamide**

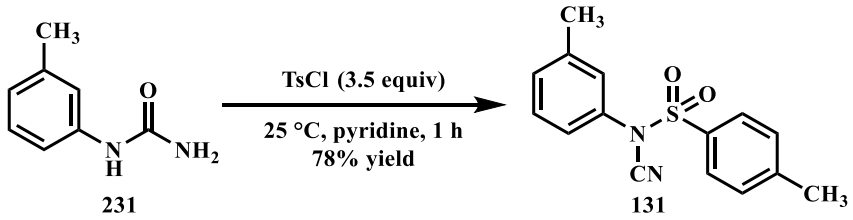


230 130

To a 500 mL round-bottom flask containing a magnetic follower was charged *p*-tolylurea **230** (4.00 g, 26.6 mmol, 1 equiv) and pyridine (186 mL). The flask was immersed in a 25 °C water bath before *p*-toluenesulfonyl chloride (17.8 g, 93.2 mmol, 3.5 equiv) was added portion wise over 5 minutes. The reaction mixture was stirred at 25 °C for 1 h. The reaction was quenched with ice-cooled water (1.02 L) and left to stir for an additional 15 min. The precipitate formed was filtered and washed with water. The crude product was recrystallised from ethanol and the pure title compound **130** (4.91 g, 18.0 mmol, 68%) was isolated as a white crystalline solid; mp 120-121 °C (EtOH); R_f = 0.47 (eluent = EtOAc 30% in hexanes); ν_{max} / cm^{-1} (film): 2232 (C≡N), 1595, 1504, 1385, 1175, 1086, 887, 806, 704, 667, 619, 579, 557, 532; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.36 (3H, s, C*H*$_3$), 2.47 (3H, s, C*H*$_3$), 7.04 (2H, d, *J* 8.1, Ar*H*), 7.16 (2H, d, *J* 8.0, Ar*H*), 7.34 (2H, d, *J* 8.0, Ar*H*), 7.63 (2H, d, *J* 8.1, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.3 (*C*H$_3$), 21.9 (*C*H$_3$), 108.9 (Ar*C*), 126.6 (Ar*C*), 128.5 (Ar*C*), 130.3 (Ar*C*), 130.5 (Ar*C*), 132.0

(Ar*C*), 132.5 (Ar*C*), 140.6 (Ar*C*), 146.7 (Ar*C*); HRMS (NSI^+) calculated for $[C_{15}H_{15}N_2O_2S]^+$ $(M+H)^+$: m/z 287.0849 found 287.0852, (+1.1 ppm).

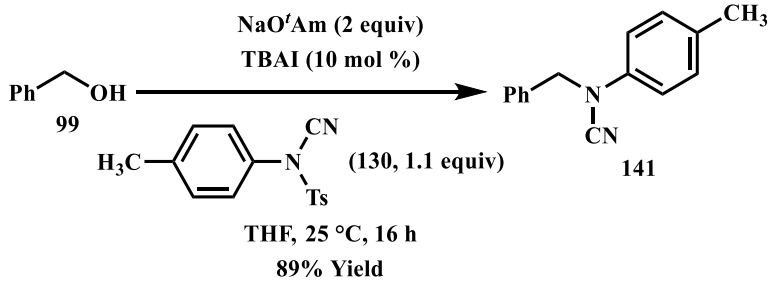
_N_-cyano-4-methyl-_N_-(_m_-tolyl)benzenesulfonamide



To a 500 mL round-bottom flask containing a magnetic follower was charged *m*-tolylurea **231** (4.42 g, 29.4 mmol, 1 equiv) and pyridine (206 mL). The flask was immersed in a 25 °C water bath before *p*-toluenesulfonyl chloride (19.6 g, 103 mmol, 3.5 equiv) was added portion wise over 5 minutes. The reaction mixture was stirred at 25 °C for 1 h. The reaction was quenched with ice-cooled water (1.13 L) and left to stir for an additional 15 min. The precipitate formed was filtered and washed with water. The crude product was recrystallised from ethanol and the pure title compound **131** (6.27 g, 22.9 mmol, 78%) was isolated as a white crystalline solid; mp 98-100 °C (EtOH); R_f = 0.52 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2228 (C≡N), 1593, 1487, 1385, 1190, 1167, 1082, 945, 814, 681, 654, 586, 548; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.33 (3H, s, C*H*$_3$), 2.47 (3H, s, C*H*$_3$), 6.95 (1H, d, *J* 7.4, Ar*H*), 7.03 (1H, s, Ar*H*), 7.22-7.26 (2H, m, Ar*H*), 7.35 (2H, d, *J* 7.9, Ar*H*), 7.65 (2H, d, *J* 7.9, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 21.3 (*C*H$_3$), 22.0 (*C*H$_3$), 108.9 (Ar*C*), 123.5 (Ar*C*), 127.2 (Ar*C*), 128.6 (Ar*C*), 129.7 (Ar*C*), 130.3 (Ar*C*), 130.9 (Ar*C*), 132.5 (Ar*C*), 134.5 (Ar*C*), 140.3 (Ar*C*), 146.8 (Ar*C*); HRMS (NSI^+) calculated for $[C_{15}H_{15}N_2O_2S]^+$ $(M+H)^+$: m/z 287.0849, found 287.0851 (+0.8 ppm).

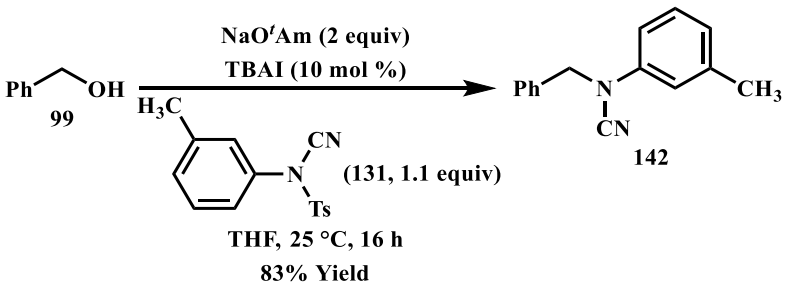
5.3.4 Substrate scope - sulfonamides

_N_-benzyl-_N_-(_p_-tolyl)cyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-cyano-4-methyl-*N*-(*p*-tolyl)benzenesulfonamide **130** (315 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 140 mm silica) the title compound **141** (198 mg, 0.89 mmol, 89% yield) as a white solid; mp 98-100 °C; R_f = 0.63 (30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3034, 2970, 2916, 2212 (C≡N) 1618, 1582, 1510, 1458, 1387, 1273,1231, 1177, 1128, 1015, 962, 822, 804, 770, 706, 494; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.29 (3H, s, C*H*$_3$), 4.77 (2H, s, PhC*H*$_2$), 7.02 (2H, d, *J* 8.6, Ar*H*), 7.13 (2H, d, *J* 8.3, Ar*H*), 7.32-7.38 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 20.7 (*C*H$_3$), 54.0 (*C*H$_2$), 114.4 (*C*≡N), 116.3 (Ar*C*), 127.5 (Ar*C*), 128.6 (Ar*C*), 129.2 (Ar*C*), 130.3 (Ar*C*), 133.6 (Ar*C*), 134.6 (Ar*C*), 137.5 (Ar*C*); HRMS (EI$^+$) calculated for $[C_{15}H_{14}N_2]^+$ $[M]^+$: m/z 222.1157, found 222.1156 (-0.5 ppm)

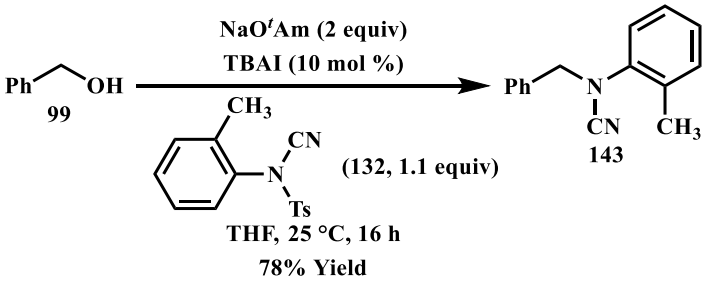
_N_-benzyl-_N_-(_m_-tolyl)cyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-cyano-4-methyl-*N*-(*m*-tolyl)benzenesulfonamide **131** (315 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 0-5% EtOAc in hexanes, 30 × 140 mm silica) the title compound **142** (183 mg, 0.83 mmol, 83% yield) as a white solid; mp

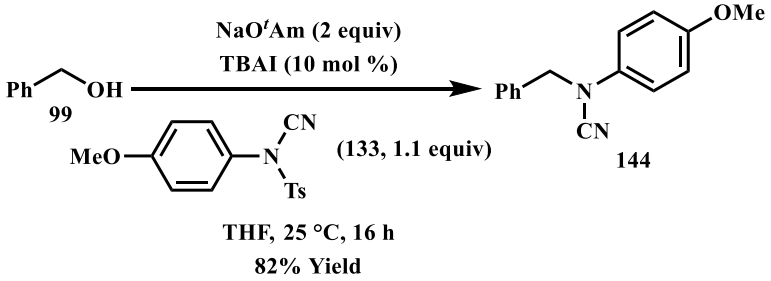
44-46 °C; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film):; 3002, 2991, 2208 (C≡N), 1608, 1587, 1490, 1251, 952, 773, 644; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H; 2.33 (3H, s, C*H*$_3$), 4.79 (2H, s, PhC*H*$_2$), 6.90 (2H, d, *J* 7.9, Ar*H*), 7.00 (1H, s, Ar*H*), 7.21 (1H, t, *J* 7.9, Ar*H*), 7.30-7.41 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 21.7 (*C*H$_3$), 53.8 (*C*H$_2$), 113.1, 114.2, 117.0 (Ar*C*), 124.7 (Ar*C*), 127.5 (Ar*C*), 128.6 (Ar*C*), 129.2 (Ar*C*), 129.6 (Ar*C*), 134.5 (Ar*C*), 139.9 (Ar*C*), 140.0 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{15}H_{15}N_2]^+$ $(M+H)^+$: m/z 223.1230, found 223.1229 (-0.3 ppm)

_N_-benzyl-_N_-(_o_-tolyl)cyanamide



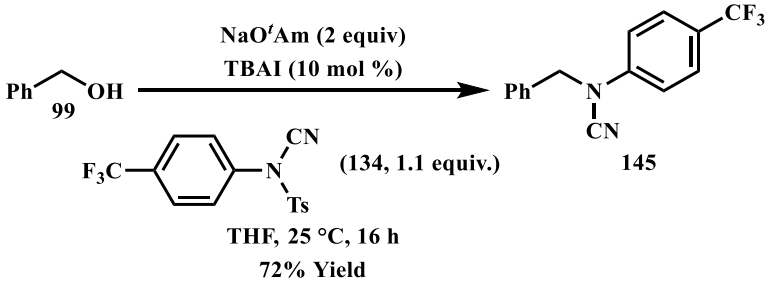
Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-cyano-4-methyl-*N*-(*o*-tolyl)benzenesulfonamide **132** (315 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 0-5% EtOAc in hexanes, 30 × 150 mm silica) the title compound **143** (162 mg, 0.78 mmol, 78% yield) as a colourless oil; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film):; 2206 (C≡N), 1487, 1448, 1217, 1182, 763, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.35 (3H, s, C*H*$_3$), 4.55 (2H, s, PhC*H*$_2$), 7.09-7.25 (4H, m, Ar*H*), 7.31-7.37 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 18.1 (*C*H$_3$), 58.3 (*C*H$_2$), 116.0 (*C*≡N), 125.2 (Ar*C*), 127.3 (Ar*C*), 128.0 (Ar*C*), 128.9 (Ar*C*), 128.9 (Ar*C*), 129.0 (Ar*C*), 131.9 (Ar*C*), 134.2 (Ar*C*), 134.6 (Ar*C*), 139.0 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{14}H_{12}N_2]^+$ $(M+H)^+$: m/z 223.1230, found 223.1229 (-0.1 ppm)

_N_-benzyl-_N_-(4-methoxyphenyl)cyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-cyano-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide **133** (333 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 0-5% EtOAc in hexanes, 30 × 140 mm silica) the title compound **144** (195 mg, 0.82 mmol, 82% yield) as a white solid; mp 50-54 °C; R_f = 0.48 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2987, 2980, 2212 (C≡N), 1510, 1456, 1369, 1288, 1176, 1018, 821, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.78 (3H, s, OC*H*$_3$), 4.74 (2H, s, PhC*H*$_2$), 6.83-6.91 (2H, m, Ar*H*), 7.02-7.06 (2H, m, Ar*H*) 7.31-7.43 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 54.8, 55.7, 114.9, 115.0, 118.4 (Ar*C*), 127.6 (Ar*C*), 128.6 (Ar*C*), 129.2 (Ar*C*), 133.3 (Ar*C*), 134.6 (Ar*C*), 156.5 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{15}H_{15}O_1N_2]^+$ $(M+H)^+$: m/z 239.1179, found 239.1179 (+0.5 ppm)

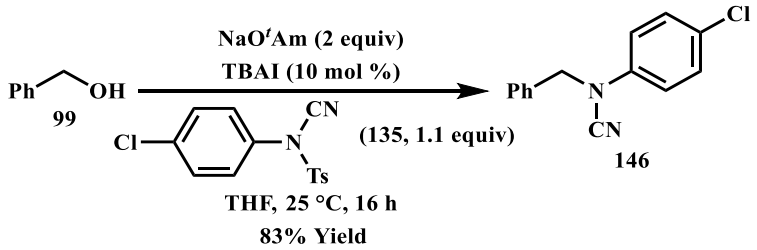
_N_-benzyl-_N_-(4-(trifluoromethyl)phenyl)cyanamide



Following general procedure 7, benzyl alcohol (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-cyano-4-methyl-*N*-(4-(trifluoromethyl)phenyl)benzenesulfonamide (374 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 140 mm silica) the title compound (195 mg, 0.72 mmol, 72% yield) as a white solid; mp 86-88 °C; R_f = 0.57 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2968, 2222 (C≡N), 1742, 1616, 1520, 1454, 1429,1371, 1215, 1161, 1105, 1074, 1009, 945, 827, 768,

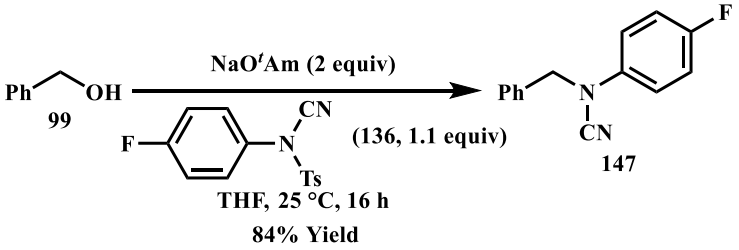
719, 700, 530, 515, 498, 482; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.86 (2H, s, PhC*H*$_2$), 7.22 (2H, d, *J* 8.8, Ar*H*), 7.35-7.43 (5H, m, Ar*H*), 7.59 (2H, d, *J* 8.8); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: -62.1; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 53.8 (*C*H$_2$), 112.9 (*C*≡N), 115.8 (Ar*C*), 124.0 (q, ^{1}J 271.5, *C*F$_3$), 125.9 (q, ^{2}J 33.1, Ar*C*), 127.1 (q, ^{3}J 3.8, Ar*C*), 127.4 (Ar*C*), 129.0 (Ar*C*), 129.4 (Ar*C*), 133.6 (Ar*C*), 142.8 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{15}H_{11}F_3N_2Na]^+$ $(M+Na)^+$: m/z 299.0767, found 299.0767 (+0.2 ppm).

_N_-benzyl-_N_-(4-chlorophenyl)cyanamide



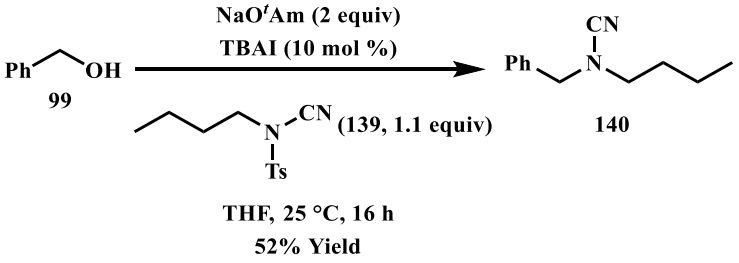
Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-(4-chlorophenyl)-*N*-cyano-4-methylbenzenesulfonamide **135** (337 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 130 mm silica) the title compound **146** (201 mg, 0.83 mmol, 83% yield) as a white solid; mp 51-53 °C; R_f = 0.43 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2990, 2216 (C≡N), 1597, 1489, 1273, 1174, 1091, 812, 696; ^{1}H NMR (400 MHz, CDCl3) δ_H ; 4.79 (2H, s, PhC*H*$_2$), 7.05 (2H, d, *J* 9.0, Ar*H*), 7.27-7.33 (2H, m, Ar*H*), 7.33-7.41 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 54.1 (*C*H$_2$), 113.7 (*C*≡N), 117.5 (Ar*C*), 127.5 (Ar*C*), 128.9 (Ar*C*), 129.3 (Ar*C*), 129.3 (Ar*C*), 129.8 (Ar*C*), 133.9 (Ar*C*), 138.6 (Ar*C*); HRMS (NSI$^+$) calculated for $[C_{14}H_{12}N_2Cl_1]^+$ $(M+H)^+$: m/z 243.0684, found 243.0686 (+1.0 ppm);

_N_-benzyl-_N_-(4-fluorophenyl)cyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-cyano-*N*-(4-fluorophenyl)-4-methylbenzenesulfonamide **136** (319 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 35 × 150 mm silica) the title compound **147** (192 mg, 0.84 mmol, 84% yield) as a white solid; mp 79-82 °C; R_f = 0.42 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2997, 2986, 2212 (C≡N), 1504, 1450, 1355, 1222, 1026, 821, 615; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ; 4.77 (2H, s, PhCH_2), 6.96-7.13 (4H, m, Ar*H*), 7.30-7.44 (5H, m, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: -119.2; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 54.5 (*C*H_2), 114.2 (*C*≡N), 116.5 (d, *J* 23.0, Ar*C*), 118.1 (d, *J* 8.0, Ar*C*), 127.5 (Ar*C*), 128.8 (Ar*C*), 129.2 (Ar*C*), 134.1 (Ar*C*), 136.1 (d, *J* 3.0, Ar*C*), 159.3 (d, *J* 244.4, Ar*C*); HRMS (NSI^+) calculated for $[C_{14}H_{12}N_2F_1]^+$ $(M+H)^+$: m/z 227.0979, found 227.0980 (0.4 ppm).

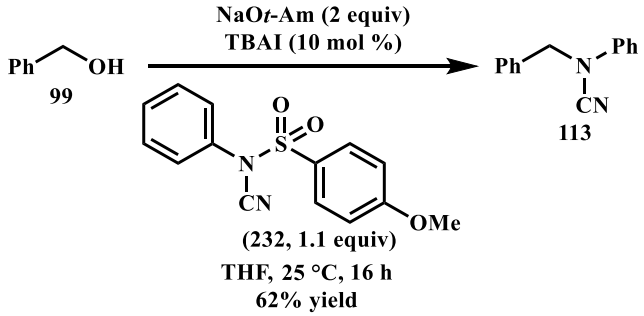
_N_-benzyl-_N_-butylcyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and *N*-butyl-*N*-cyano-4-methylbenzenesulfonamide **139** (220 mg, 1.1 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 40 × 110 mm silica) the title compound **140** (97 mg, 0.52 mmol, 52% yield) as a colourless oil; R_f = 0.57 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2956, 2932, 2872, 2361, 2342, 2205 (C≡N), 1454, 1364, 1142, 1078, 737, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.91 (3H, t, *J* 7.4, CHCH_3), 1.36 (2H, sextet, *J* 7.4, CH_2), 1.63 (2H, quintet, *J* 7.4, CH_2), 2.92

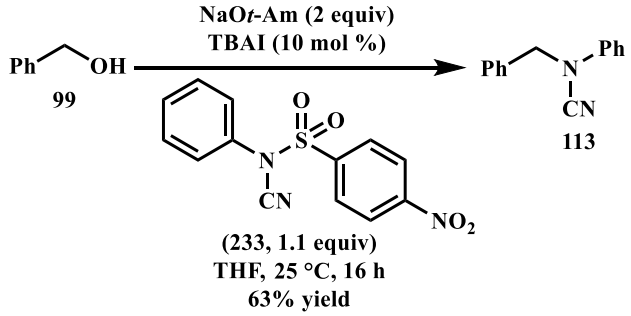
(2H, t, *J* 7.3, C*H*$_2$), 4.19, (2H, s, PhC*H*$_2$), 7.33-7.40 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 13.8 (*C*H$_3$), 19.8 (CH$_2$), 29.6 (*C*H$_2$), 50.2 (*C*H$_2$), 56.0 (*C*H$_2$), 118.2 (*C*≡N), 128.5 (Ar*C*), 128.7 (Ar*C*), 129.0 (Ar*C*), 135.0 (Ar*C*); HRMS (AP$^+$) calculated for $[C_{12}H_{17}N_2]^+$ (M+H)$^+$: m/z 189.1392 found 189.1398 (+3.2 ppm).

_N_-benzyl-_N_-phenylcyanamide



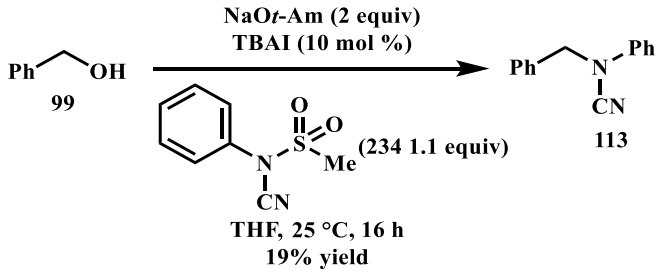
Following general procedure 7, benzyl alcohol **99** (104 µL, 1.00 mmol, 1 equiv), THF (5 mL), TBAI (36.9 mg, 0.10 mmol, 0.1 equiv), NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) and *N*-cyano-4-methoxy-*N*-phenylbenzenesulfonamide **232** (317 mg, 1.10 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 x 110 mm silica) the title compound **113** (129 mg, 0.62 mmol, 62% yield) as a white solid with physical properties and spectroscopic data identical to those reported previously.

_N_-benzyl-_N_-phenylcyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1.00 mmol, 1 equiv), THF (5 mL), TBAI (36.9 mg, 0.10 mmol, 0.1 equiv), NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) and *N*-cyano-4-nitro-*N*-phenylbenzenesulfonamide **233** (334 mg, 1.10 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 x 110 mm silica), the title compound **113** (132 mg, 0.63 mmol, 63% yield) as a white solid with physical properties and spectroscopic data identical to those reported previously.

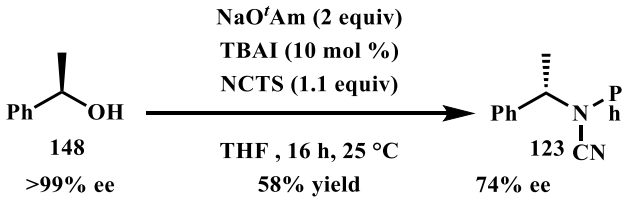
N-benzyl-*N*-phenylcyanamide



Following general procedure 7, benzyl alcohol **99** (104 µL, 1.00 mmol, 1 equiv), THF (5 mL), TBAI (36.9 mg, 0.10 mmol, 0.1 equiv), NaO*t*Am (220 mg, 2.00 mmol, 2 equiv) and *N*-phenylmethanesulfonamide **234** (216 mg, 1.10 mmol, 1.1 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 x 110 mm silica), the title compound **113** (39.8 mg, 0.19 mmol, 19% yield) as a white solid with physical properties and spectroscopic data identical to those reported previously.

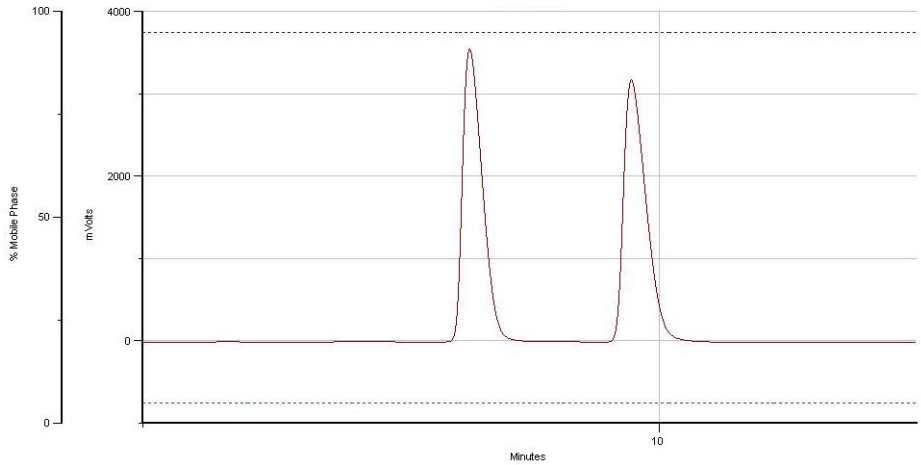
5.3.5 Mechanistic studies

(*S*)-*N*-phenyl-*N*-(1-phenylethyl)cyanamide

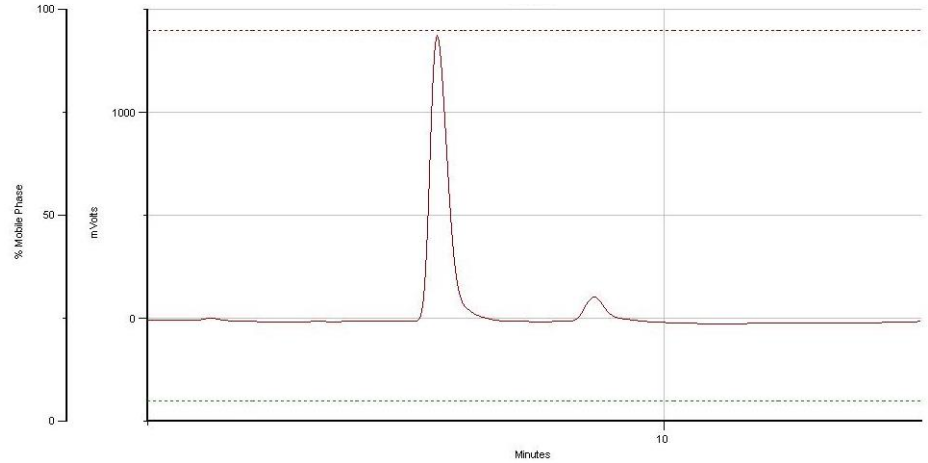


Following general procedure 7, (*R*)-1-phenylethan-1-ol **148** (120 µL, 1 mmol, 1 equiv), THF (5 mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv) and NCTS **101** (544 mg, 2 mmol, 2 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 120mm silica) the title compound **123** as a white solid (129 mg, 0.58 mmol, 58% yield) with physical and spectroscopic properties identical to those reported previously. Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm).

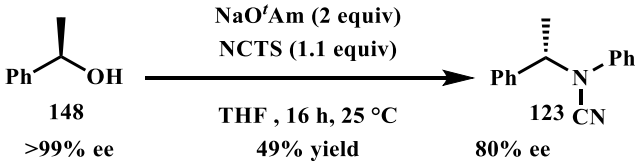
	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	8.17	79092888.00	49.65
2	1.00	*2	9.73	80220400.00	50.35



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	8.16	55022120.00	86.96
2	1.00	*2	9.78	8253515.00	13.04

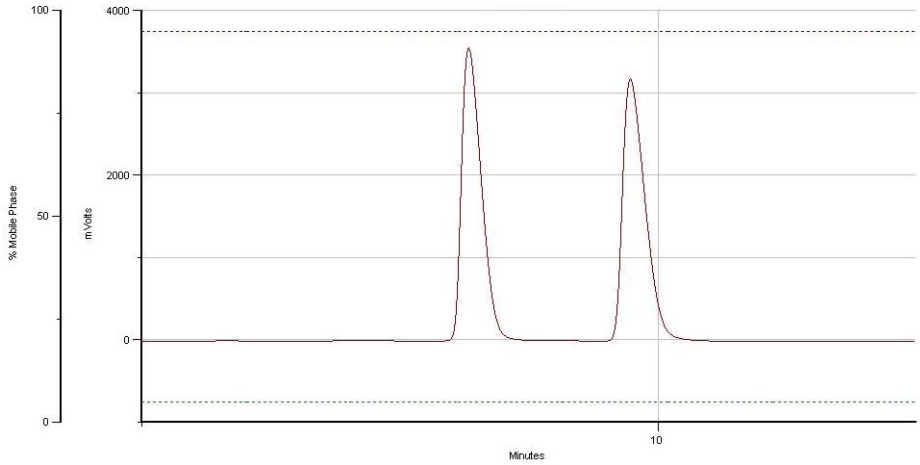


(*S*)-*N*-phenyl-*N*-(1-phenylethyl)cyanamide

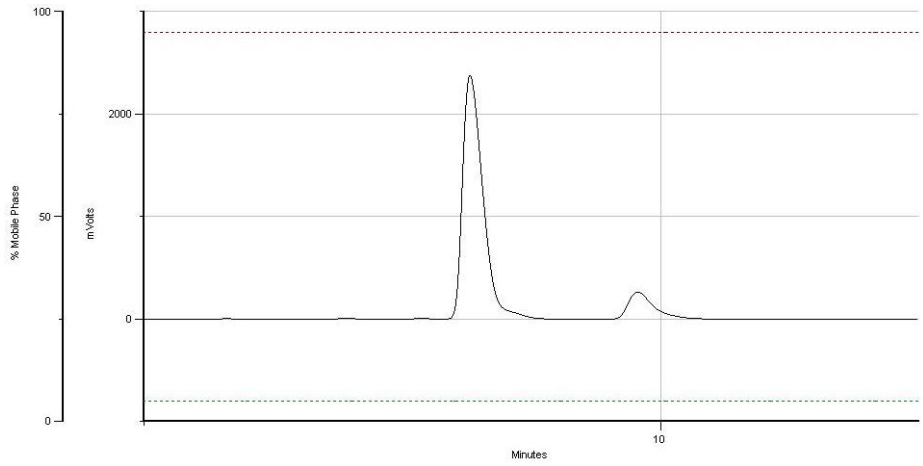


Following general procedure 7, (*R*)-1-phenylethan-1-ol **148** (120 µL, 1 mmol, 1 equiv), THF (5mL), NaO*t*Am (221 mg, 2 mmol, 2 equiv) and NCTS **101** (544 mg, 2 mmol, 2 equiv) gave after flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 120mm silica) the title compound **123** as a white solid (109 mg, 0.49 mmol, 49% yield) with physical and spectroscopic properties identical to those reported previously. Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm).

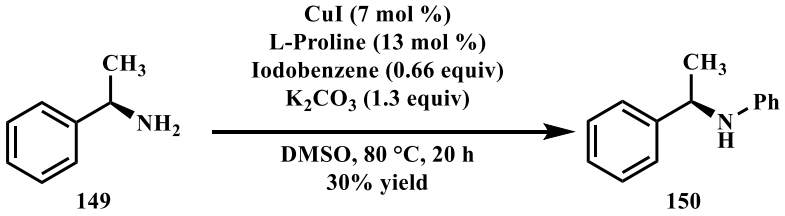
	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	8.17	79092888.00	49.65
2	1.00	*2	9.73	80220400.00	50.35



	Inj. Number	Peak Name	R. Time	Area	Area %
1	1.00	*1	7.81	28225798.00	90.34
2	1.00	*2	9.33	3019863.50	9.66

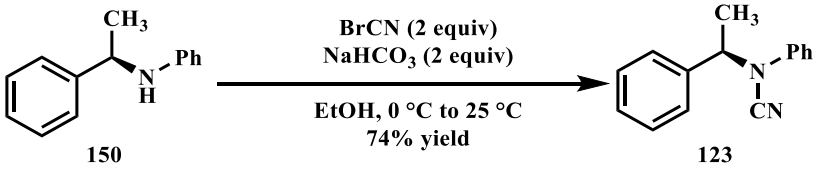


(*R*)-*N*-(1-phenylethyl)aniline



Following a modified procedure,[11] (*R*)-1-phenylethan-1-amine **149** (954 µL, 7.5 mmol, 1 equiv) and iodobenzene (570 µL, 5 mmol, 0.66 equiv) were added to a 100 mL round bottomed flask with 40 mL anhydrous DMSO. In order CuI (95.0 mg, 0.5 mmol, 0.07 equiv), L-proline (115 mg, 1 mmol, 0.13 equiv) and K_2CO_3 (1.38 g, 10 mmol, 1.3 equiv) were added. The mixture was heated to 80 °C for 20 h. After cooling to 25 °C the mixture was partitioned between water and CH_2Cl_2. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 × 3. The combined organic phase was dried over $MgSO_4$, filtered and volatiles removed *in vacuo*. The crude oil was then purified by flash silica column chromatography (eluent 0-5% EtOAc in hexanes, 40 × 120mm silica) to give the title compound **150** as a yellow oil with physical properties and spectroscopic data in accordance with the literature (291 mg, 1.5 mmol, 30% yield);[11] Rf = 0.43 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2980, 1597, 1504, 1446, 1371, 1253, 1132, 748, 505; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.52 (3H, d, *J* 6.7, C*H*$_3$), 4.03 (1H, br.s,, N*H*), 4.49 (1H, q, *J* 6.7, C*H*), 6.51 (2H, d, *J* 7.8, Ar*H*), 6.64 (1H, t, *J* 7.3, Ar*H*), 7.04-7.13 (2H, m, Ar*H*), 7.23 (1H, t, *J* 7.2, Ar*H*), 7.32 (2H, dd, *J* 10.4, 4.9, Ar*H*), 7.34-7.40 (2H, m, Ar*H*).

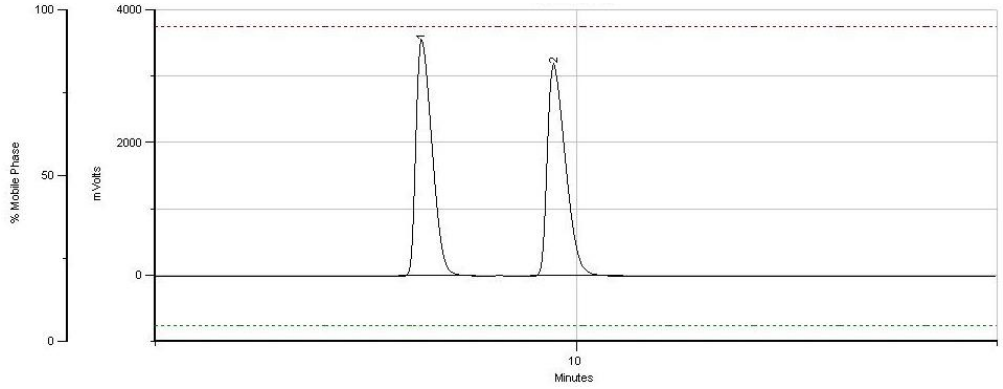
(*R*)-*N*-phenyl-*N*-(1-phenylethyl)cyanamide



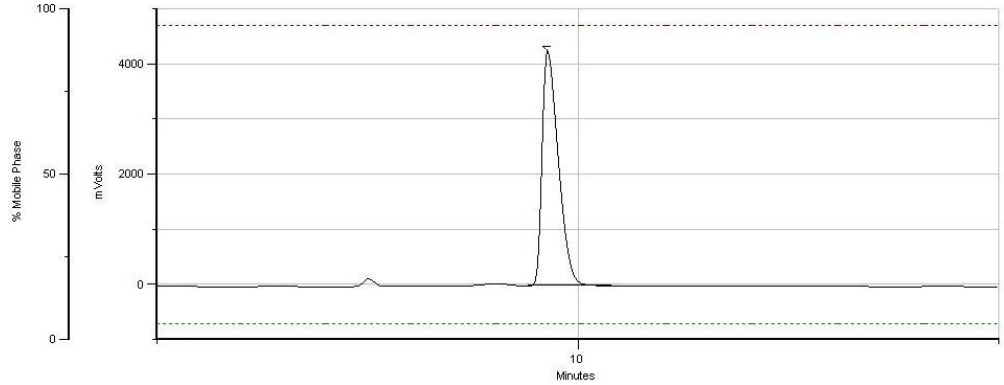
150 123

(*R*)-*N*-(1-phenylethyl)aniline **150** was added to a flame dried reaction vial with EtOH (2 mL) followed by $NaHCO_3$ (168mg, 2 mmol, 2 equiv). The solution was cooled to 0 °C and BrCN (212 mg, 2 mmol, 2 equiv) was then added and the reaction stirred and allowed to warm to 25 °C overnight. The reaction was then diluted with sat. aq. $NaHCO_3$ and extracted into EtOAc × 3. The organic phase was washed with brine, dried over $MgSO_4$ and filtered before the volatiles were removed *in vacuo* to yield the title compound **123** (165 mg, 0.74 mmol, 74% yield) as a white solid with all physical and spectroscopic data in accordance with those reported previously.

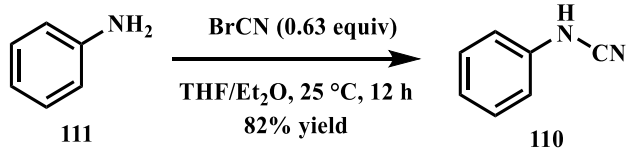
Inj. Number	Peak Name	R. Time	Area	Area %
1.00	*1	8.17	79092888.00	49.65
1.00	*2	9.73	80220400.00	50.35



Inj. Number	Peak Name	R. Time	Area	Area %
1.00	*1	9.64	96007184.00	100.00

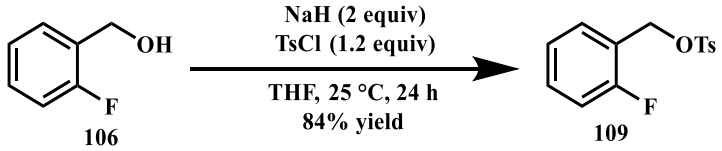


_N_-phenylcyanamide



To a 100 mL round-bottom flask containing a magnetic follower was charged cyanogen bromide **30** (1.82 g, 17 mmol, 0.63 equiv), THF (18 mL) and diethyl ether (6 mL). The solution was cooled to 0 °C before addition of aniline **111** (2.48 mL, 27 mmol, 1 equiv). The reaction mixture was then stirred for 12 h at 25 °C. The mixture was then concentrated in vacuo to give a crude solid. The solid was dissolved in water, and a precipitate was formed. The mixture was then filtered and washed with hexanes to give the title product **110** (1.64 g, 14 mmol, 82% yield) as a brown solid with physical properties and spectroscopic data in accordance with the literature;[12] mp 37-38 °C ; Rf = 0.3 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3387, 3150, 3098, 2986, 2909, 2224 (C≡N), 1599, 1497, 1435, 1252, 735, 681, 484; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.75 (1H, s, N*H*), 7.00-7.03 (2H, m, Ar*H*), 7.09-7.13 (1H, m, Ar*H*), 7.33-7.37 (2H, m, Ar*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 111.6 (*C*≡N), 115.5 (Ar*C*), 123.7 (Ar*C*), 129.9 (Ar*C*), 137.4 (Ar*C*).

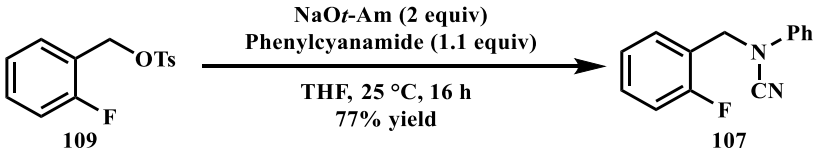
2-fluorobenzyl 4-methylbenzenesulfonate



To a 10 mL microwave vial containing a magnetic follower was charged in order 2-fluorobenzyl alcohol **106** (218 µL, 2.00 mmol, 1 equiv), THF (10 mL), 60% sodium hydride in mineral oil (160 mg, 2.00 mmol, 2 equiv) and tosyl chloride (458 mg, 2.40 mmol, 1.2 equiv). The reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was quenched by addition of water (20 mL) and the product extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. The solid was recrystallised from hexanes and the pure title compound **109** (441 mg, 1.68 mmol, 84%) was isolated as a white crystalline solid; mp 56-58 °C (hexanes); R_f = 0.55 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2974, 2365, 1495, 1454, 1379, 1346, 1302, 1244, 1188, 1171, 1096, 924, 880, 829, 814, 764, 719, 664, 608, 552, 529, 500, 457, 430; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 2.45 (3H,

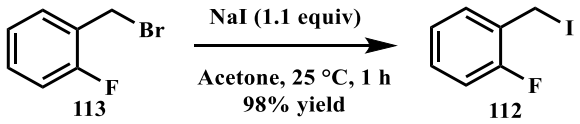
s, C*H*$_3$), 5.12 (2H, s, PhC*H*$_2$), 7.01 (1H, t, *J* 9.0, Ar*H*), 7.11 (1H, t, *J* 7.0, Ar*H*), 7.30-7.34 (4H, m, Ar*H*), 7.81 (2H, d, *J* 7.8, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: -117.6; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.8 (*C*H$_3$), 65.7 (d, *J* 4.4, *C*H$_2$), 115.6 (d, *J* 20.9, Ar*C*), 120.9 (d, *J* 14.3, Ar*C*), 124.4 (d, *J* 3.7, Ar*C*), 128.1 (Ar*C*), 130.0 (Ar*C*), 131.0 (d, *J* 3.2, Ar*C*), 131.3 (d, *J* 8.2, Ar*C*), 133.2 (Ar*C*), 145.0 (Ar*C*), 161.5 (d, *J* 249.8, Ar*C*); HRMS (ASAP$^+$) calculated for $[C_{14}H_{17}NO_3FS]^+$ $(M+NH_4)^+$: m/z 298.0913 found 298.0915 (+0.7 ppm).

_N_-(2-fluorobenzyl)-_N_-phenylcyanamide



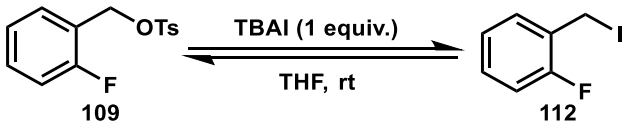
To a 10 mL reaction vial containing a magnetic follower was charged 2-fluorobenzyl 4-methylbenzenesulfonate **109** (280 mg, 1.00 mmol, 1 equiv), THF (5 mL) and NaOt-Am (220 mg, 2.00 mmol, 2 equiv). The solution was stirred at 25 °C for 15 min. Phenylcyanamide (130 mg, 1.10 mmol, 1.1 equiv) was then added. The reaction mixture was stirred at 25 °C for 16h. The reaction was quenched by addition of sat. aq. NH_4Cl and the product extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 x 110 mm silica), gave the title compound **107** (173 mg, 0.77 mmol, 77%) as a white solid with all physical and spectroscopic data in accordance with those reported previously.

1-fluoro-2-(iodomethyl)benzene



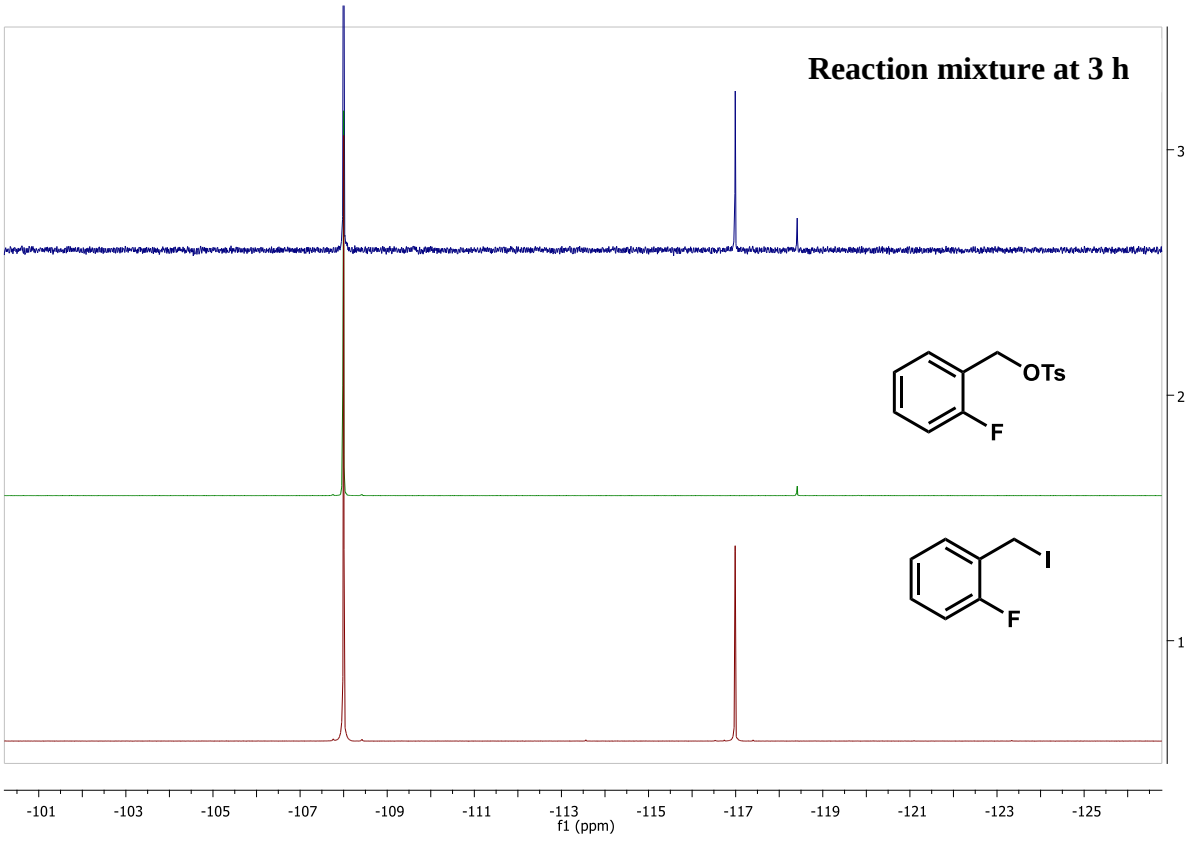
To a 100 mL round-bottom flask containing a magnetic follower was charged in order sodium iodide (1.65 g, 11.0 mmol, 1.1 equiv), acetone (40 mL) and 2-fluorobenzyl bromide **113** (1.21 mL, 10.0 mmol, 1 equiv). The reaction mixture was stirred for 1 h at 25 °C. The mixture was then filtered and the filtrate was concentrated *in vacuo* to give the title product **112** (2.31 g, 9.79 mmol, 98 %) as a yellow oil; R_f = 0.79 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 1614, 1584, 1491, 1458, 1234, 1198, 1155, 1128,

1070, 1030, 939, 854, 750, 577, 523, 503, 442; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.46 (2H, s, PhC*H*$_2$), 7.02 (1H, t, *J* 9.1, Ar*H*), 7.08 (1H, t, *J* 7.5, Ar*H*), 7.23-7.29 (1H, m, Ar*H*), 7.36 (1H, td, *J* 7.7, 1.7, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: -116.2; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: -3.5 (d, *J* 4.4, *C*H$_2$), 116.0 (d, *J* 21.1, Ar*C*), 124.6 (d, *J* 3.8, Ar*C*), 126.8 (d, *J* 14.5, Ar*C*), 130.0 (d, *J* 8.2, Ar*C*), 130.9 (d, *J* 3.2, Ar*C*), 160.4 (d, *J* 249.7, Ar*C*); HRMS (EI$^+$) calculated for C_7H_6FI [M]$^+$: *m/z* 235.9498, found 235.9493 (-2.1 ppm).



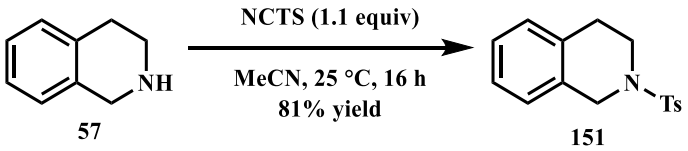
To a reaction vial was added 2-fluorobenzyl 4-methylbenzenesulfonate (280 mg, 1.00 mmol, 1 equiv), followed by THF (5 mL) and 1,3,5-trifluorobenzene (104 µL, 1 mmol, 1 equiv) as internal standard. TBAI (369.4 mg, 1 mmol, 1 equiv) was then added and the solution was stirred at 25 °C. At t= 30 min, 1h, 3h, 6h and 23 h the reaction was sampled by taking aliquots into a borosilicate NMR tube and diluting with THF. The reaction was monitored by $^{19}F\{^{1}H\}$ NMR analysis. Each $^{19}F\{^{1}H\}$ NMR was analysed to determine to composition of the reaction mixture quoted as a mixture of 2-fluorobenzyl 4-methylbenzenesulfonate and 1-fluoro-2-(iodomethyl)benzene.

	Reaction composition/ %		
Time	2-fluoro-4- methylbenzene sulfonate **109**	1-fluoro-2-(iodomethyl)benzene **112**	Other
30 min	14	86	0
1 h	16	84	0
3 h	16	84	0
6 h	16	84	0
23 h	16	74	10



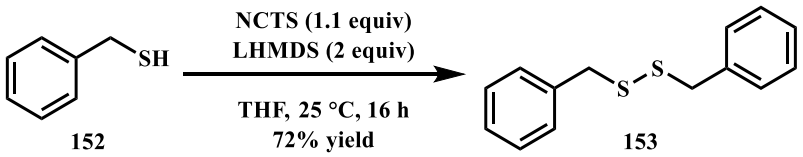
5.3.6 Further investigations with NCTS

2-tosyl-1,2,3,4-tetrahydroisoquinoline



To a round bottomed flask was added in order 1,2,3,4-tetrahydroisoquinoline **57** (125.2 µl, 1 mmol, 1 equiv), MeCN (5 mL) and NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv). The reaction was stirred at 25 °C for 16 h. The reaction was concentrated *in vacuo* and the crude residue diluted with H_2O and the product extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Recrystallisation from Et_2O gave the title compound **151** (232 mg, 0.81 mmol, 81%) as a white crystalline solid with physical and spectroscopic data in accordance literature.[13] R_f = 0.15 (eluent = 20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s, CH_3) 2.95 (2H, t, *J* 5.9, C(3)H_2), 3.38 (2H, t, *J* 5.9, C(3)H_2), 4.27 (2H, s, C(8)H_2), 7.01-7.06 (m, 1H, Ar*H*), 7.07-7.12 (1H, m, Ar*H*), 7.13-7.20 (2H, m, Ar*H*), 7.35 (2H, d, *J* 8.0, Ar*H*) 7.75 (2H, d, *J* 8.3, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.8 (*C*H_3), 29.0 (*C*(3)), 43.9 (*C*H_2), 47.7 (*C*H_2), 126.5 (Ar*C*), 126.5 (Ar*C*), 126.9 (Ar*C*), 127.9 (Ar*C*), 129.0 (Ar*C*), 129.8 (Ar*C*), 131.8 (Ar*C*), 133.2 (Ar*C*), 133.6 (Ar*C*), 143.8 (Ar*C*); HRMS (ASAP+) calculated for $C_{16}H_{18}NO_2S$ $[M+H]^+$: *m/z* 288.1058, found 288.1057 (-0.3 ppm).

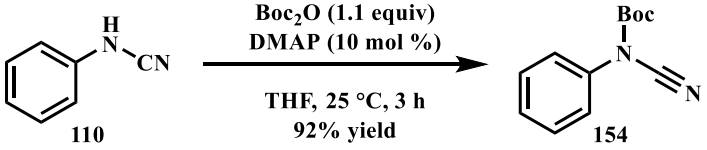
1,2-dibenzyldisulfane



To a round bottomed flask was added in order benzyl mercaptan **152** (59 µl, 0.5 mmol, 1 equiv), THF (2.5 mL) and LHMDS 1M in THF (1 mL, 1 mmol, 2 equiv). The mixture was stirred at 25 °C for 10 minutes before NCTS **101** (150 mg, 0.55 mmol, 1.1 equiv) was added. The reaction was stirred at 25 °C for 16 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the product extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give

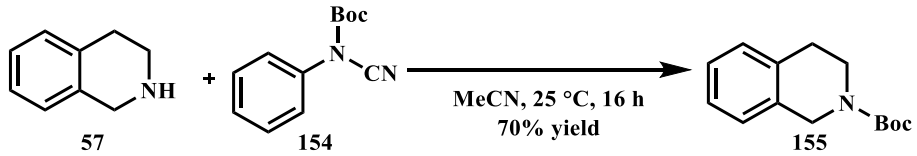
the crude product. Purification by flash silica column chromatography (eluent = Hexanes, 30 x 110 mm silica), gave the title compound **153** (44.1 mg, 0.18 mmol, 72%) as a white solid with physical and spectroscopic data in accordance literature.[14] R_f = 0.78 (eluent = 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.60 (4H, s, 2×CH_2), 7.12-7.41 (10H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 43.4 (2×*C*H_2), 127.6 (Ar*C*), 128.6 (Ar*C*), 129.6 (Ar*C*), 137.5 (Ar*C*).

_N_-cyano-_N_-_t_-butyl phenylcarbamate



To a round bottomed flask was added phenyl cyanamide **110** (500 mg, 4.2 mmol, 1 equiv), Boc_2O (1.02g, 4.7 mmol, 1.1 equiv), dimethylaminopyridine (51.7 mg, 0.4 mmol, 0.1 equiv) in THF (20 mL). The reaction was stirred at 25 °C and monitored by TLC. After 5 h the reaction was determined complete and concentrated *in vacuo*. The crude residue was dissolved in H_2O and the title compound extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was concentrated *in vacuo* to yield the pure title compound **154** as a white solid (849.5 mg, 3.89 mmol, 92%); mp 64-67 °C; R_f = 0.59 (eluent = 20% EtOAc in hexanes)**;** ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.58 (9H, s, *t*-bu*H*), 7.34-7.39 (1H, m, Ar*H*), 7.40-7.47 (4H, m, Ar*H*)'); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.0 (*C*H_3), 86.8 (*C*H), 109.09 (*C*≡N), 124.9 (Ar*C*), 128.60 (Ar*C*), 129.6 (Ar*C*), 135.2 (Ar*C*), 150.1 (*C*=O).

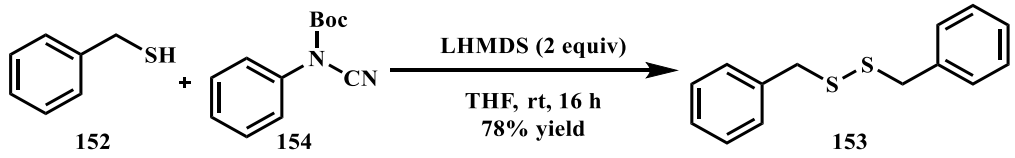
tert-butyl 3,4-dihydroisoquinoline-2(1H)-carboxylate



To a reaction vial was added in order 1,2,3,4-tetrahydroisoquinoline **57** (62.6 µl, 0.5 mmol, 1 equiv), MeCN (2.5 mL) and *N*-cyano-*N*-*t*-butyl phenylcarbamate **154** (109.1 mg, 0.5 mmol, 1 equiv). The reaction was stirred at 25 °C for 16 h. The reaction was then concentrated *in vacuo* and the crude residue dissolved in H_2O and extracted with CH_2Cl_2. The organic phase was concentrated *in vacuo* to give the pure title compound **155** (81.6 mg, 0.35 mmol, 70%) as a yellow solid with physical and spectroscopic data in accordance with literature.[15] mp 30-34 °C; {lit.[16] mp 36-38 °C}R_f = 0.35 (eluent = 20%

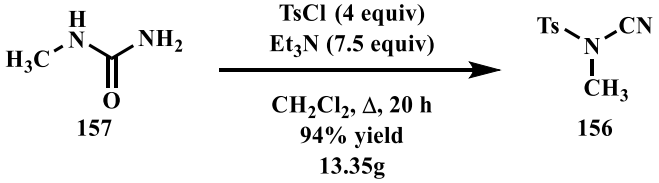
EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.49 (s, 9H, 3×CH_3), 2.83 (2H, t, *J* 5.6, C(1)H_2), 3.65 (2H, s, C(8)H_2), 4.57 (2H, br.s), 7.08-7.21 (4H, m); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 27.6 (*C*H_3), 28.6 (*C*H_2), 29.1 (*C*H_2), 31.4 (*C*H_2), 85.3 (*C*H(CH_3)$_3$), 126.3 (Ar*C*), 126.4 (Ar*C*), 128.7 (Ar*C*), 128.9 (Ar*C*), 134.9 (Ar*C*), 146.9 (Ar*C*), 155.1 (*C*=O).

1,2-dibenzyldisulfane



To a round bottomed flask was added in order benzyl mercaptan **152** (59 µl, 0.5 mmol, 1 equiv), THF (2.5 mL) and LHMDS 1M in THF (1 mL, 1 mmol, 2 equiv). The mixture was stirred at 25 °C for 10 minutes before N-cyano-N-t-butyl phenylcarbamate **154** (120 mg, 0.55 mmol, 1.1 equiv) was added. The reaction was stirred at 25 °C for 16 h. The reaction was quenched by addition of sat. aq. NH4Cl and the product extracted with EtOAc (3 × 15 mL). The combined organic fraction was dried (MgSO4), filtered and concentrated in vacuo to give the crude product. Purification by flash silica column chromatography (eluent = Hexanes, 30 x 110 mm silica), gave the title compound **153** (48.0 mg, 0.2 mmol, 78%) as a white solid physical and spectroscopic data in accordance with those reported previously.

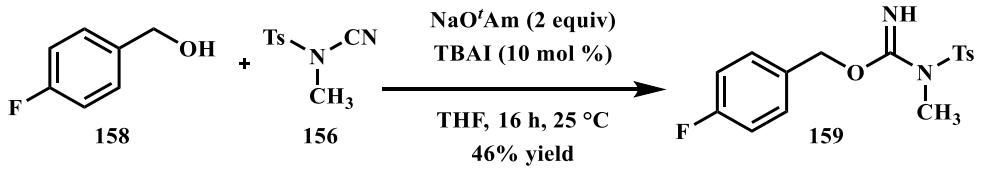
N-cyano-N,4-dimethylbenzenesulfonamide



To a round bottomed flask was added methyl urea **157** (5.0 g, 67 mmol, 1 equiv), CH_2Cl_2 (150 mL), tosyl chloride (25.7 g, 134 mmol, 2 equiv) and Et_3N (29.3 mL, 253 mmol, 3.75 equiv). The flask was heated to reflux for 3 h before further tosyl chloride (25.7 g, 134 mmol, 2 equiv) and Et_3N (29.3 mL, 253 mmol, 3.75 equiv) were added. The reaction was set to reflux for a further 16 h. After 16 h the reaction was cooled to room temperature before concentration *in vacuo* to yield a crude brown oil. Purification by flash silica column chromatography (eluent = 0-20% EtOAc/Hexanes, 95 x 150 mm silica), gave the

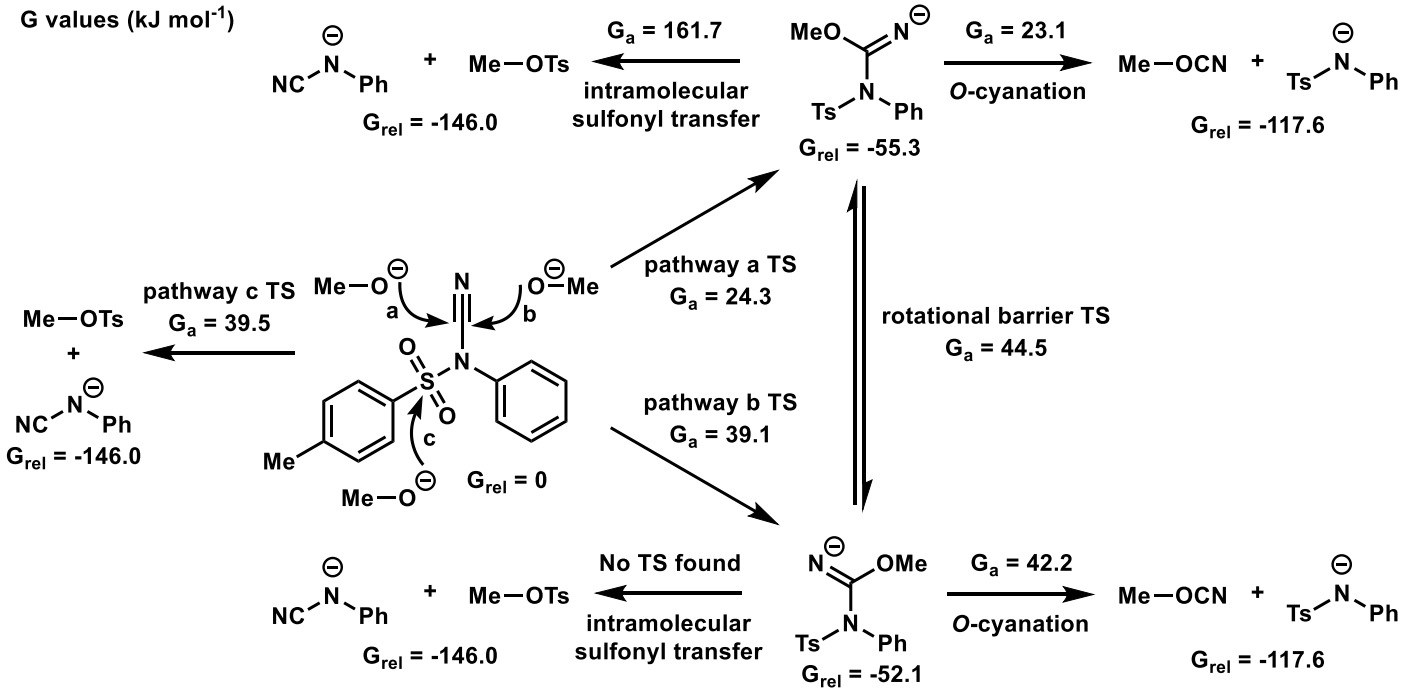
title compound **156** (13.35 g, 63 mmol, 94%) as an off white solid; mp 74-76 °C; R_f = 0.16 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2991, 2227 (C≡N), 1591, 1375, 1166, 947, 678, 540; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.49 (3H, s, ArCH_3), 3.13 (3H, s, NCH_3), 7.39-7.46 (2H, m, Ar*H*), 7.8-7.87 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.9 (Ar*C*H$_3$), 37.01 (N*C*H$_3$), 109.6, 128.1, 130.6, 132.7, 146.7. HRMS (ASAP+) calculated for $C_9H_{10}N_2O_2S$ $[M+H]^+$: *m/z* 210.0463, found 210.0458 (-2.4 ppm).

4-fluorobenzyl methyl(tosyl)carbamimidate



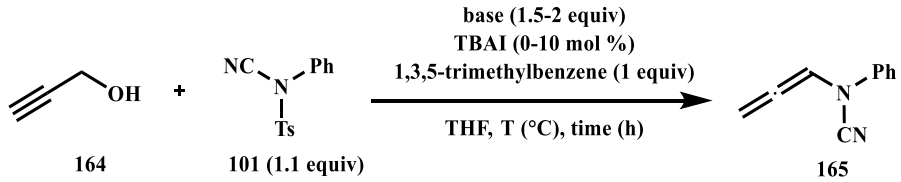
To a reaction vial was added 4-fluorobenzyl alcohol **158** (109.1 µL, 1 mmol, 1 equiv), THF (5 mL), TBAI (36.9 mg, 0.1 mmol, 0.1 equiv), N-cyano-N,4-dimethylbenzenesulfonamide **156** (231.3 mg, 1.1 mmol, 1.1 equiv) and NaH (80 mg, 2 mmol, 2 equiv). The reaction was stirred at 25 °C for 16 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the product extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Purification by flash silica column chromatography (eluent = 0-20% EtOAc/Hexanes, 95 x 150 mm silica), gave the title compound **159** (155 mg, 0.46 mmol, 46%) as an off white solid. mp 58-62 °C; R_f = 0.42 (eluent = 20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.46 (3H, s, ArCH_3), 2.57 (3H, s, CH_3), 4.09 (2H, s, ArCH_2O), 7.02 (2H, t, *J* 8.5, Ar*H*), 7.28 (2H, m, Ar*H*), 7.35 (2H, d, *J* 7.9, Ar*H*), 7.72 (2H, d, *J* 8.0, Ar*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: -114.4; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.7 (*C*H$_3$), 34.4 (*C*H$_3$), 53.60 (Ar*C*H$_2$O), 115.6 (d, *J* 24.7, ArC), 127.7 (Ar*C*), 129.9 (Ar*C*), 130.2 (d, *J* 8.2, Ar*C*), 131.6 (d, *J* 3.1, Ar*C*), 134.4 (Ar*C*), 143.7 (Ar*C*), 161.6, 163.6;

5.3.7 Computational data



5.4 Experimental and characterisation data for chapter 3

5.4.1 Reaction optimisation



General procedure 9

To a reaction vial was added propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv) followed by THF ([**164**] = 0.2 mol dm^{-3}) base (1.5-2 equiv). 1,3,5-trimethylbenzene (139 µL, 1 mmol, 1 equiv) as internal standard, NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv) and TBAI (0-10 mol %) as an additive, the reactions were stirred at constant temperature. The reaction was monitored taking aliquots at specified times (T1= 1 h, T2= 3 h, T3= 6 h, T4 = 23 h) *via* ^{1}H NMR analysis. Each ^{1}H NMR was analysed to determine the amount of product **165** present within the reaction mixture.

Entry	Base (eq.)	Solvent	Additive (mol %)	**T1 = 1h Product 165/ %**	**T2 = 3 h Product 165/ %**	**T3 = 6 h Product 165/ %**	**T4 = 23 h Product 165/ %**
1	NaH (2)	THF	TBAI (10)	30	74	76	56
2	NaO*t*Am (2)	THF	TBAI (10)	35	63	61	58
3	KO*t*Bu (2)	THF	TBAI (10)	7	17	18	19
4	DBU (2)	THF	TBAI (10)	0	0	0	5
5	LHMDS (2)	THF	TBAI (10)	0	0	0	0
6	DBN (2)	THF	TBAI (10)	0	0	0	0
7	NaH (2)	THF	-	8	26	36	40
8	NaO*t*Am (2)	THF	-	20	30	33	40
9	NaO*t*Am (2)	DME	TBAI (10)	47	59	73	73

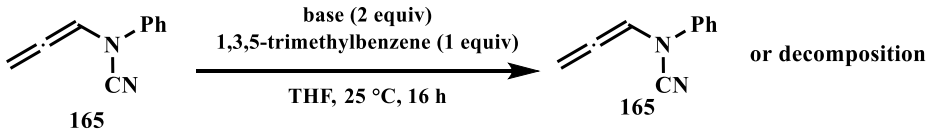
General procedure 10

To a reaction vial was added propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv) followed by THF ([**164**] = 0.2 mol dm^{-3}), 1,3,5-trimethylbenzene (139 µL, 1 mmol, 1 equiv) as internal standard, NCTS **2** (300 mg, 1.1 mmol, 1.1 equiv) and TBAI (0-10 mol %) as an additive and stirred for 5 min. Base (1.5-2 equiv) is then added and the reactions were stirred at constant temperature. The reaction was monitored taking aliquots at specified

times (T1= 1 h, T2= 3 h, T3= 6 h, T4 = 23 h) *via* ^{1}H NMR analysis. Each ^{1}H NMR was analysed to determine the amount of product **165** present within the reaction mixture.

Entry	Base (eq.)	Solvent	Additive (mol %)	**T1 = 1h Product 165/ %**	**T2 = 3 h Product 165/ %**	**T3 = 6 h Product 165/ %**	**T4 = 23 h Product 165/ %**
1	NaO*t*Am (2)	DME	TBAI (10)	55	61	73	75
2	**NaH (2)**	**THF**	**TBAI (10)**	**38**	**73**	**73**	**76**
3	NaH (2)	DME	TBAI (10)	40	75	75	74
4	NaO*t*Am (1.5)	THF	TBAI (10)	24	27	46	42
5	NaH (1.5)	THF	TBAI (10)	31	44	52	56

5.4.2 Stability tests



To a reaction vial was added *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** (31 mg, 0.2 mmol, 1 equiv) followed by THF (1 mL), base (2 equiv), 1,3,5-trimethylbenzene (28 µL, 0.2 mmol, 1 equiv) as internal standard and the reactions were stirred at constant temperature. The reaction was monitored taking aliquots at T= 16 h *via* ^{1}H NMR analysis. Each ^{1}H NMR was analysed to determine the amount of *N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide **165** remaining in the reaction.

		% Allenamide **165** remaining			
Entry	Base	T= 1 h	T= 3 h	T= 6 h	T= 23 h
1	NaH	87	81	82	60
2	NaO*t*Am	68	62	52	43
3	KOtBu	0	0	0	0
4	KO*t*Bu (THF 1M)	0	0	0	0
5	Cs_2CO_3	100	100	100	100
6	K_2CO_3	100	100	100	100
7	DIPEA	100	100	100	100
8	KOH	100	100	98	97
9	No Base	100	100	100	100

5.4.3 Substrate scope

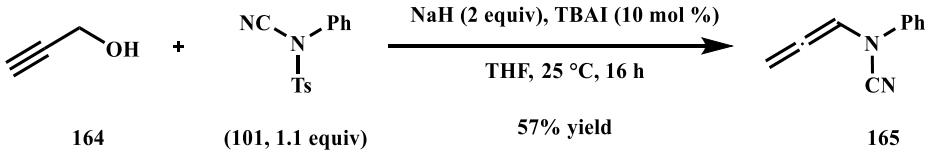
General procedure 11

To an oven dried reaction vial was added propargyl alcohol **164**(1 equiv) followed by THF ([**164**] = 0.2 mol dm^{-3}), the requisite sulfonamide (1.1 equiv) and TBAI (10 mol %). The reaction was stirred and NaH (2 equiv) was added. The reaction was stirred for 16 h at rt. After 16 h the reaction was quenched with sat. aq. NH_4Cl and diluted with H_2O. The product was extracted with EtOAc (× 3). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

General procedure 12

To an oven dried reaction vial was added propargyl alcohol **164** (1 equiv) followed by THF ([**164**] = 0.2 mol dm^{-3}), the requisite sulfonamide (1.1 equiv) and TBAI (10 mol %). The reaction was stirred and NaH (2 equiv) was added. The reaction was stirred for 16 h at rt. After 16 h the reaction was quenched and diluted with H_2O. The product was extracted with EtOAc (× 3). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

***N*-phenyl-*N*-(propa-1,2-dien-1-yl)cyanamide**

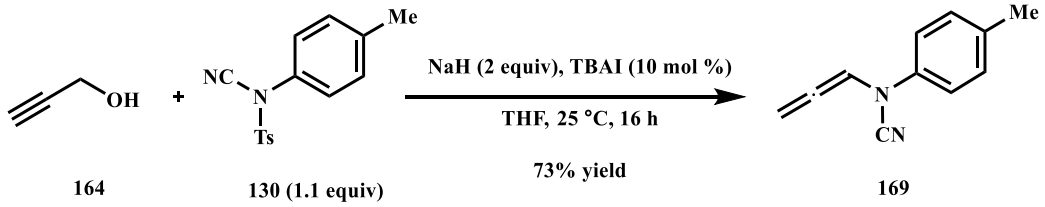


164 **(101, 1.1 equiv)** **57% yield** **165**

Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), NCTS **101** (300 mg, 1.1 mmol, 1.1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **165** (89 mg, 0.57 mmol, 57% yield) as a clear oil. R_f = 0.59 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1}: 2223 (C≡N), 1593, 1494, 1436, 1352, 1238, 838, 734, 673, 486; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.60 (2H, d, *J* 6.1, C*H*$_2$), 6.38 (1H, t, *J* 6.1, C*H*), 7.19 (1H, t, *J* 7.4, Ar*H*), 7.24 (2H, d, *J* 7.8, Ar*H*), 7.39-7.42 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 89.9 (*C*H_2), 99.0 (*C*H), 111.3 (*C*≡N), 117.8 (Ar*C*), 125.2 (Ar*C*), 129.9 (Ar*C*),

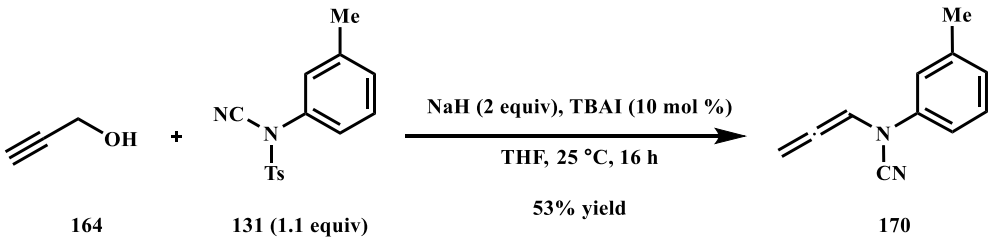
139.0 (Ar*C*), 203.2 (CH_2*C*CH); HRMS (NSI+) calculated for $[C_{10}H_9N_2]^+(M+H)^+$: m/z 157.0760, found 157.0757 (-2.1 ppm).

_N_-(propa-1,2-dien-1-yl)-_N_-(_p_-tolyl)cyanamide



Following general procedure 11, propargyl alcohol **164** (795 µL, 13.7 mmol, 1 equiv), THF (70 mL), N-cyano-4-methyl-N-(p-tolyl)benzenesulfonamide **130** (4.3 g, 15.0 mmol, 1.1 equiv), TBAI (506 mg, 1.37 mmol, 0.1 equiv) and NaH (60%) (1.09 g, 27.3 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **169** (1.69 g, 9.93 mmol, 73% yield) as a white solid; mp 48-50 °C; R_f = 0.76 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2223 (C≡N), 1510, 1438, 1359, 1128, 893, 796, 615, 484; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.34 (3H, s, C*H*$_3$), 5.58 (2H, d, *J* 6.1, C*H*$_2$), 6.35 (1H, t, *J* 6.1, C*H*), 7.11-7.14 (2H, m, Ar*H*), 7.19 (2H, d, *J* 8.1, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.9 (*C*H$_3$), 89.9 (*C*H$_2$), 99.6 (*C*H), 111.6 (*C*≡N), 118.2 (Ar*C*), 130.4 (Ar*C*), 135.2 (Ar*C*), 136.6 (Ar*C*), 202.9 (CH_2*C*CH); HRMS (NSI+) calculated for $[C_{11}H_{11}N_2]^+(M+H)^+$: m/z 171.0917, found 171.0915 (-1.0 ppm).

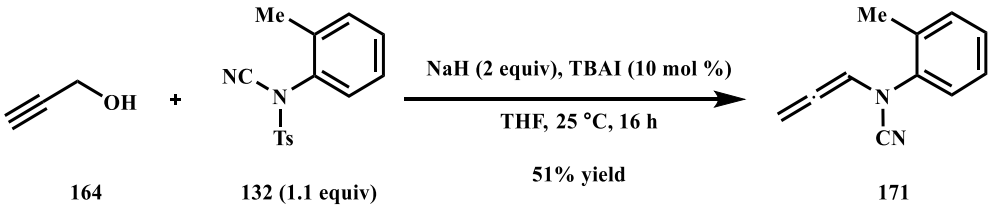
_N_-(propa-1,2-dien-1-yl)-_N_-(_m_-tolyl)cyanamide



Following general procedure 11, propargyl alcohol **165** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-cyano-4-methyl-*N*-(*m*-tolyl)benzenesulfonamide **131** (315 mg, 1.1 mmol, 1.1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **170** (96 mg, 0.53 mmol, 53% yield) as a clear oil. R_f = 0.74 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2223 (C≡N), 1606, 1494, 1357,

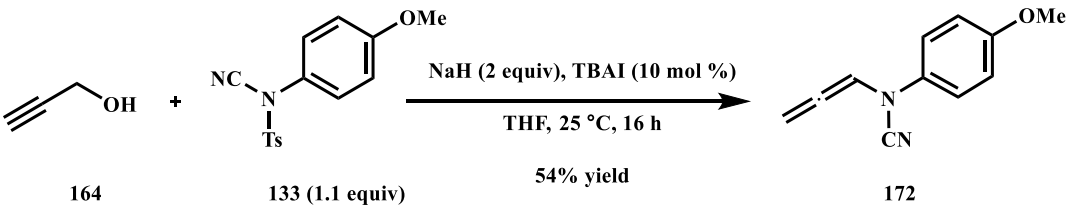
1273, 1184, 887, 686, 497; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.37 (3H, s, C*H*$_3$), 5.59 (2H, d, *J* 6.1, C*H*$_2$), 6.37 (1H, t, *J* 6.1, C*H*), 6.98-7.03 (2H, m, Ar*H*), 7.06 (1H, s, Ar*H*), 7.27-7.29 (1H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.6 (*C*H$_3$), 89.8 (*C*H$_2$), 99.1 (*C*H), 111.4, (*C*≡N), 114.8 (Ar*C*), 118.4 (Ar*C*), 126.0 (Ar*C*), 129.7 (Ar*C*), 139.0 (Ar*C*), 140.2 (Ar*C*), 203.2 (CH$_2$*C*CH); HRMS (NSI+) calculated for $[C_{11}H_{11}N_2]^+(M+H)^+$: m/z 171.0917, found 171.0914 (-1.6 ppm).

_N_-(propa-1,2-dien-1-yl)-_N_-(_o_-tolyl)cyanamide



Following general procedure 11, propargyl alcohol **165** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-cyano-4-methyl-*N*-(*o*-tolyl)benzenesulfonamide **132** (315 mg, 1.1 mmol, 1.1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **171** (87 mg, 0.51 mmol, 51% yield) as a clear oil. R_f = 0.56 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2223 (C≡N), 1492, 1363, 1259, 1230, 1122, 1109, 891, 761, 501; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s C*H*$_3$), 5.48 (2H, d, *J* 6.2, C*H*$_2$), 6.25 (1H, t, *J* 6.2, C*H*), 7.24-7.30 (4H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 17.8 (*C*H$_3$), 90.7 (*C*H$_2$), 103.5 (*C*H), 112.7 (*C*≡N), 125.9 (Ar*C*), 127.4 (Ar*C*), 128.8 (Ar*C*), 131.8 (Ar*C*), 134.7 (Ar*C*), 137.0 (Ar*C*), 200.7 (CH$_2$*C*CH); HRMS (NSI+) calculated for $[C_{11}H_{11}N_2]^+(M+H)^+$: m/z 171.0917, found 171.0915 (-1.0 ppm).

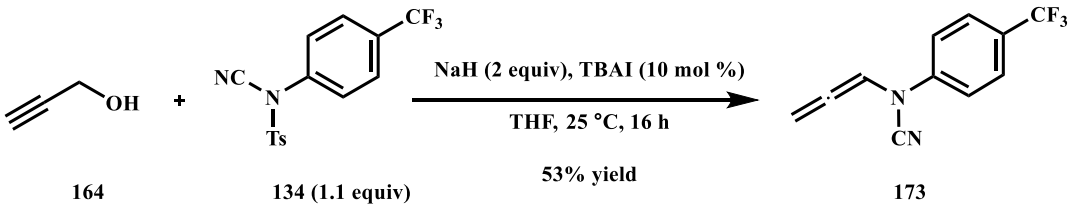
_N_-(4-methoxyphenyl)-_N_-(propa-1,2-dien-1-yl)cyanamide



Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-cyano-*N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide **133** (333 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2

equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **172** (100 mg, 0.54 mmol, 54% yield) as a white solid; mp 60-64 °C; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2223 (C≡N), 1508, 1249, 1184, 1031, 926, 889, 825, 773, 613; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.81 (3H, s, OC*H*$_3$) 5.56 (2H, d, *J* 6.1, C*H*$_2$), 6.31 (1H, t, *J* 6.1, C*H*), 6.90-6.93 (2H, m, Ar*H*), 7.17-7.19 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 55.8 (O*C*H$_3$), 90.1 (C*H*$_2$), 100.6 (C*H)*, 112.1 (*C*≡N), 115.04 (Ar*C)*, 120.76 (Ar*C)*, 132.1 (Ar*C)*, 157.6 (Ar*C)*, 202.5 (CH$_2$*C*CH); HRMS (NSI+) calculated for $[C_{11}H_{11}N_2O_1]^+(M+H)^+$: m/z 187.0866, found 187.0864 (-1.0 ppm).

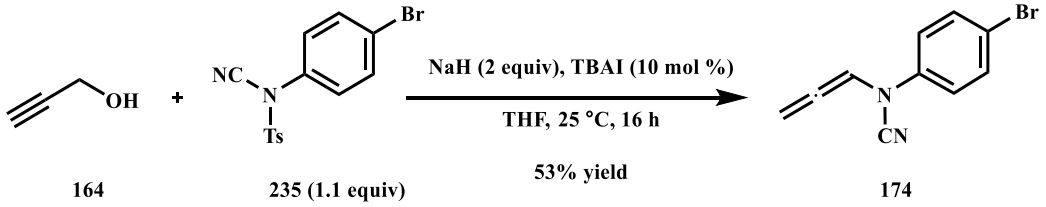
_N_-(propa-1,2-dien-1-yl)-_N_-(4-(trifluoromethyl)phenyl)cyanamide



164 **134 (1.1 equiv)** **173**

Following general procedure 12, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-cyano-4-methyl-*N*-(4-(trifluoromethyl)phenyl)benzenesulfonamide **134** (374 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 5% EtOAc in hexanes, 30 × 120 mm silica) the title compound **173** (122 mg, 0.55 mmol, 53% yield) as a white solid; mp 32-34 °C; R_f = 0.52 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2227 (C≡N), 1612, 1325, 1271, 1166, 1114, 1063, 829; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.65 (2H, d, *J* 6.1, C*H*$_2$), 6.41 (1H, t, *J* 6.1, C*H*), 7.33 (2H, d, *J* 8.7, Ar*H*), 7.67 (2H, d, *J* 8.7, Ar*H*); 19F{1H} NMR (376 MHz, $CDCl_3$) δ_F: -62.2; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 90.1 (*C*H$_2$), 98.0 (*C*H), 110.2 (*C*≡N), 117.1 (Ar*C)*, 123.9 (q, ^{1}*J* 272.2, *C*F$_3$), 127.1 (q, *J* 66.8, Ar*C*), 127.3 (q, *J* 3.8, Ar*C*), 141.9 (Ar*C)*, 203.6 (CH$_2$*C*CH); HRMS (ASAP+) calculated for $[C_{11}H_8N_2F_3]^+(M+H)^+$: m/z 225.0640, found 225.0643 (+1.0 ppm).

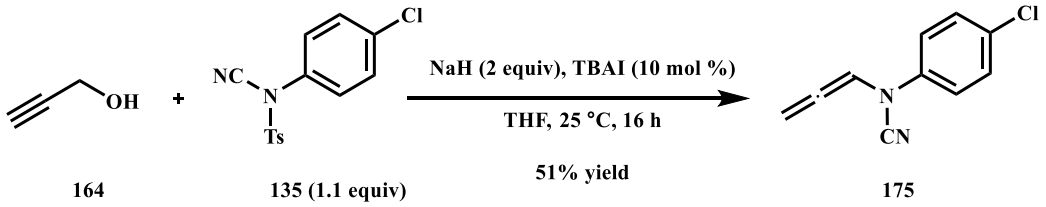
***N*-(4-bromophenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide**



164 235 (1.1 equiv) 174

Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-(4-bromophenyl)-*N*-cyano-4-methylbenzenesulfonamide **235** (386 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **174** (125 mg, 0.53 mmol, 53% yield) as a white solid; mp 42-44 °C; R_f = 0.54 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2220 (C≡N), 1485, 1379, 1265, 1236, 1155, 1078, 950, 813; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.61 (2H, d, *J* 6.1, C*H*$_2$), 6.33 (1H, t, *J* 6.1, C*H*), 7.05 (2H, d, *J* 9.0, Ar*H*), 7.45 (2H, d, *J* 9.0, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 90.2 (*C*H$_2$), 98.7 (*C*H), 110.8 (*C*≡N), 118.1 (Ar*C)*, 119.3 (Ar*C)*, 132.9 (Ar*C)*, 138.1 (Ar*C)*, 203.2 (CH$_2$*C*CH); HRMS (ASAP+) calculated for $[C_{10}H_8N_2Br_1]^+(M+)^+$: m/z 234.9871, found 234.9869 (-0.9 ppm).

***N*-(4-chlorophenyl)-*N*-(propa-1,2-dien-1-yl)cyanamide**

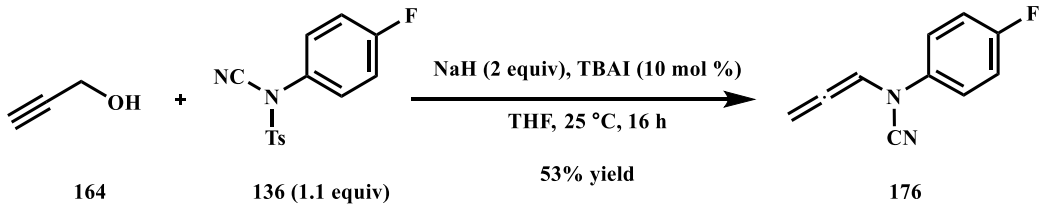


164 135 (1.1 equiv) 175

Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-(4-chlorophenyl)-*N*-cyano-4-methylbenzenesulfonamide **135** (337 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **175** (98 mg, 0.51 mmol, 51% yield) as a white solid; mp 35-37 °C; R_f = 0.50 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2231 (C≡N), 1593, 1490, 1357, 1267, 1095, 962, 887, 810, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.61 (2H, d, *J* 6.1, C*H*$_2$), 6.33 (1H, t, *J* 6.1, C*H*), 7.16-7.19 (2H, m, Ar*H*), 7.35-7.28 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 90.1 (*C*H$_2$), 98.9 (*C*H), 110.9 (*C*≡N), 119.1

(Ar*C*), 130.0 (Ar*C*), 130.7 (Ar*C*), 137.7 (Ar*C*), 203.2 (CH_2*C*CH); HRMS (NSI+) calculated for $[C_{10}H_8N_2Cl_1]^+(M+H)^+$: m/z 191.0371, found 191.0370 (-0.3 ppm)

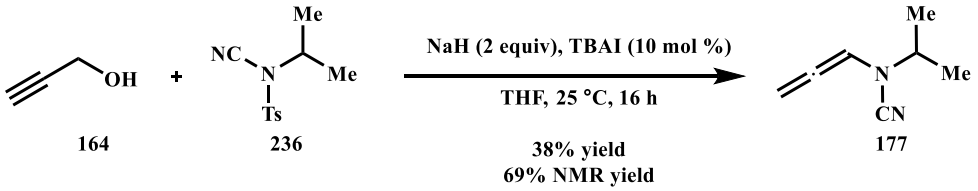
_N_-(4-fluorophenyl)-_N_-(propa-1,2-dien-1-yl)cyanamide



164 136 (1.1 equiv) 176

Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-cyano-*N*-(4-fluorophenyl)-4-methylbenzenesulfonamide **136** (319 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **176** (92 mg, 0.53 mmol, 53% yield) as a white solid; mp 40-44 °C; R_f = 0.50 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2223 (C≡N), 1508, 1442, 1363, 1232, 1103, 889, 775, 619; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.59 (2H, d, *J* 6.1, CH_2), 6.32 (1H, t, *J* 6.1, C*H*), 7.08-7.12 (2H, m, Ar*H*), 7.20-7.23 (2H, m, Ar*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: -116.9; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 90.2 (*C*H_2), 99.7 (*C*H), 111.5 (*C*≡N), 116.8 (d, ^{2}*J* 23.3, Ar*C*) , 120.2 (d, ^{3}*J* 8.3, Ar*C*), 135.1 (d, ^{4}*J* 2.8, Ar*C*), 160.24 (d, ^{1}*J* 245.6, Ar*C*), 202.9; HRMS (NSI+) calculated for $[C_{10}H_8N_2F_1]^+(M+H)^+$: m/z 175.0662, found 175.0666 (-1.7 ppm).

_N_-isopropyl-_N_-(propa-1,2-dien-1-yl)cyanamide

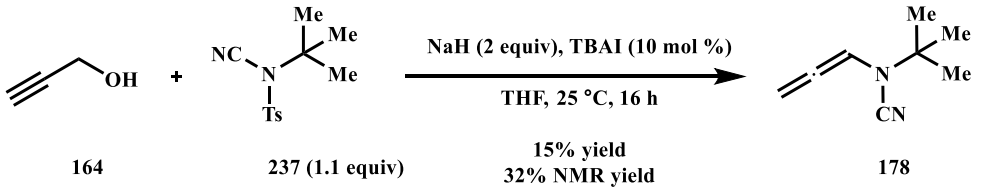


164 236 177

Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-cyano-*N*-isopropyl-4-methylbenzenesulfonamide **236** (262 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **177** (46 mg, 0.38 mmol, 38% yield) as a volatile colourless oil; R_f = 0.42 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2216 (C≡N), 1454, 1398, 1332, 1234, 1178, 1126, 1064, 887, 792, 717, 514; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.31

(6H, d, *J* 6.6, 2×C*H*$_3$), 3.40 (1H, hept, *J* 6.6, (CH$_3$)$_2$C*H*), 5.47 (2H, d, *J* 6.3, C*H*$_2$), 6.11 (1H, t, *J* 6.3, C*H*); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 20.5 (2×*C*H$_3$), 51.5 (CH$_3$*C*H), 89.6 (*C*H$_2$), 101.8 (C*H*), 113.1 (*C*≡N) , 200.4 (CH$_2$*C*CH); HRMS (ASAP+) calculated for $[C_7H_{11}N_2]^+(M+H)^+$: m/z 123.0922, found 123.0912 (-8.1 ppm).

_N_-(tert-butyl)-_N_-(propa-1,2-dien-1-yl)cyanamide

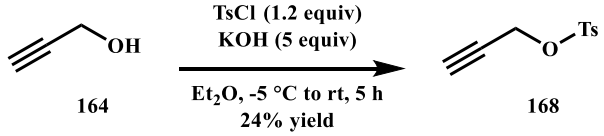


164 237 (1.1 equiv) 178

Following general procedure 11, propargyl alcohol **164** (58 µL, 1 mmol, 1 equiv), THF (5 mL), *N*-(tert-butyl)-*N*-cyano-4-methylbenzenesulfonamide **237** (277 mg, 1.1 mmol, 1 equiv), TBAI (37 mg, 0.1 mmol, 0.1 equiv) and NaH (60%) (80 mg, 2 mmol, 2 equiv) gave after flash column chromatography (eluent = 15-30% Et$_2$O/Petrol 40-60, 30 × 120 mm silica) the title compound **178** (20 mg, 0.15 mmol, 15% yield) as a volatile colourless oil; R_f = 0.30 (eluent = 30% Et$_2$O/Petrol 40-60); ν_{max} / cm^{-1} (film): 2976, 2208 (C≡N), 1444, 1373, 1300, 1197, 1004, 881; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 1.37 (9H, s, 3×C*H*$_3$), 5.43 (2H, d, *J* 6.1, C*H*$_2$), 6.02 (1H, t, *J* 6.1, C*H*); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 27.9 (3×*C*H$_3$), 57.8 ((CH$_3$)$_3$*C*H), 88.3 (*C*H$_2$), 97.4 (*C*H), 113.2 (*C*≡N), 202.6 (CH$_2$*C*CH); HRMS (EI+) calculated for $[C_8H_{12}N_2]^+(M)^+$: m/z 136.1000, found 136.1001 (+0.7 ppm).

5.4.4 Mechanistic studies

prop-2-yn-1-yl 4-methylbenzenesulfonate

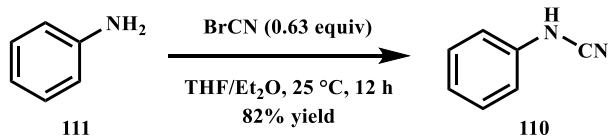


164 168

Following a modified literature procedure,[19] to a 100 mL round bottomed flask was added propargyl alcohol **164** (1.75 mL, 30 mmol, 1 equiv) followed by Et$_2$O (30 mL) and tosyl chloride (6.9 g, 36 mmol, 1.2 equiv). The solution was cooled to -5 °C in an ice/water/NaCl bath before powdered KOH (8.4 g, 150 mmol, 5 equiv) was added portionwise. The reaction was stirred for 1 h at -5 °C before gradually warming to rt over 4 hours. The mixture was poured onto cold water (25 mL) and the layers separated. The

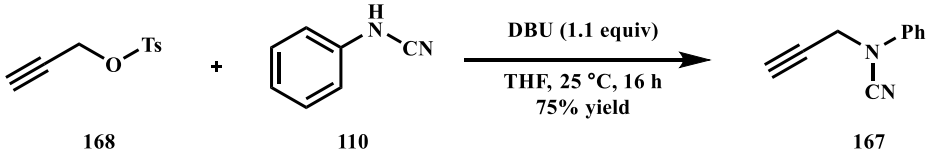
aqueous layer was extracted with Et_2O (× 3) and the combined ether extracts were dried over Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and the resulting oil was purified by column chromatography (140 × 30mm silica, EtOAc 5%/hexanes) to yield the title product **168** as clear brown oil with physical properties and spectroscopic data in accordance with the literature (1.48 g, 7.0 mmol, 24%);[19] R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{max}/cm^{-1} (film): 3284, 1598, 1352, 1170, 1091, 975, 921, 802, 661, 547; ; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.45 (3H, s, C*H*$_3$), 2.47 (1H, t, *J* 2.5, C*H*), 4.69 (2H, d, *J* 2.5, C*H*$_2$), 7.35 (2H, d, *J* 8.0, Ar*H*), 7.81 (2H, d, *J* 8.4, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 21.8 (*C*H$_3$), 57.5 (*C*H$_2$), 75.47 (*C*H), 77.4 (C), 128.3 (Ar*C)*, 130.0 (Ar*C)*, 133.0 (Ar*C)*, 145.4 (Ar*C)*; MS (ASAP+) $[C_{10}H_{11}O_3S]^+$ 211.04.

_N_-phenylcyanamide



To a 100 mL round-bottom flask containing a magnetic follower was charged cyanogen bromide (1.82 g, 17 mmol, 0.63 equiv), THF (18 mL) and diethyl ether (6 mL). The solution was cooled to 0 °C before addition of aniline **111** (2.48 mL, 27 mmol, 1 equiv). The reaction mixture was then stirred for 12 h at 25 °C. The mixture was then concentrated in vacuo to give a crude solid. The solid was dissolved in water, and a precipitate was formed. The mixture was then filtered and washed with hexanes to give the title product **110** (1.64 g, 14 mmol, 82% yield) as a brown solid with physical properties and spectroscopic data in accordance with the literature;[12] mp 37-38 °C (Lit. 44-46 °C)[12]; Rf = 0.3 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3387, 3150, 3098, 2986, 2909, 2224 (C≡N), 1599, 1497, 1435, 1252, 735, 681, 484; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 5.75 (1H, s, N*H*), 7.00-7.03 (2H, m, Ar*H*), 7.09-7.13 (1H, m, Ar*H*), 7.33-7.37 (2H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 111.6 (*C*≡N), 115.5 (Ar*C)*, 123.7 (Ar*C)*, 129.9 (Ar*C)*, 137.4 (Ar*C)*.

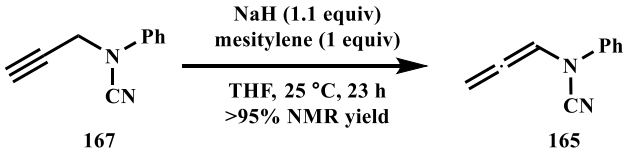
_N_-phenyl-_N_-(prop-2-yn-1-yl)cyanamide



168 110 167

To a reaction vial was added prop-2-yn-1-yl 4-methylbenzenesulfonate **168** (547 mg, 2.73 mmol, 1 equiv) followed by *N*-phenylcyanamide **110** (322 mg, 2.37 mmol, 1 equiv) and THF (10 mL). The solution was stirred before DBU (512 µL, 3.0 mmol, 1.1 equiv) was added. The reaction was stirred for 16 h at rt. The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (× 3). The combined organic phase was then was with brine and dried over $MgSO_4$ filtered. The solution was concentrated *in vacuo* before purification by silica gel column chromatography (120 × 30 mm, EtOAc 10%/hexanes) to yield the title compound **167** as off white crystals (320.3 mg, 2.05 mmol, 75%); mp 33-35 °C; R_f = 0.36 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3284, 2960, 2221 (C≡N),1598, 1498, 1373, 1330, 1188, 1043, 923, 740, 680, 486; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.50 (1H, t, *J* 2.5, C*H*), 4.38 (2H, d, *J* 2.5, CH_2), 7.16 (1H, t, *J* 7.4, Ar*H*), 7.19 (2H, d, *J* 8.0, Ar*H*), 7.41 (2H, dd, *J* 8.7, 7.5, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 40.2 (*C*H_2), 75.8, 75.9, 112.9 (*C*≡N), 116.2 (Ar*C*), 124.4 (Ar*C*), 129.9 (Ar*C*), 139.1 (Ar*C*); HRMS (EI$^+$) calculated for $[C_{10}H_8N_2]^+$: m/z 156.0687 found 156.0681 (-3.8 ppm).

_N_-phenyl-_N_-(propa-1,2-dien-1-yl)cyanamide

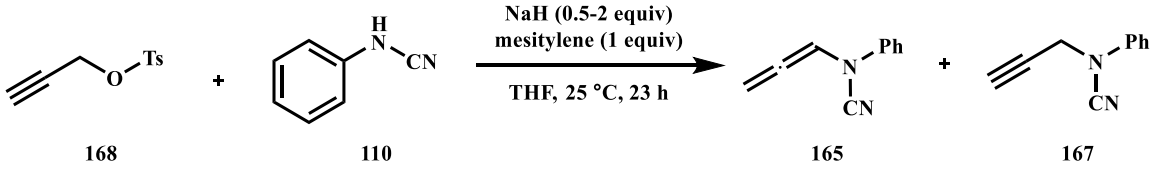


167 165

To a reaction vial was added *N*-phenyl-*N*-(prop-2-yn-1-yl)cyanamide **167** (31 mg, 0.2, 1 equiv) followed by THF (1 mL) and mesitylene (28 µL, 0.2 mmol, 1 equiv). The solution was stirred before NaH (9 mg, 0.22 mmol, 1.1 equiv) was added. The reaction was stirred for 23 h at rt before an aliquot was taken and added to an NMR tube with $CDCl_3$. The reaction was analysed by ^{1}H NMR to determine the conversion to the allene with

mesitylene as internal standard. The title compound **165** was observed in >95% NMR yield with all spectroscopic data in accordance with those previously obtained.

_N_-phenyl-_N_-(propa-1,2-dien-1-yl)cyanamide



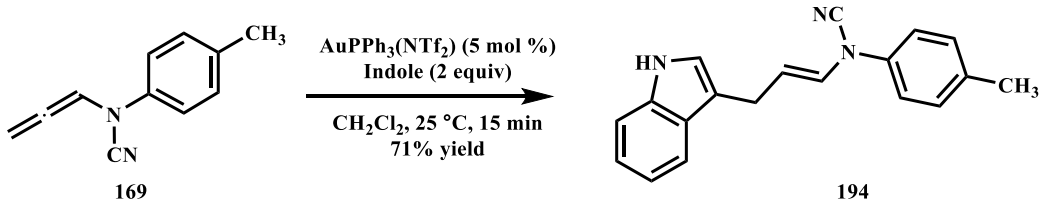
168 110 165 167

To a reaction vial was added prop-2-yn-1-yl 4-methylbenzenesulfonate **168** (53 mg, 0.25 mmol, 1 equiv), *N*-phenylcyanamide **110** (29 mg, 0.25 mmol, 1 equiv), mesitylene and THF (1 mL). The requisite amount of NaH (0.5-2 equiv) was then added and the reaction was stirred for 23 h at rt. Aliquots were then taken and added to an NMR tube with $CDCl_3$. The reactions were analysed by ^1H NMR with mesitylene as internal standard to determine the composition of the reaction mixture of with regards to the formation of 165.

NaH used (equiv)	0.5	1	1.5	2
Propargyl tosylate **168** remaining (%)	51	27	25	<5
Conversion to propargylamide **167** (%)	49	30	19	<5
Conversion to *N*-allenyl cyanamide **165** (%)	0	31	46	90

5.4.5 Derivatisation of *N*-cyano allenamides

(*E*)-*N*-(3-(indolin-3-yl)prop-1-en-1-yl)-*N*-(*p*-tolyl)cyanamide

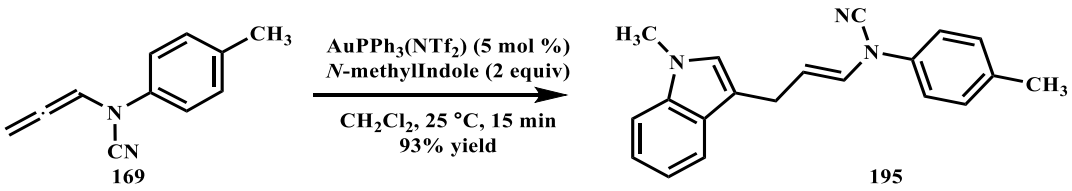


169 194

Following a modified literature procedure,[20] to a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (54 mg, 0.32 mmol, 1 equiv), CH_2Cl_2 (1 mL) and indole (75 mg, 0.64 mmol, 2 equiv). The solution was stirred and $AuPPh_3(NTf_2)$ (25 mg, 0.016 mmol, 0.05 equiv) was added. The reaction was stirred at rt and monitored by TLC. After completion (15 min) the reaction mixture was filtered through celite and the crude mixture purified by silica gel column chromatography (eluent = 5-15% EtOAc in hexanes, 25 × 120 mm silica) the title compound **194** (65 mg, 0.23 mmol, 71% yield) as

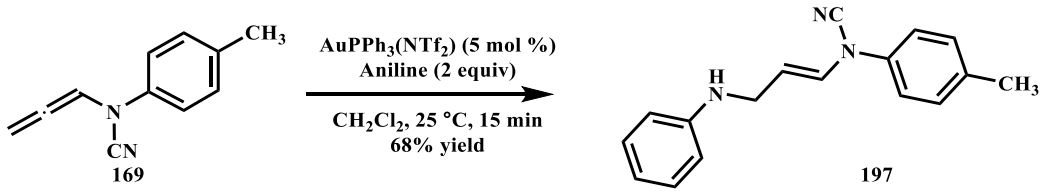
a white solid; mp 74-76 °C; R_f = 0.26 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2357, 2330, 2231 (C≡N), 1662, 1514, 1452, 1334, 1230, 1087, 810, 740, 497; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.32 (3H, s, C*H*$_3$), 3.61-3.63 (2H, m, C*H*$_2$), 5.99 (1H, dt, *J* 13.4, 6.5, C*H*), 6.15 (1H, dt, *J* 13.6, 1.5, C*H*), 7.03-7.05 (3H, m, Ar*H*), 7.13-7.16 (3H, m, Ar*H*), 7.20,7.23 (1H, m, Ar*H*), 7.38 (1H, d, *J* 8.1, Ar*H*), 7.61 (1H¸ d, *J* 7.5, Ar*H*), 8.01 (1H, s, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.9 (*C*H$_3$), 25.4 (*C*H$_2$), 111.4, 111.7, 113.8, 115.4, 117.7, 118.3, 119.0, 119.7, 122.0, 122.4, 126.1, 127.2, 130.4, 135.2, 136.8; HRMS (NSI+) calculated for $[C_{19}H_{18}N_3]^+(M)^+$: m/z 288.1495, found 288.1498 (+1.0 ppm).

(*E*)-*N*-(3-(1-methylindolin-3-yl)prop-1-en-1-yl)-*N*-(*p*-tolyl)cyanamide



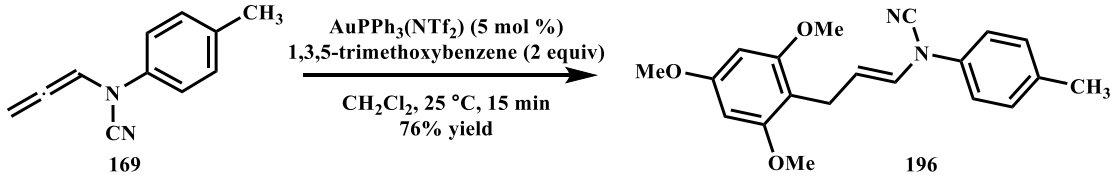
Following a modified literature procedure,[20] to a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(p-tolyl)cyanamide **169** (54 mg, 0.32 mmol, 1 equiv), CH_2Cl_2 (1 mL) and *N*-methylindole (84 mg, 0.64 mmol, 2 equiv). The solution was stirred and $AuPPh_3(NTf_2)$ (25 mg, 0.016 mmol, 0.05 equiv) was added. The reaction was stirred at rt and monitored by TLC. After completion (15 min) the reaction mixture was filtered through celite and the crude mixture purified by silica gel column chromatography (eluent = 5-15% EtOAc in hexanes, 25 × 120 mm silica) the title compound **195** (90 mg, 0.30 mmol, 93% yield) as a white solid; mp 91-94 °C; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2214 (C≡N), 1662, 1610, 1512, 1469, 1377, 1327, 1232, 1006, 935, 813, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.31 (3H, s, C*H*$_3$), 3.58-3.60 (2H, m, C*H*$_2$) 3.76 (3H, s, NC*H*$_3$), 5.93-6.00 (1H, m, Ar*H*), 6.14 (1H, dt *J* 13.6, 1.5, C*H*), 6.88 (1H, s, CH_3NC*H*), 7.02-7.04 (2H, m, Ar*H*), 7.12-7.16 (3H, m, Ar*H*), 7.22 (1H, dd, *J* 8.2, 1.2, Ar*H*), 7.30 (1H, d *J* 8.2, Ar*H*), 7.56-7.59 (1H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 20.9 (*C*H_3), 25.3 (*C*H_2), 32.8 (N*C*H_3), 110.9, 111.3, 112.2, 117.4, 117.9, 118.3, 119.1, 119.1, 121.9, 125.9, 125.9, 126.8, 130.4, 135.2, 136.8; HRMS (NSI+) calculated for $[C_{20}H_{20}N_3]^+(M)^+$: m/z 302.1656, found 302.1652 (+1.4 ppm).

(*E*)-*N*-(3-(phenylamino)prop-1-en-1-yl)-*N*-(*p*-tolyl)cyanamide



Following a modified literature procedure,[21] to a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (54 mg, 0.32 mmol, 1 equiv), CH_2Cl_2 (1 mL) and aniline (31 mg, 0.34 mmol, 1.05 equiv). The solution was stirred and $AuPPh_3(NTf_2)$ (25 mg, 0.016 mmol, 0.05 equiv) was added. The reaction was stirred at rt and monitored by TLC. After completion the reaction mixture was filtered through celite and the crude mixture purified by silica gel column chromatography (eluent = 10% EtOAc in hexanes, 25 × 120 mm silica) the title compound **197** (57 mg, 0.22 mmol, 68% yield) as a white solid; mp 95-97 °C; R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2218 (C≡N) 1602, 1508, 1236, 931, 810, 752, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.33 (3H, s, C*H*$_3$), 3.82 (1H, br s, N*H*), 3.89-3.90 (2H, m, NHC*H*$_2$), 5.78 (1H, dt, *J* 13.6, 5.7, CH_2CHCH), 6.35 (1H, d, *J* 13.7, NCNC*H*), 6.65 (2H, d, *J* 8.4), 6.75 (1H, t, *J* 7.2), 7.04 (2H, d, *J* 8.4), 7.17-7.22 (4H, m); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.9 (*C*H$_3$), 43.3 (NH*C*H$_2$), 111.2, 113.2, 114.1, 118.2, 118.8, 127.8, 129.5, 130.5, 135.8, 136.5, 147.7; HRMS (NSI+) calculated for $[C_{17}H_{17}N_3]^+(M+H)^+$: m/z 264.1495, found 264.1399 (+1.4 ppm).

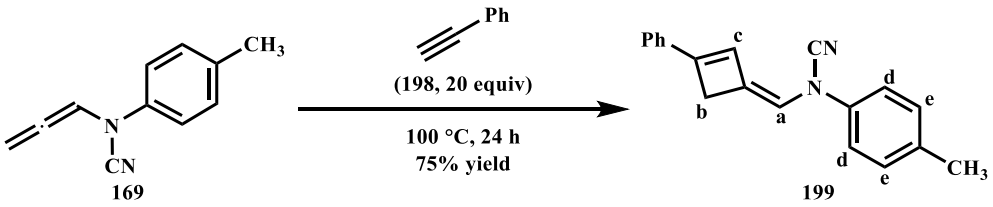
(*E*)-*N*-(*p*-tolyl)-*N*-(3-(2,4,6-trimethoxyphenyl)prop-1-en-1-yl)cyanamide



Following a modified literature procedure,[20] to a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(p-tolyl)cyanamide **169** (54 mg, 0.32 mmol, 1 equiv), CH_2Cl_2 (1 mL) and 1,3,5-trimethoxybenzene (108 mg, 0.64 mmol, 2 equiv). The solution was stirred and $AuPPh_3(NTf_2)$ (25 mg, 0.016 mmol, 0.05 equiv) was added. The reaction was stirred at rt and monitored by TLC. After completion (1 h) the reaction mixture was filtered through celite and the crude mixture purified by silica gel column chromatography (eluent = 10% EtOAc in hexanes, 25 × 120 mm silica) the title compound **196** (82.3 mg, 0.24 mmol,

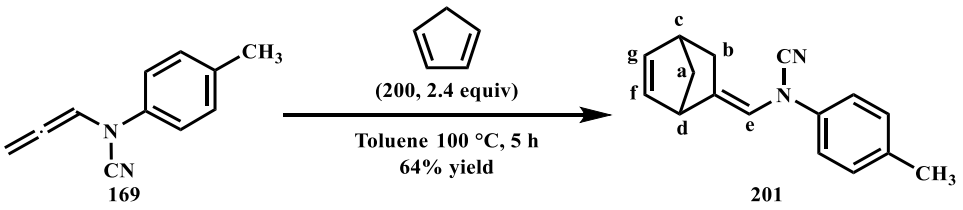
76% yield) as a white solid; mp 77-79 °C; R_f = 0.36 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2222 (C≡N), 1608, 1593, 1510, 1454, 1228, 1207, 1188, 1147, 1058, 950, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.32 (3H, s, C*H*$_3$), 3.37 (2H, dd, *J* 6.8, 1.3, NHC*H*$_2$), 3.81 (9H, s, 3×OC*H*$_3$), 5.81 (1H, dt, *J* 13.6, 6.8, CH_2C*H*CH), 6.04 (1H, dt, *J* 13.5, 1.4, NCNC*H*), 6.14 (2H, s, Ar*H*), 7.03 (2H, d, *J* 8.6, Ar*H*), 7.16 (2H, d, *J* 8.7, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 20.8 (*C*H$_3$), 22.6 (O*C*H$_3$), 55.5, 55.9, 90.7, 108.2, 111.8, 118.0, 118.5, 124.9, 130.3, 134.8, 137.1, 158.8, 160.0; HRMS (NSI+) calculated for $[C_{20}H_{23}N_2O_3]^+$(M+H)$^+$: m/z 339.1703, found 339.1708 (+1.4 ppm).

(*Z*)-*N*-((3-phenylcyclobut-2-en-1-ylidene)methyl)-*N*-(*p*-tolyl)cyanamide



Following a modified literature procedure,[22] to a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (50 mg, 0.29 mmol, 1 equiv) and phenylacetylene **198** (640 µL, 5.8 mmol, 20 equiv) and the reaction stirred at 100 °C for 24 h. After 24 h the reaction was concentrated *in vacuo* and purified by silica gel column chromatography (eluent = 10% EtOAc in hexanes, 25 × 120 mm silica) the title compound **199** (59 mg, 0.22 mmol, 75% yield) as a white solid; mp 110-112 °C; R_f = 0.58 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2218 (C≡N), 1685, 1514, 1274, 1247, 802, 752, 686, 497; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.35 (3H, s, C*H*$_3$), 3.33 (2H, s, CH_2^b), 5.64 (1H, s, CH^a), 6.94 (1H, s, CH^c), 7.13-7.15 (2H, m, Ar*H*^{e}), 7.20 (2H, d, *J* 7.2, Ar*H*^{d}), 7.33 (1H, d, *J* 7.2, Ar*H*), 7.36-7.40 (2H, m, Ar*H*), 7.46 (2H, d, *J* 7.0, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.8 (*C*H$_3$), 34.8 (*C*H$_2^b$), 109.1, 112.7, 117.3, 124.8, 125.9, 128.7, 129.2, 129.3, 130.3, 133.4, 134.6, 137.4, 151.1; HRMS (ASAP+) calculated for $[C_{19}H_{17}N_2]^+$(M+H)$^+$: m/z 273.1386, found 273.1388 (+0.6 ppm).

(*E*)-*N*-(bicyclo[2.2.1]hept-5-en-2-ylidenemethyl)-*N*-(*p*-tolyl)cyanamide



Following a modified literature procedure,[23] to a reaction vial was added *N*-(propa-1,2-dien-1-yl)-*N*-(*p*-tolyl)cyanamide **169** (50 mg, 0.29 mmol, 1 equiv) and freshly distilled cyclopentadiene **200** (59 µL, 0.70 mmol, 2.4 equiv) and toluene (0.5 mL) the reaction stirred at 100 °C for 5 h. After 5 h the reaction was concentrated *in vacuo* and purified by silica gel column chromatography (eluent = 10% EtOAc in hexanes, 30 × 120 mm silica) the title compound **201** (45 mg, 0.19 mmol, 64% yield) as a white solid; mp 71-73 °C; R_f = 0.65 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 2980, 2360, 2212 (C≡N), 1510, 1276, 1224, 810, 715, 497; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.49 (1H, d *J* 8.4, C*H*^{a}), 1.69 (1H, ddt, *J* 8.4, 3.2, 1.6, C*H*^{a}), 1.97-2.01 (1H, m, C*H*^{b}), 2.32 (3H, s, C*H*$_3$), 2.40-2.42 (1H, m, C*H*^{b}), 3.10 (1H, s, C*H*^{c}), 3.38 (1H, d, *J* 1.4, C*H*^{c}), 6.02 (1H, t, *J* 1.8, C*H*^{e}), 6.08 (1H, dd, *J* 5.4, 3.1, CH^f), 6.25 (1H, dd, *J* 5.5, 3.0, C*H*^{g}), 7.00-7.02 (2H, m, Ar*H*), 7.15 (2H, d, *J* 8.2, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.8 (*C*H$_3$), 31.7, 42.0, 49.0, 50.9, 111.9, 114.0, 116.2, 130.2, 133.4, 133.9, 137.5, 138.3, 142.8; HRMS (NSI+) calculated for $[C_{16}H_{17}N_2]^+$(M+H)$^+$: m/z 237.1386, found 273.1389 (+1.2 ppm).

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