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Investigating the Different Mechanisms Involved in a Silane-Alkoxide System

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

Signed: Date:

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List of Publications

1) **Electron-Transfer and Hydride-Transfer Pathways in the Stoltz-Grubbs Reducing System (KO^tBu/Et_3SiH)**. A. J. Smith, A. Young, S. Rohrbach, E. F. O'Connor, M. Allison, H.-S. Wang, D. L. Poole, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.*, 2017, **56**, 13747-13751.
2) **Concerted Nucleophilic Aromatic Substitution Reactions**. S. Rohrbach, A. J. Smith, J. H. Pang, D. L. Poole, T. Tuttle, S. Chiba, J. A. Murphy, *Angew. Chem. Int. Ed.*, 2019, **58**, 16368-16388.
3) **The Role of Organic Electron Donors in the Initiation of BHAS Base-Induced Coupling Reactions Between Haloarenes and Arenes**. A. J. Smith, D. L. Poole, J. A. Murphy, *Science China Chem*., 2019, **62**, 1425–1438.
4) **A New Rearrangement of *N*-Arylindoles Triggered by the Stoltz-Grubbs Reagent Et_3SiH/KO^tBu**. A. J. Smith, D. D. Dimitrova, J. N. Arokianathar, K. Kolodziejczak, A. Young, M. Allison, D. L. Poole, S. G. Leach, J. A. Parkinson, T. Tuttle, J. A. Murphy, *Manuscript submitted.*
5) **Concerted Nucleophilic Aromatic Substitution (cS_NAr) Reactions for the Conversion of Benzylnitriles to Indolines and Indoles: Hydride Transfer and Electron Transfer from Et_3SiH/KO^tBu (Working Title)**. A. J. Smith, J. N. Arokianathar, D. D. Dimitrova, S. Rohrbach, K. F. Clark, M. Allison, D. L. Poole, T. Tuttle, J. A. Murphy, *manuscript in preparation*.

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Abbreviations

°C – degrees Celsius

ΔG^* – Gibbs free energy change

ΔG_{rel} – relative Gibbs free energy change

µm – micrometre

Ac – acetyl

acac - acetylacetonate

AIBN – azobisisobutyronitrile

app – apparent

aq – aqueous

Ar – aryl

ATR – attenuated total reflectance

BHAS – base-promoted homolytic aromatic substitution

Bn – benzyl

CI – chemical ionisation

cS_NAr – concerted nucleophilic aromatic substitution

cm – centimetres

CPCM - Conductor-like polarisable continuum model

Da – Daltons

DCM – dichloromethane

DEAD – diethyl azodicarboxylate

DESI-MS – desorption ionisation mass spectrometry

DCE – 1,2-dichloroethane

DFT – density functional theory

DMAP – 4-dimethylaminopyridine

DME – dimethoxyethyane

DMF – *N*,*N*-dimethylformamide

DMP – Dess-Martin periodinane

DMPU – *N,N'*-dimethylpropyleneurea

DMSO – dimethyl sulfoxide

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

EI – electron ionisation

EPR – electron paramagnetic resonance

equiv. – equivalents

ESI-MS – electrospray ionisation mass spectrometry

Et – ethyl

ET – electron transfer

FTIR – Fourier transform infra-red

g – grams

GC-MS – gas chromatography mass spectrometry

h – hours

HAT – hydrogen atom transfer

HRMS – high resolution mass spectrometry

^{i}Pr – isopropyl

IR – infrared

J – coupling constant

kcal – kilocalories

KHMDS – potassium hexamethyldisilazide

KIE – kinetic isotope effect

kJ – kilojoules

LB – Lewis base

LDA – lithium diisopropylamine

LG – leaving group

LiHMDS – lithium hexamethyldisilazide

LUMO – lowest unoccupied molecular orbital

M – molarity

m – metres

m – meta

mbar – millibar

*m*CPBA – *meta*-chloroperoxybenzoic acid

Me – methyl

mes – mesityl

mg – milligrams

MHz – megahertz

min – minutes

mL – millilitres

mm – millimetres

mmol – millimoles

mol – moles

MOM – methoxymethyl

Mp – melting point

m/z – mass to charge ratio

ND – not determined

nm – nanometres

NMR – nuclear magnetic resonance

^{n}Bu – normal butyl

^{n}Hex – normal hexyl

^{n}Oct – normal octyl

^{n}Pr – normal propyl

o – ortho

o/n – overnight

p – para

PCC – pyridinium chlorochromate

Ph – phenyl

Phen – phenanthroline

ppm – parts per million

psi – pound-force per square inch

PT – proton transfer

Py – pyridine

rt – room temperature

s – seconds

SCE – saturated calomel electrode

SEM – [2-(trimethylsilyl)ethoxy]methyl acetal

SET – single electron transfer

S_H2 – bimolecular homolytic substitution

S_N2 – bimolecular nucleophilic substitution

S_NAr – nucleophilic aromatic substitution

SOMO – singly occupied molecular orbital

SR_N1 – radical nucleophilic aromatic substitution

T – temperature

TBAB – tetrabutylammonium bromide

TBAF – tetrabutylammonium fluoride

TBAT – tetrabutylammonium difluorotriphenylsilicate

^{t}Bu – *tert*-butyl

TEMPO – (2,2,6,6-tetramethylpiperidin-1-yl)oxyl free radical

Tf – triflate

TFA – trifluoroacetic acid

TFAA – trifluoroacetic anhydride

THF – tetrahydrofuran

TLC – thin layer chromatography

TMS – trimethylsilyl

Ts – tosyl

TTMSS – tris(trimethylsilyl)silane

UV – ultraviolet

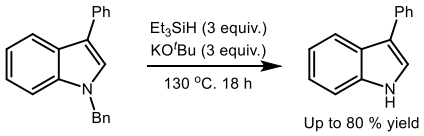
V – Voltz

w/v – weight by volume

Abstract

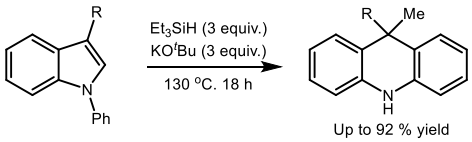
Recent publications by Grubbs and Stoltz have focussed on the combination of triethylsilane with potassium *tert*-butoxide to afford a system which is capable of carrying out a number of synthetically useful transformations. This includes i) the reductive cleavage of C-O bonds in ethers, ii) the reductive cleavage of C-S bonds in thioethers, and iii) the regioselective silylation of arenes and heteroarenes. A number of mechanistic studies have been carried out, but so far no conclusive mechanism is known for these transformations.

Recent work in the Murphy group has focussed on the combination of small molecules with potassium *tert*-butoxide to form *in situ* electron donors. This thesis will focus on mechanistic studies on the combination of triethylsilane with potassium *tert*-butoxide, which is capable of carrying out the reductive debenzylation of *N*-benzylindoles (Scheme 1). Experimental and computational studies show that it is likely that this transformation proceeds via single electron transfer.



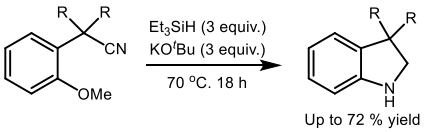
Scheme 1 - Debenzylation of N-Benzylindoles Mediated by Et_3SiH/KO^tBu

N-arylindoles were shown to undergo ring-opening and subsequent ring-closure to afford 9,10-dihydroacridines (Scheme 2). Mechanistic studies suggest that this transformation may either proceed via single electron transfer or via hydrogen atom transfer.



Scheme 2 - Conversion of N-Arylindoles to 9,10-Dihydroacridines Mediated by Et_3SiH/KO^tBu

Finally, the reduction and subsequent cyclisation of nitriles was shown to proceed via hydride transfer from the Et_3SiH/KO^tBu system, with the displacement of the methoxide group occurring via a concerted nucleophilic aromatic substitution (*i.e.* without the formation of a Meisenheimer intermediate, Scheme 3).



Scheme 3 - Concerted Nucleophilic Aromatic Substitution to Afford Indolines

1: Introduction

Recent research by Grubbs, Stoltz *et al*. has focussed on the combination of Et_3SiH and KO^tBu to produce a highly reactive system that is capable of carrying out a number of synthetically useful transformations.[1–7] This thesis will focus on studies into the possible reaction intermediates in the Et_3SiH/KO^tBu system, the different mechanisms which are possible from these reaction intermediates, and novel transformations which can be mediated by such a system.

Recent interest in the Murphy group has focussed on electron transfer chemistry from organic electron donors. This has developed in recent years from electron-rich alkenes which are capable of donating electrons to aryl halides,[8] to simple small molecules such as diols or diamines which react with a strong base *in situ* (usually KO^tBu) to form electron donors.[9] Section 1.1 will discuss the combination of small molecules with KO^tBu to form *in situ* electron donors, and Section 1.2 will discuss the applications of the Et_3SiH/KO^tBu system in the literature, and the current mechanistic proposals.

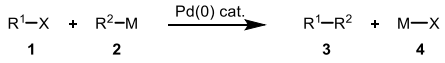
1.1: Transition Metal-free Biaryl Couplings Mediated by Electron Transfer

In recent years, there has been an explosion of interest in the transition metal-free coupling of haloarenes with arenes. This is an attractive procedure, as it avoids the use of expensive and toxic catalytic palladium complexes, as used in conventional cross-coupling reactions. However, the disadvantage of the transition metal-free processes is that the regiochemistry can only be controlled at the haloarene coupling partner, and not at the arene. Further work in this area is necessary to allow for complete control of the regiochemistry.

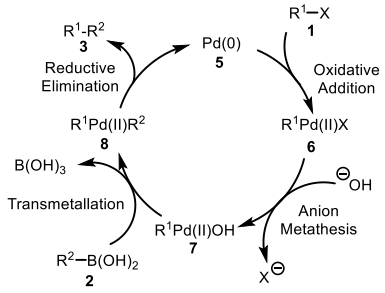
The coupling partners generally involved in palladium-catalysed cross-coupling reactions involve an aryl halide or triflate with organoborons (Suzuki),[10] organozincs (Negishi),[11] organomagnesiums (Kumada),[12] organotins (Stille),[13] organocoppers from deprotonated alkynes (Sonogashira),[14] or organosilicons (Hiyama).[15] Some of the advantages of these reactions include the toleration of a broad range of functional groups, the mild reaction conditions, high product yields, and the high regio- and stereoselectivity seen.[16]

The most common palladium-mediated reaction in the literature is the Suzuki reaction.[17] The general reaction scheme is shown in Scheme 4. Here, the aryl halide or triflate **1** reacts with organometallic compound **2** under palladium catalysis to yield coupled product **3**, with salt **4** as a by-product. The general mechanism involved in the Suzuki reaction involves oxidative addition of aryl halide **1** to Pd (0) complex **5** to form Pd (II) species **6** (Scheme 5). Anion metathesis affords species **7**, before transmetallation with boronic acid **2** affords **8** and boric acid. Reductive

elimination from **8** affords coupled product **3** and regenerates the Pd (0) species **5** to continue the catalytic cycle.



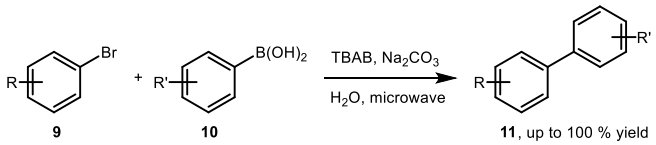
Scheme 4 - Overall Reaction Scheme of Palladium-Catalysed Cross-Coupling Reactions



Scheme 5 - General Catalytic Cycle of the Suzuki Reaction

Some drawbacks of palladium-catalysed cross-coupling reactions are the high cost of palladium complexes required for the catalysis and the toxicity of the palladium complexes. This has led chemists to explore new methods of carrying out these reactions, such as using cheaper, less toxic metals for catalysis, or avoiding the use of transition metals altogether.

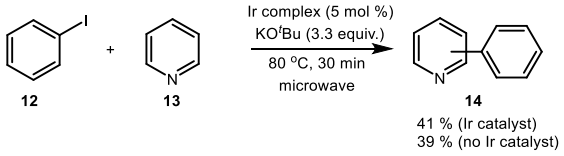
Transition metal-free coupling was first reported by Leadbeater in 2003.[18,19] It was shown that the coupling of bromoarenes **9** with aryl boronic acids **10** could proceed to afford coupled products **11** in the absence of a transition metal catalyst, and with only sodium carbonate as base and tetrabutylammonium bromide (TBAB) as a phase transfer agent in water (Scheme 6). As with a palladium-catalysed Suzuki reaction, these transition metal-free coupling reactions were found to proceed with complete control of regioselectivity. However, Leadbeater later published a revision to this work and now claims that their reactions are not truly transition metal-free, and are in fact catalysed by parts per billion quantities of palladium contaminants found in their sodium carbonate.[20]



Scheme 6 - Transition Metal-Free Suzuki Reactions Reported by Leadbeater

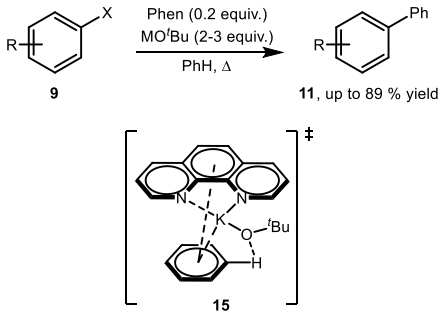
Transition metal-free coupling involving KO^{t}Bu was first reported by Itami in 2008 (Scheme 7).[21] During the exploration of iridium catalysts in the coupling of iodobenzene **12** with pyridine **13** to produce coupled product **14**, it was found that the best performing iridium catalyst gave a comparable result to the reaction with no iridium catalyst present (41% and 39% respectively).

The use of common radical scavengers such as TEMPO resulted in a dramatic decrease in yield (to < 1%), leading to the proposal of a radical intermediate in these reactions. The mechanism suggested by Itami was that the reaction proceeded either via homolytic aromatic substitution, or via an $S_{RN}1$ type reaction, although it is not clear how an $S_{RN}1$ process would afford **14**.



Scheme 7 - Original Report by Itami

In 2010, the groups of Shi, and Shirakawa and Hayashi independently reported on the use of substoichiometric amounts of phenanthroline-based additives, which along with alkali metal *tert*-butoxides, can promote the transition metal-free coupling of a variety of iodo- and bromoarenes with different aromatic coupling partners (Scheme 8).[22-23] The transition state **15**, proposed by Shi, involves the complexation of the 1,10-phenanthroline, potassium cation and the aromatic substrate via π-π stacking and cation-π interaction, which promotes the reactivity of the unactivated benzene. However, the iodoarene is not present in this transition state, and no mention of the involvement of the iodoarene in the mechanism was made.

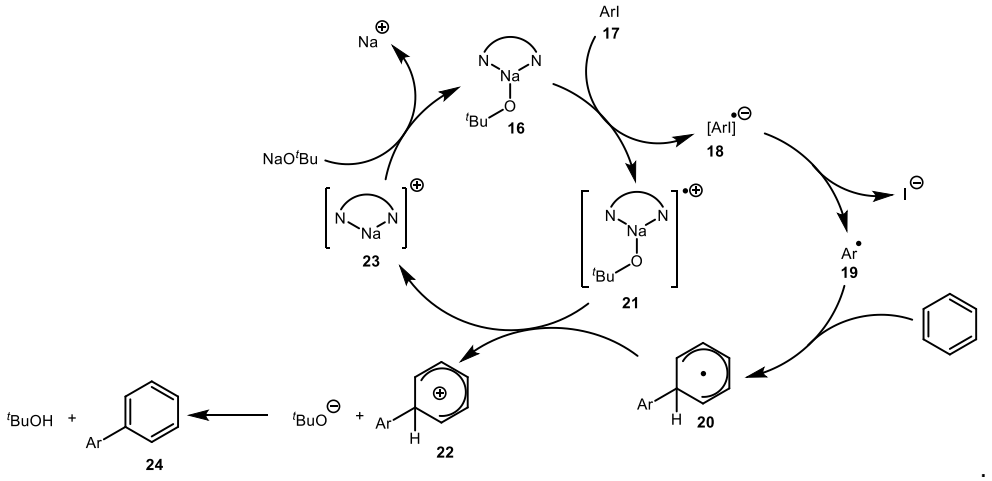


Scheme 8 –Transition State Suggested by Shi

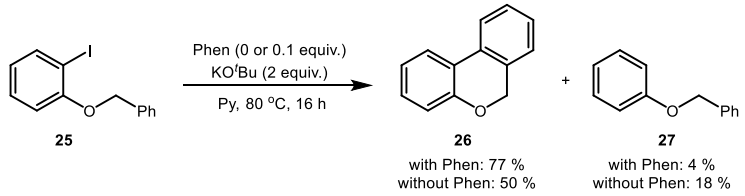
It was suggested by Shirakawa and Hayashi that the complex of NaO^{t}Bu with phenanthroline (**16**, Scheme 9) is capable of donating a single electron to the aryl iodide **17** to produce a radical anion **18**. This then dissociates into an aryl radical **19** and an iodide anion. Aryl radical **19** attacks benzene to produce a cyclohexadienyl radical **20**, which is subsequently oxidised by radical cation **21** to produce a *tert*-butoxide anion, cation **22**, and complex **23**. Deprotonation of **22** by *tert*-butoxide affords coupled product **24** and *tert*-butanol. The sodium-phenanthroline complex **23** can then react with more sodium *tert*-butoxide to regenerate **16** and continue the cycle.

Studies by Charette also showed an intramolecular arylation of **25** with phenanthroline and KO^{t}Bu in pyridine as solvent, affording **26** and **27** (Scheme 10).[24] This was also shown to afford **26** and **27** without the addition of phenanthroline. When KO^{t}Bu was replaced with NaO^{t}Bu, no reaction occurred and only starting material was recovered. The authors proposed that this reaction

proceeds via electron transfer to the aryl iodide **25** to afford an aryl radical which undergoes cyclisation, but they do not comment on the exact mechanism for the initial electron transfer.

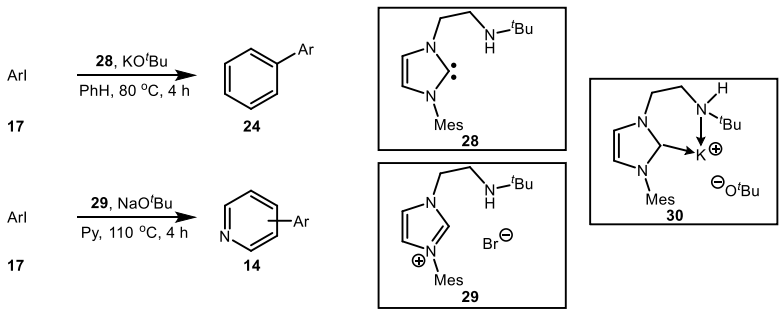


Scheme 9 - Mechanism Suggested by Hayashi



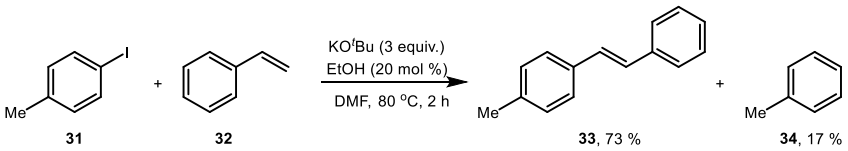
Scheme 10 - Charette's Intramolecular Cyclisations

Chen and Ong have also reported on the arylation of benzene and pyridine promoted by heterocyclic carbene **28** and by carbene precursor **29**.[25] In this work, various iodoarenes **17** were coupled to benzene or pyridine using KO^{t}Bu or NaO^{t}Bu with either a heterocyclic carbene (*e.g.* **28**) or an imidazolium salt as a precursor to a heterocyclic carbene (*e.g.* **29**) as an initiator, to produce coupled products **24** and **14** (Scheme 11). On the arylation of pyridine to produce **14**, the lack of regioselectivity was demonstrated by observation of ~2:2:1 *ortho*:*meta*:*para* ratio of products. Upon mixture of KO^{t}Bu with **28**, a dark red solution in toluene was observed, which produced a broad signal upon EPR analysis. However, this signal was too broad for the authors to be able to make any meaningful interpretation. The group proposed that this chemistry is initiated via SET from a complex of the carbene additive with KO^{t}Bu, *e.g.* **30**.

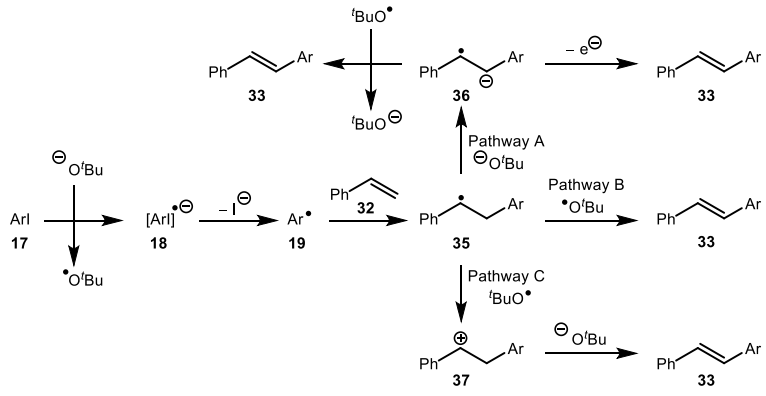


Scheme 11 - Chen and Ong's Arylation of Benzene and Pyridine with Carbenes

A number of publications have also presented KO^{t}Bu-mediated Heck-type reactions, where an aryl halide and an alkene are coupled without the use of palladium catalysis.[26–29] Shirakawa and Hayashi firstly reported on the coupling of aryl halides, *e.g.* 4-iodotoluene **31** with styrene **32**, where KO^{t}Bu in EtOH/DMF afforded the Heck-type product **33** in good yield (Scheme 12). The authors propose that electron transfer from KO^{t}Bu to the aryl halide **17** generates the aryl radical anion **18**, which fragments to form the aryl radical **19** (Scheme 13). This aryl radical can add on to the styrene **32** regioselectively to form benzylic radical intermediate **35**. They propose that this radical can then undergo loss of a proton and an electron by three different pathways. Pathway A involves deprotonation of radical intermediate **35** by KO^{t}Bu to form radical anion **36** which can then either donate an electron back to the starting aryl halide to form the product **33** and propagate the cycle, or can donate an electron back to a *tert*-butoxyl radical to regenerate the *tert*-butoxide anion and product **33**. Alternatively, intermediate **35** can lose a hydrogen atom to the *tert*-butoxyl radical, forming the product **33** and *tert*-butanol via pathway B. The final option via pathway C involves the oxidation of intermediate **35** by the *tert*-butoxyl radical to form cation **37**, which can then be deprotonated by *tert*-butoxide to form **33**. Based on later work by Studer and Curran (to be discussed below), it is likely that pathway A is the one occurring in this chemistry, with electron transfer occurring from **36** to the starting aryl iodide **17**.[30] Further work by Murphy (also to be discussed later) also shows that KO^{t}Bu is unlikely to be acting as a direct electron donor to these substrates, but instead will form an *in situ* electron donor from either DMF or ethanol.[9,31,32]



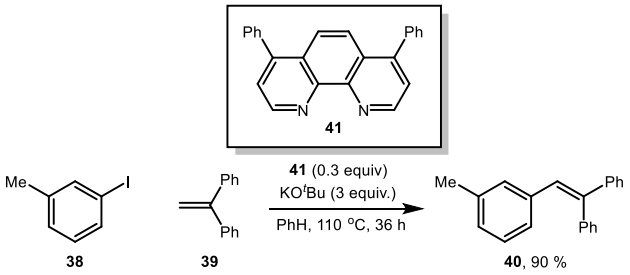
Scheme 12 - Transition Metal-free Heck-type Coupling Reported by Shirakawa and Hayashi



Scheme 13 - Mechanism for Heck-type Coupling as Proposed by Shirakawa and Hayashi

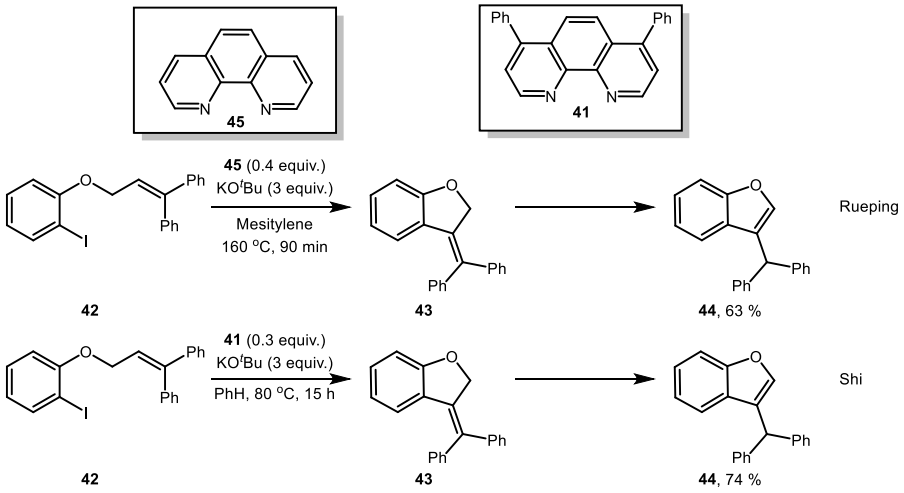
A similar publication by Shi reported on the coupling of aryl halides *e.g.* **38** and 1,1-diphenylethylene **39**, mediated by KO^{t}Bu and phenanthroline derivatives.[27] Here, bathophenanthroline **41** was found to be the best-performing phenanthroline-derived additive, with which the coupling of **38** and **39** occurred to form **40** in 90 % isolated yield (Scheme 14). The authors proposed a similar mechanism to that shown in Scheme 13, where a KO^{t}Bu/phenanthroline complex acts as the electron donor to form radical anion **18**, which can

then proceed as before to the analogous radical of **35**. The authors then propose that either pathway A or pathway C can be followed as before, allowing for the formation of product **40**. Again, as was proposed by Murphy *et al.* in their transition metal-free Heck-type couplings, it is likely that these reactions proceed via pathway A, with the SET initiation occurring from a phenanthroline dimer rather than from KO^{t}Bu.[29] This initiation step will be discussed later.



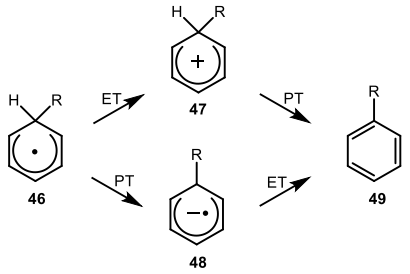
Scheme 14 - Palladium-free Heck-type Reaction Reported by Shi

Transition metal-free Heck-type reactions were also shown by Rueping[26] and by Shi[27] to be applicable to the formation of heterocycles. Here, an intramolecular Heck-type reaction on substrate **42** afforded benzofuran product **44** in 63 % and 74 % yield respectively. The mechanism proposed by the Rueping group is the same as that proposed by the Shi group, with SET occurring from the KO^{t}Bu/phenanthroline system. This heterocycle formation involves a final alkene regioisomerisation step from **43** to form the heterocycle **44**.



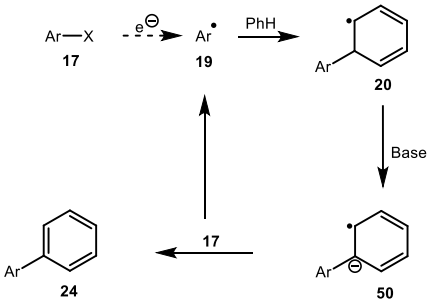
Scheme 15 - Heterocycle Formation by Metal-free Heck-type Reactions and Reported by Rueping and Shi

In 2011, Studer and Curran further explored the mechanism for KO^{t}Bu-mediated electron transfer reactions.[30] They proposed that a cyclohexadienyl radical intermediate **46** can oxidise to form aromatic product **49** via two methods – i) electron transfer (ET) affording intermediate cation **47**, followed by proton transfer (PT) (as suggested in Hayashi's mechanism), or ii) proton transfer to afford intermediate radical anion **48**, followed by electron transfer (Scheme 16). Due to the presence of the strong potassium *tert*-butoxide base, it is thought that the radical anion **48** will form more rapidly than the electron transfer step to form **47**. Radical anion **48** is also known to be a good reducing radical, giving further support to this pathway. This provides the basis of their base-promoted homolytic aromatic substitution (BHAS) mechanism (Scheme 17).



Scheme 16 – Possible Methods of Rearomatisation Suggested by Studer and Curran

In the BHAS mechanism, aryl halide **17** gains an electron and dissociates with loss of an iodide anion to produce aryl radical **19**. This aryl radical can then undergo addition to a molecule of benzene to produce radical **20**, which is deprotonated by potassium *tert*-butoxide to form radical anion **50**. This radical anion can then undergo single electron transfer (SET) to another molecule of **17**, producing rearomatised coupled product **24** while regenerating another aryl radical **19**, which can propagate the chain. However, the source of the electron in the initiation step was still unknown at this point.

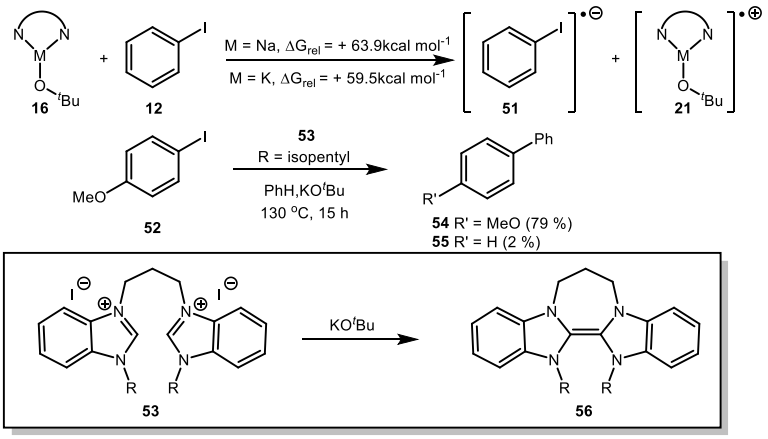


Scheme 17 – Studer's and Curran's BHAS Cycle

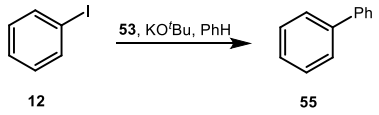
In 2013, Tuttle and Murphy *et al.* further studied the source of the initial electron transfer in the initiation step of the BHAS cycle.[33] It was calculated computationally that the free energy change for the electron transfer from the sodium ion complex with phenanthroline (**16**) suggested by Shirakawa and Hayashi to iodobenzene **12** was ΔG = + 63.9 kcal, mol^{-1}, and ΔG = + 59.5 kcal, mol^{-1} for the analogous potassium ion case (Scheme 18). This was sufficiently high that it was ruled out as the source of the initial electron transfer, and it was suggested that the addition of heterocycles must be promoting the reaction in some other way. As the Murphy group's super electron donors had already been shown to reduce aryl iodides to aryl radicals or aryl anions,[8] it was thought that a super electron donor could be formed *in situ* and this could be the source of the initiating electron. The initial test reaction used donor precursor salt **53**, 4-iodoanisole **52**, and potassium *tert*-butoxide in benzene. The expected coupling product, 4-methoxybiphenyl **54** was formed in 79 % yield, along with 2 % biphenyl **55** as a by-product. Salt **53** forms an electron donor in the presence of a strong base, and the structure of this electron donor is **56**.

In order to show that the electron donor is only required in initiator quantities, the amount of donor salt **53** was varied in the coupling reaction of iodobenzene **12** with benzene at 180 °C. It was

found that using 0.1 equiv., 0.05 equiv., and 0.01 equiv. of **53** still allowed for the formation of biphenyl **55** in 65 %, 67 % and 73 % respectively, supporting the proposal that the donor salt is only needed for the initiation of the reaction (Scheme 19). Upon lowering the temperature to 130 °C, the coupling of **12** to benzene to afford **55** was still successful in 80 % yield with 0.05 equiv. of **53**. However, when the donor salt **53** was omitted from the reaction, the yield of coupled product was found to significantly decrease to 30 %.



*Scheme 18 - Coupling Reaction with Murphy's Super Electron Donor Precursor **53**[a]*

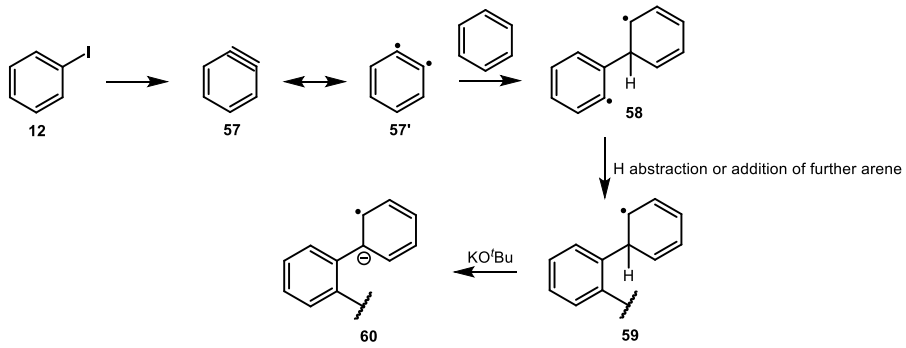


Scheme 19 - Coupling of Iodobenzene with Benzene to Produce Biphenyl

Biphenyl-type products always form in lower yields in additive-free conditions (*i.e.* with a haloarene, arene and KO*t*Bu alone) than when an additive is used and this is proposed to come from a benzyne background reaction (Scheme 20). Here, iodobenzene **12** can be deprotonated *ortho* to the iodine and form benzyne **57** upon subsequent loss of iodide. Benzyne **57** is in resonance with diradical **57'**,[34–37] and this can undergo addition to a molecule of benzene to produce diradical **58**. Although this could form a cyclobutene product via radical recombination, it has been found that the ΔG^{*} for this reaction is 23.6 kcal, mol^{-1}, with a ΔG_{rel} of + 6.4 kcal, mol^{-1}.[38,b] These values suggest that even though cyclobutene formation is feasible, any cyclobutene that is formed is likely to reopen to **58**. However, a further hydrogen abstraction or addition to another molecule of benzene can also occur, producing **59**, which upon subsequent deprotonation with potassium *tert*-butoxide produces radical anion **60**. This then acts as an electron donor to **12** in an analogous fashion to the previously discussed radical anions, propagating the BHAS cycle. The ΔG^{*} for the formation of **60** from **59** is 1.5 kcal, mol^{-1}, and

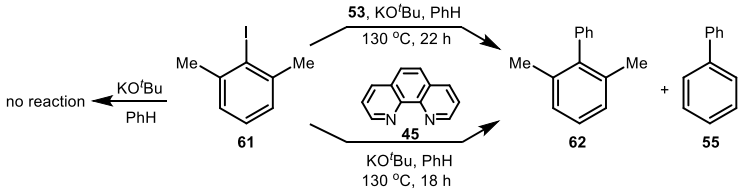
[a] Geometry optimization and energy calculations were performed with the M06L method using the 6-311G(d,p) basis set for all atoms. Solvation was implicity modelled (solvent = benzene) using the CPCM solvation model.
[b] Geometry optimization and energy calculations were performed with the M06-2X method with 6-311++G(d,p) basis set on all atoms. Solvation was implicity modelled (solvent = benzene) using the CPCM solvation model.

$\Delta G_{rel} = -32.7$ kcal, mol^{-1}, suggesting that the formation of **60** is much more favourable than the formation of a strained cyclobutene side-product.[38]

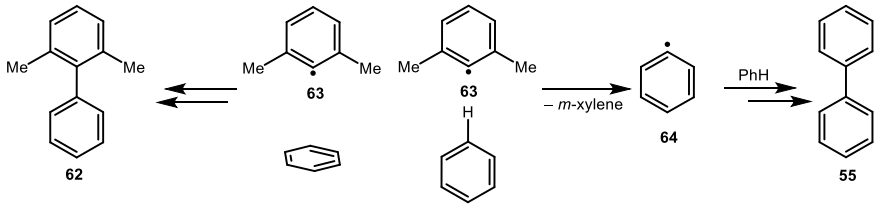


Scheme 20 - Benzyne Background Reaction

To support this theory, a substrate which cannot undergo benzyne formation was subjected to reaction both with an additive and under additive-free conditions. The substrate used was 2,6-dimethyliodobenzene **61**, which is blocked in the *ortho*-positions by methyl groups. No reaction occurred in additive-free conditions, supporting the theory that this background reaction is occurring via a benzyne mechanism. When the reaction was repeated in the presence of the donor salt **53**, the expected coupling product **62** was formed in 5% yield, along with 19% biphenyl **55** and recovery of 36% of starting material **61** (Scheme 21). The distribution of products from this reaction suggests that the 2,6-dimethylphenyl radical **63** is too sterically hindered to undergo efficient coupling with benzene, and is more likely to undergo hydrogen abstraction from benzene to form the volatile *m*-xylene and phenyl radical **64**, which can undergo addition to benzene to form biphenyl **55** (Scheme 22).



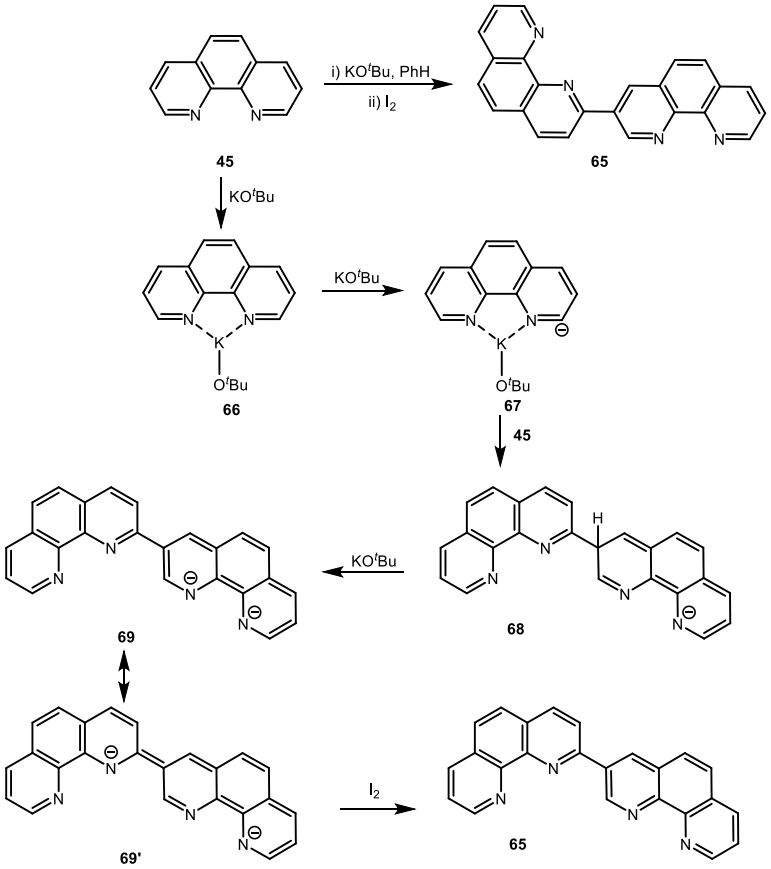
*Scheme 21 - Reaction of 2,6-Dimethyliodobenzene **61***



*Scheme 22 - Different Pathways of 2,6-Dimethylphenyl Radical **63***

The reaction of substrate **61** with 1,10-phenanthroline **45** (20 mol %) and potassium *tert*-butoxide (2 equiv.) in benzene produced coupled product **62** and biphenyl **55** in the same yields as those seen with donor precursor salt **53**. 1,10-Phenanthroline is an electron-deficient heterocycle, and the best way to convert this to an electron-rich species would be via the addition of a nucleophile. Heating **45** and potassium *tert*-butoxide gave rise to the formation of a dark-green solid. When this green solid was exposed to air, it was found to be pyrophoric. This green solid was instead

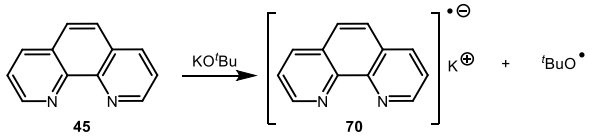
quenched with iodine (as an electron acceptor), and a red oil was isolated which was found to be phenanthroline dimer **65** (Scheme 23). Here, **45** complexes to potassium *tert*-butoxide to form **66**, which is subsequently deprotonated to form anion **67**. Anion **67** can then act as a nucleophile and attack at the 3-position of another molecule of phenanthroline **45** to form intermediate **68**, which upon further deprotonation forms dianion **69**. Dianion **69** is in resonance with **69'**, and the similarity of this to other super electron donors is clear, as they all contain an electron-rich alkene which is capable of donating an electron to an aryl iodide to initiate the BHAS cycle. Once two electrons have been lost, **69'** is restored to full aromaticity (**65**). This is the likely mechanism occurring in Shi, and Shirikawa and Hayashi's work rather than the energetically unfavourable electron donation directly from the potassium *tert*-butoxide and phenanthroline complex.[22,23]



*Scheme 23 - Formation of Phenanthroline Dimer **69** as an in situ Electron Donor*

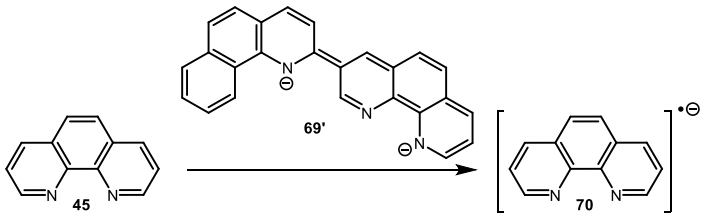
Electron transfer from a KO^{t}Bu/1,10-phenanthroline complex was also proposed by Jutand and Lei, who used electrochemical methods and electron paramagnetic resonance (EPR) spectroscopy to determine that radicals are present when KO^{t}Bu and 1,10-phenanthroline are combined.[39] They found that the combination of these two reagents led to an EPR signal, consistent with the formation of radicals, and proposed that these radicals must be the relatively long-lived species **70**, formed from electron transfer from the butoxide anion to phenanthroline **45** (Scheme 24). They proposed that this species is the one which then reduced the aryl iodide to an aryl radical, and initiated the coupling reaction. However, their electrochemical studies do not support this, as they show that the *tert*-butoxide anion (with an oxidation potential of + 0.10 V vs. SCE in DMF) is not capable of directly reducing aryl iodides (reduction potential of – 2.0 V vs.

SCE in DMF) by an outer-sphere mechanism. It is therefore unlikely that the *tert*-butoxide anion will reduce phenanthroline (first reduction potential of – 2.06 V vs. SCE in DMF) as the authors suggest. The authors propose that this reduction occurs due to the formation of a phenanthroline-potassium *tert*-butoxide complex where the complexation with a potassium cation brings the butoxide close to the phenanthroline, aiding the electron transfer.



Scheme 24 - Jutand and Lei's Suggestion for the Role of Phenanthroline

Murphy *et al.* have suggested that if the phenanthroline dimer **69/69'** forms, then this should be a strong enough electron donor to reduce a neutral molecule of phenanthroline **45** (reduction potential of – 2.05 V vs. SCE in DMF) to its radical anion **70**, and this is the reason for the observation of radical species in the EPR experiments of Jutand and Lei.[31] Cyclic voltammetry of **65** showed three peaks of – 1.70 V, – 1.94 V, and – 2.19 V, corresponding to reversible 1 e^-, 1 e^-, 2 e^- reductions respectively. It has been shown by Jutand and Lei that mixtures of phenanthroline and KO^{t}Bu are capable of reducing aryl bromides (reduction potential of – 2.67 V vs. SCE in DMF), and therefore the reduction of a neutral molecule of phenanthroline should be easier.[39]

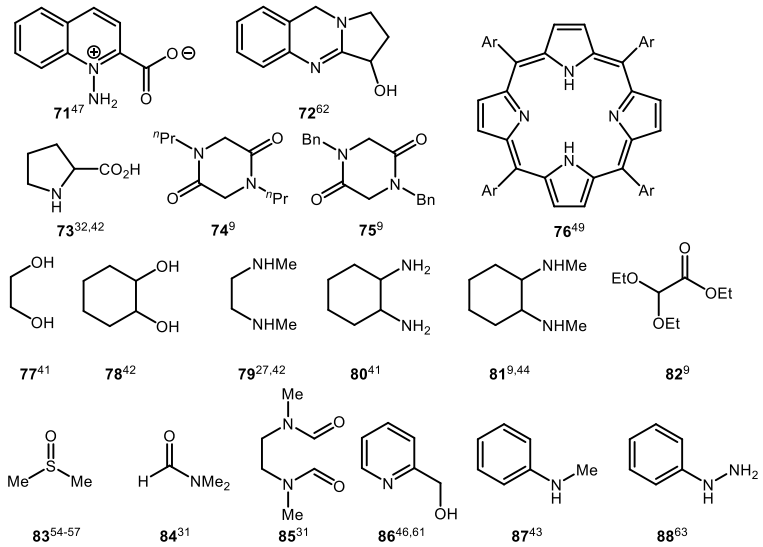


*Scheme 25 - Murphy's Proposal for the Formation of Radicals with Phenanthroline **45** and KOtBu*

Yuan *et al.* have shown that KO^{t}Bu can donate an electron to phenanthroline under photoactivation, forming phenanthroline radical anion **70**.[40] This radical anion **70** can then donate an electron to an aryl halide to generate an aryl radical and initiate the coupling reaction to benzene. An EPR signal, proposed to be that of **70**, was observed when phenanthroline and KO^{t}Bu were mixed under visible light irradiation, but was not observed when these components were mixed in the dark.

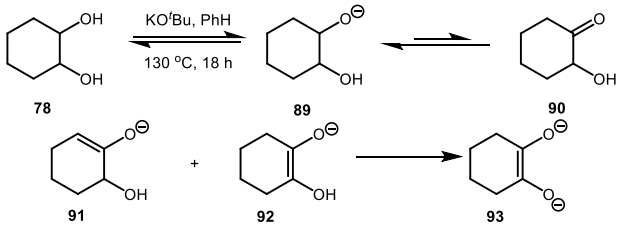
Other organic additives are known to be able to promote the coupling of iodoarenes to arenes, including alcohols,[32,41,42] amines,[32,42–44] amino acids,[45] pyridinols,[46] formamides,[31] and DMSO,[31] amongst others.[9,47–49] (Scheme 26). The role of a large number of these additives was identified by Murphy *et al*.[9,31] It was proposed that these additives can form electron-rich alkenes *in situ* which act as single electron donors, and it is these electron donors which initiate the coupling reactions. These electron-rich alkenes can be simple enolates of ester species such as **82**, or can form through simple double deprotonation of porphyrin compounds such as **76**. Indeed, previous work by Rossi, Bunnett and Scamehorn had shown that enolates of simple ketones such as

pinacolone or acetone can act as efficient electron donors to aryl halides.[50–53] DMSO **83** has also previously been reported to act as an electron donor via formation of the dimsyl anion.[54–57]



Scheme 26 - A Selection of Additives Which Promote Coupling Reactions

Alcohols such as 1,2-dihydroxycyclohexane (**78**, both *cis*- and *trans*- isomers) were able to form *in situ* electron donors, as shown by the increase in yield in the coupling of 2,6-dimethyliodobenzene **61** with benzene to form an inseparable mixture of **55** and **62** with a combined mass of 32 mg and 63 mg for the *cis*- and *trans*- isomer respectively (with none of the 232 mg of starting material remaining in either case). These results were from experiments where 1 mmol of substrate **61** (232 mg) was subjected to the reaction conditions [KO^{t}Bu (2 equiv.) and additive (0.2 equiv.) in benzene as a solvent], and the combined mass of **55** and **62** was used as a guide to determine if the additive was able to form an effective electron donor. Effective electron donors produced **55** and **62** in a combined yield of > 25 mg. Cyclohexanol was a much less effective electron donor, allowing for formation of **55** and **62** in a combined mass of 7 mg (with 50 % of the starting material remaining). It was thought that the electron-rich alkene might arise by formation of the corresponding enolate (Scheme 27).

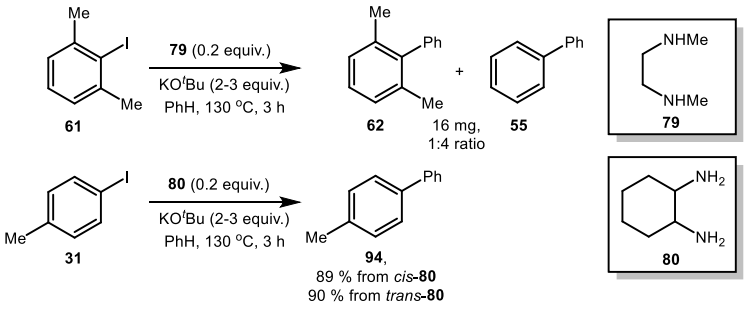


*Scheme 27 – Formation of Electron Donors **91**-**93** from **78***

Alkoxides are normally oxidised to ketones via the Oppenauer oxidation, but it has been shown by Woodward that potassium *tert*-butoxide in toluene could also allow this reaction to occur.[58] It wa proposed that the electron donor is formed from the deprotonation of **78** to form alkoxide **89**, which can subsequently eliminate a hydride anion to form **90**. Deprotonation adjacent to the ketone then gives enolate **91** or **92**. It is proposed that **92** is the better electron donor as it forms

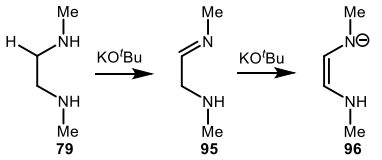
a more electron-rich enolate than the enolate in **91**. Furthermore, donor **92** can form a dianion by a second deprotonation on the hydroxyl group, forming the stronger donor **93**.

Simple amines such as dibutylamine were found to exhibit no electron transfer activity with substrate **61**, however *N*,*N*'-dimethylethylenediamine **79** was able to form an electron donor, allowing for the formation of **55** and **62** in a combined yield of 16 mg (Scheme 28). Cyclohexane-1,2-diamine **80** was found to form one of the best electron donors, allowing for the coupling of 4-iodotoluene **31** to benzene to afford **94** in 89% and 90% yields for the *trans*- and *cis*- isomers respectively.[9]

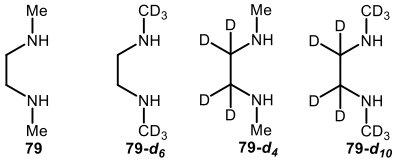


Scheme 28 – Amine Additives in Transition Metal-free Coupling Reactions

The mechanism proposed for the formation of the active electron donor from 1,2-diamines involves the generation of the corresponding imine *e.g.* **95** from amine **79** by deprotonation and expulsion of a hydride (Scheme 29). Upon deprotonation of **95**, electron-rich alkene **96** can be formed, and this is proposed as the electron-donating species. This is further backed up by use of deuterated **79** (Scheme 30). When **79**, **79-*d*$_6$**, **79-*d*$_4$**, and **79-*d*$_{10}$** were compared in side-by-side coupling reactions, **79** outperformed all of the deuterated analogues, with **79-*d*$_4$**, and **79-*d*$_{10}$** returning only trace amounts of coupled products. This is consistent with the cleavage of an internal methylene C-H (or C-D) being involved in the rate determining step of the reaction, and is not consistent with a simple complex between additive and base being the electron-donating species.

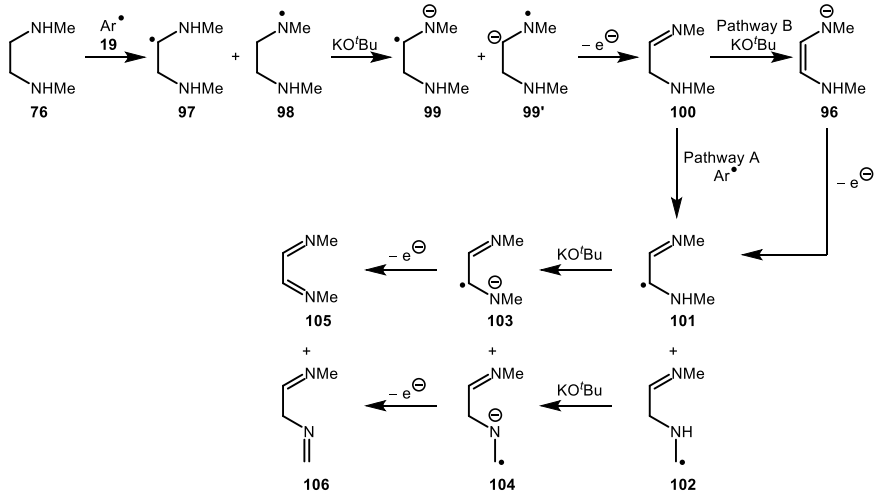


*Scheme 29 - Formation of Proposed Active Electron Donor **96***

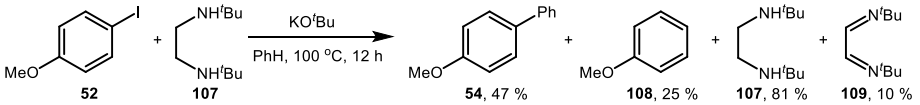


*Scheme 30 - Use of Deuterated **79***

The mechanism of the diamine initiation was also studied by Jiao *et al.*, who proposed a modification to the mechanism after experimental and computational studies (Scheme 31).[59] They proposed that the diamine **79** was able to "initiate" the coupling reactions by firstly transferring a hydrogen atom to an aryl radical **19** (although they do not state how this initial radical forms, so this is not really a study of an initiation process), forming radical **97** or **98**, which can be deprotonated by KO^{t}Bu to form radical anion **99** and **99'**. This radical anion **99**/**99'** can then transfer an electron to the aryl iodide **17** to form the aryl radical **19** and initiate the reaction. The resulting compound **100** can then either transfer a hydrogen atom to an aryl radical to form the arene and radicals **101** and/or **102** via pathway A, or can be deprotonated to form electron-rich alkene **96**. Species **96** can also transfer an electron to the aryl iodide to initiate the coupling reactions, as previously proposed by Murphy *et al*., via pathway B. The resulting radicals **101** and/or **102** can be deprotonated and generate radical anions **103** and **104**, which are capable of further initiating the coupling reactions by electron transfer, forming species **105** and **106**. When **107** was used in the coupling reaction of **52** and benzene, compound **109** was detected by NMR and GC-MS, with data consistent to that of an independently prepared sample of **109** (Scheme 32). This provides evidence that the intermediates proposed by Jiao and by Murphy are forming in the reaction mixture.



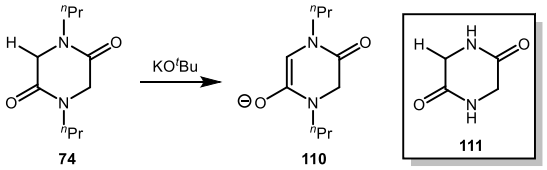
*Scheme 31 - Jiao's Proposal for Initiation with Diamine **79***



*Scheme 32 - Use of **107** in the Coupling of **52** to Benzene*

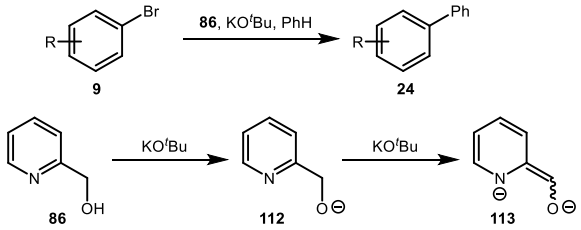
Secondary amino acids such as proline **73** are also precursors to efficient electron donors, whereas primary amino acids are less effective and tertiary amino acids are ineffective. As secondary amines and carboxylic acids are able to form *N*-alkyl amides or cyclic piperazinedione dimers upon heating alone,[60] it is thought that small amounts of these compounds could form and the enolate of such a species could act as the electron donor. *N*,*N*'-dialkylpiperazinedione **74** was prepared independently and was shown to be a good electron donor *via* enolate **110** (Scheme 33), whereas analogue **111** was ineffective. This is thought to be due to the competing

deprotonation between the CH_2 and the NH in **111**. As the NH is more acidic, no electron-rich enolate would form and instead deprotonation on nitrogen would occur, preventing the formation of the electron donor, and therefore no electron transfer would take place.



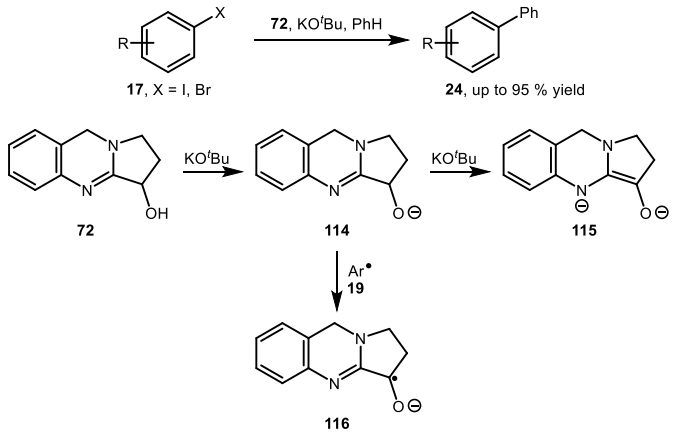
*Scheme 33 - Formation of Electron Donor **110** and Structure of Inactive Piperazinedione **111***

Pyridinols such as **86** have also been shown to react with KO^{t}Bu to facilitate the coupling of haloarenes **9** to benzene to form **24** (Scheme 34).[46,61] This was proposed to form an electron-rich alkene via double deprotonation of **86**, firstly forming **112** followed by **113**. It is this doubly-deprotonated species which is proposed to act as an electron donor in this case, and this is capable of reducing both aryl iodides and aryl bromides.



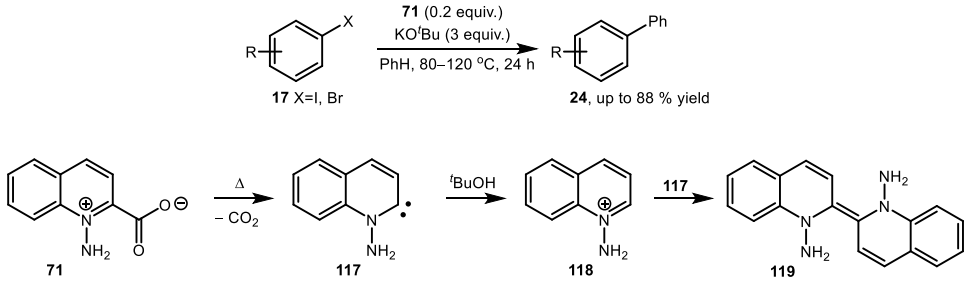
*Scheme 34 - Formation of Electron Donor **113** from Pyridinemethanol **86***

In a similar way, compound **72** can likely be doubly-deprotonated to form dianion **115** via **114** (Scheme 35).[9] Alternatively, **114** may propagate by undergoing hydrogen atom transfer to an aryl radical **19** in solution, forming radical anion **116** which could then act as an electron donor. Compound **72** has previously been shown by Kumar *et al*. to facilitate the coupling of various iodo- and bromoarenes **17** to benzene with KO^{t}Bu to from **24**, although the authors propose a direct electron transfer from a KO^{t}Bu-**72** complex, which is unlikely due to the high barriers for electron transfer from KO^{t}Bu.[62] The formation of dianion **115** as proposed by Murphy is the more likely mechanism.



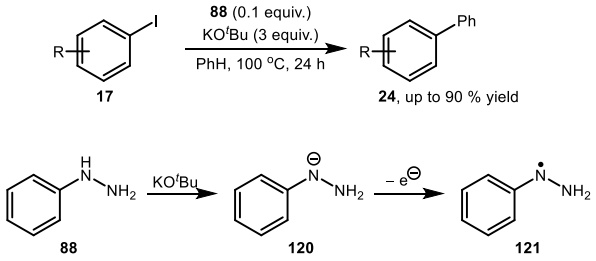
*Scheme 35 - Formation of Electron Donor **115** and/or **116** from **72***

Compound **71** has been shown to also facilitate the coupling of haloarenes **17** to benzene to form **24** (Scheme 36).[47] The role of this additive was proposed by Murphy *et al.* to begin with thermal decarboxylation of **71** to form carbene **117**.[9,63] This carbene can then be quenched with *tert*-butanol generated under the reaction conditions to produce **118**. Dimerisation between **118** and another molecule of **117** can ultimately produce electron-rich alkene **119**, which is proposed to be the active electron donor in this case.



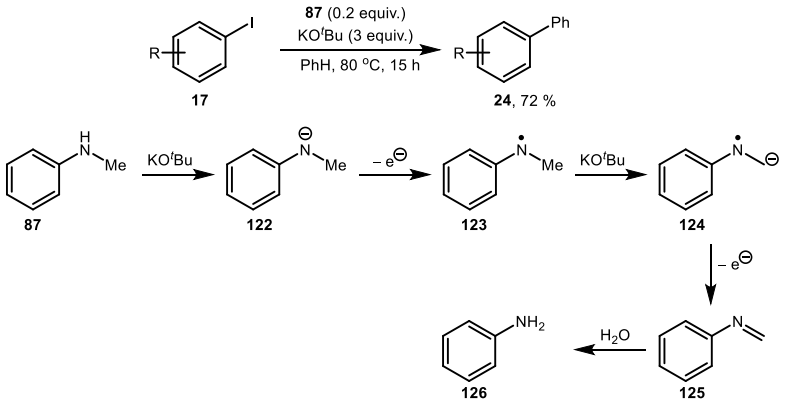
*Scheme 36 - Formation of Electron Donor **119***

Studer *et al.* have shown that phenylhydrazine **88** is also effective in the coupling of iodoarenes **17** to benzene (Scheme 37).[64] Phenylhydrazines were proposed to be good initiators due to the α-effect from the lone pair of electrons on the adjacent nitrogen atoms which can stabilise the resulting radical after electron transfer. They propose that deprotonation of phenylhydrazine **88** occurs to form phenylhydrazide **120**, which can then act as an electron donor and form stabilised radical **121**. The aryl iodide radical anion formed from **17** can then fragment and propagate as previously, ultimately forming **24**.



*Scheme 37 - Phenylhydrazide **120** as an Electron Donor*

N-methylaniline derivatives were shown by Jiao to promote the coupling reaction between aryl iodides **17** and benzene (Scheme 38).[43] The group proposed that deprotonation of *N*-methylaniline **87** to form anion **122** occurs, and this species is the active electron donor, donating an electron to the aryl iodide **17** to initiate the chain process. The resulting radical **123** formed after oxidation can be deprotonated to form radical anion **124**, which can donate a second electron to a second molecule of aryl iodide, resulting in imine **125**. This imine could then hydrolyse upon work-up to produce aniline **126**, which is detected in the reaction mixture by GC-MS after aqueous work-up.

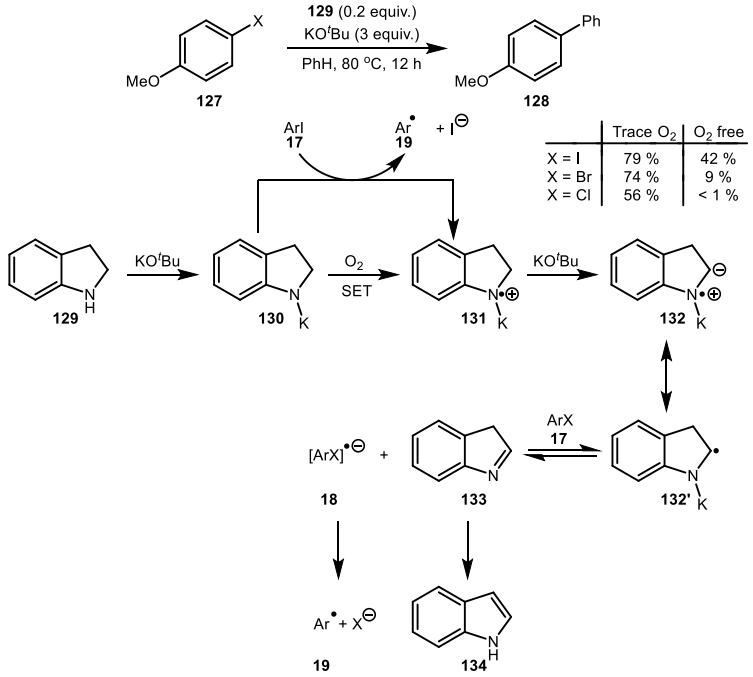


*Scheme 38 - Formation of an Electron Donor from N-methylaniline **87***

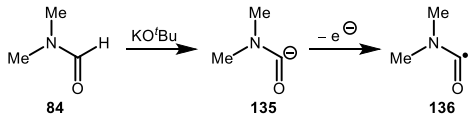
Similarly, indoline **129** was also shown to be able to form a powerful *in situ* electron donor with KO^{t}Bu which was able to reduce the more challenging aryl chlorides (these are more challenging to reduce due to their increased C-X bond strength and more negative reduction potential).[65] Indole **134** was generated in high yield as a by-product from this reaction, which suggests that the driving force for the electron transfer is the gain of aromaticity. Indolines which were not able to aromatise, such as 3,3-dimethylindoline, were only able to efficiently reduce aryl iodides, and not the more difficult aryl bromides or chlorides. The inclusion of a trace amount of oxygen was found to be key to the reactivity, as when this was rigorously excluded, the yields decreased. Through computational and experimental studies, the group proposed a mechanism which firstly involves deprotonation of indoline **129** to form the weak electron donor **130** (Scheme 39). This weak electron donor is capable of donating an electron to aryl iodides **17**, which fragments to form aryl radical **19** and initiates the coupling reactions of these substrates. In the presence of a trace amount of oxygen, **130** can be oxidised to form radical cation **131**. Deprotonation of this radical cation forms **132**, which is a resonance form of **132'**. This radical anion is a more powerful electron donor (which is capable of carrying out the reversible reduction of aryl bromides and chlorides), forming radical anion **18** and indolenine **133**. Cleavage of this radical anion to form an aryl radical **19** initiates the coupling reaction, and the indolenine **133** can aromatise in the presence of KO^{t}Bu to form indole **134**. Alternatively, hydrogen atom abstraction from **130** by oxygen could afford **132'** directly.

Formamides have been shown to be effective additives in the coupling of iodoarenes to benzene. Previous literature had suggested that the anion of DMF (**135**) could act as an electron donor to various substrates, including to another molecule of DMF[66–69] or aryl iodides (Scheme 40).[70] Here, DMF **84** is deprotonated by KO^{t}Bu to form anion **135**, which was proposed to act as a single electron donor to form radical **136**. Murphy *et al.* proposed that, as the anion of DMF **135** has been shown to act as a nucleophile,[71,72] that perhaps this could act as a nucleophile towards a neutral molecule of DMF, forming dimer **137** (Scheme 41). Proton transfer would afford the enolate **138**, which has the electron-rich alkene structure reminiscent of an electron donor. Alternatively, further deprotonation could afford dianion **139**, which could be a more powerful electron donor. Evidence for the formation of this dimer was given by the use of formamides **85**

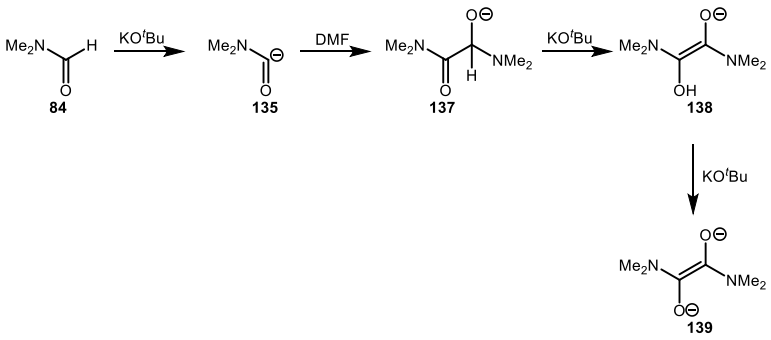
and **140** (Scheme 42). These formamides were found to be more active in the electron transfer to **61** than DMF even at half the concentration, suggesting that the dimerisation step is necessary for the formation of the active electron donor (it would be easier to form a dimer from **85** and **140** than from DMF due to the 1,6-relationship of the formamide groups).



*Scheme 39 - Formation of an Electron Donor from Indoline **129***



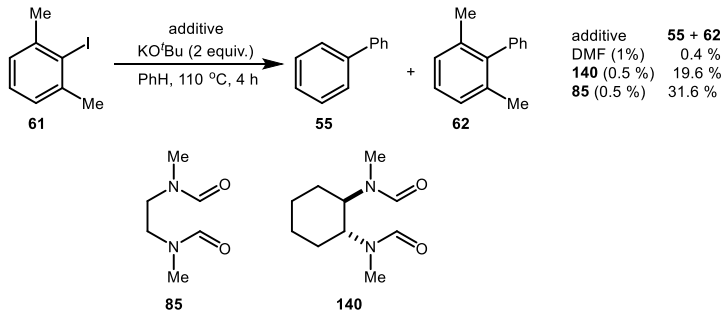
Scheme 40 - Previous Proposals for Electron Transfer from DMF



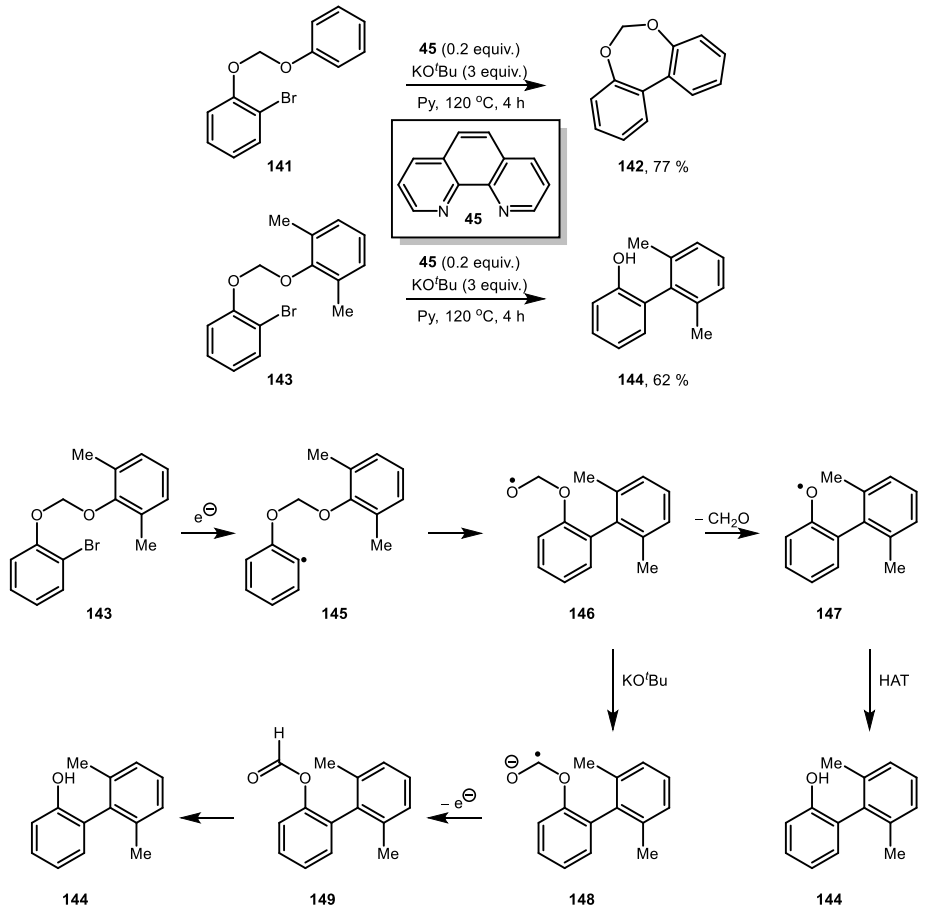
Scheme 41 - Formation of an Electron Donor from DMF as Proposed by Murphy

In all of the examples shown previously, it has only been possible to control the regiochemistry at the aryl halide coupling partner, and not at the arene. Alabugin *et al.* reported in 2016 that an intramolecular acetal linking group between the two coupling partners could allow for some regioselectivity in the formation of an aryl-aryl bond (Scheme 43).[73] However, a drawback to this procedure is that it is only applicable to 2,6-disubstituted derivatives such as **143**. Non-substituted derivatives such as **141** undergo *ortho*-substitution to afford products such as **142**. The proposed

mechanism involves electron transfer from the phenanthroline dimer to **143** to form radical **145**. Cyclisation into the *ipso*-position and cleavage of the C-O bond affords **146**, which can extrude CH_2O to form **147**, followed by abstraction of a hydrogen atom to form the product **144**. Alternatively, **146** can be deprotonated by KO^{t}Bu to afford **148**, which can act as an electron donor to propagate the chain and afford formate **149**. This formate presumably converts to product through either transesterification by KO^{t}Bu, or by hydrolysis upon aqueous work-up.



Scheme 42 - Comparison of Formamides in Electron Transfer Reactions

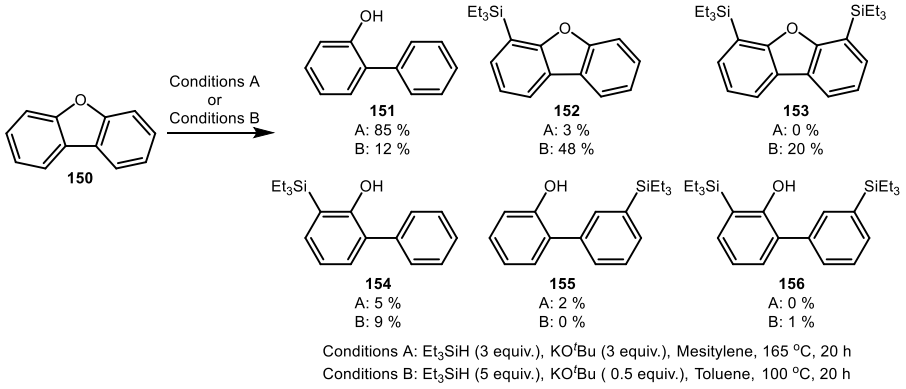


Scheme 43 - A Regioselective Intramolecular Coupling Reaction

1.2: Scope and Mechanistic Studies of Silane-Alkoxide Systems

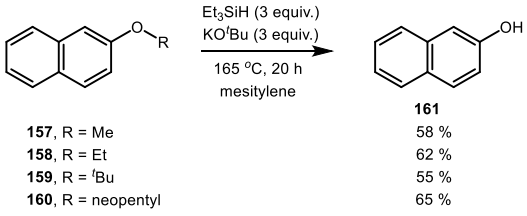
In 2013, Grubbs *et al.* reported on the cleavage of carbon-oxygen bonds in aryl-aryl and aryl-alkyl ethers, using triethylsilane and potassium *tert*-butoxide.[1] These types of cleavages were

previously only reported with transition metal-catalysed processes,[74–83] extremely high temperatures,[84] or with excess alkali metals.[85,86] Dibenzofuran **150** was chosen as the model substrate for this bond cleavage to **151**, as this has applications in the degradation of lignin (Scheme 44). *ortho*-Silylated compounds **152**-**156** were also detected from this reaction in low yields, and these silyl group could provide a useful synthetic handle for further functionalisation at a later stage. Variation of the reaction conditions allowed for selectivity of C-O bond cleavage over silylation products, and *vice versa*, *e.g.* C-O bond cleavage is more predominant with less equivalents of silane relative to KO^{t}Bu, whereas silylation is predominant with more equivalents of silane relative to KO^{t}Bu. This is exemplified by two sets of conditions, A and B, shown in Scheme 44.



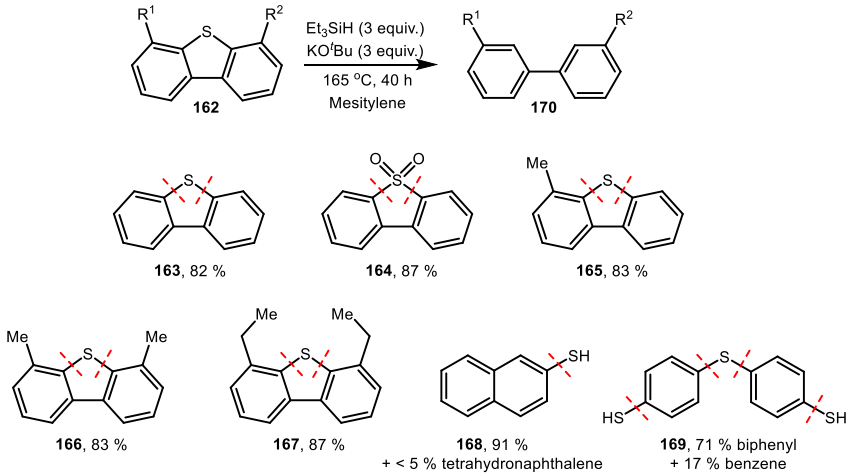
Scheme 44 - Cleavage of Aryl-Aryl Ethers by Et$_3$SiH/KO^{t}Bu

When KO^{t}Bu was used with 18-crown-6, or when it was replaced with NaO^{t}Bu or LiO^{t}Bu, no reaction occurred, suggesting that the potassium counterion is necessary to produce the active reductant. An EPR spectrum could also be generated from the reaction mixture, suggesting that radical species are forming in solution. It was proposed by Grubbs at this time that the active reductant may be an organosilicate species. Headspace analysis of the reaction mixture indicated the formation of hydrogen gas. When the reaction was left open to an argon line, a decrease in yield of **151** was observed to 5 % (*cf.* 38 % under identical conditions where H_2 was not released), whereas the yield of the silylated products **152** and **153** increased to 28 % and 46 % respectively when H_2 was released, compared to 16 % and 10 % of **152** and **153** when H_2 was present. These results indicate that the hydrogen gas may be necessary to avoid decomposition of the active reductant. Aryl-alkyl ethers *e.g.* **157**-**160** were also cleaved in a similar manner (Scheme 45), with 2-naphthol **161** being the major product, with trace amounts of further reduced products detected.



Scheme 45 - Cleavage of Aryl-Alkyl Ethers by Et$_3$SiH/KO^{t}Bu

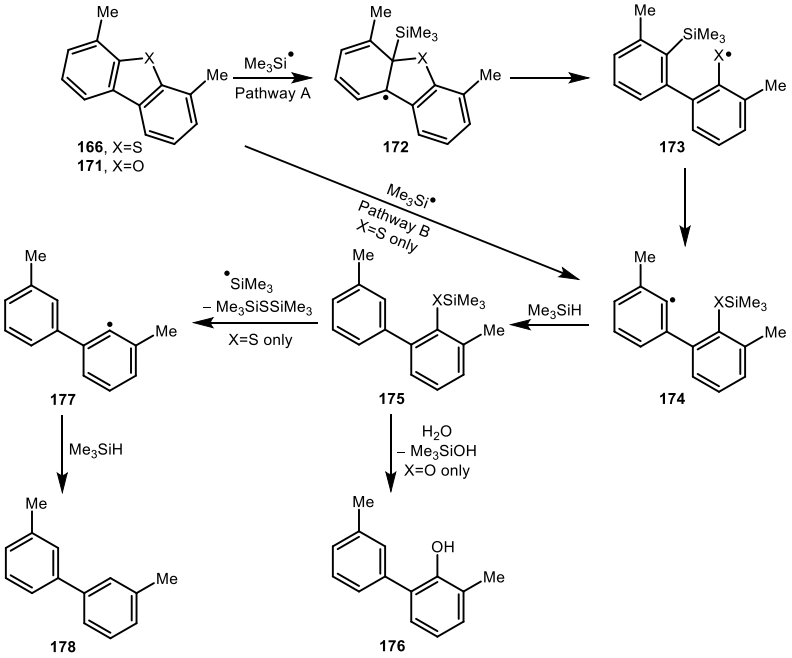
Similar reductive cleavages of C-S bonds in aryl thioethers were also studied by Grubbs and Houk *et al.* in 2017.[7] Here they reported that substrates **162**-**169** were reductively cleaved to the parent arene *e.g.* **170**, with complete desulfurisation occurring (Scheme 46). This process has applications to the desulfurisation of fuels[7,87] and is a possible alternative to the current method, which involves high temperatures and high pressures of hydrogen gas (up to 400 °C, 150-2250 psi) over a cobalt catalyst.[88] Recent advances in transition metal-catalysed methods still pose problems, such as the formation of stable metal-sulfur compounds upon reaction at the metal centre.[89–91]



Scheme 46 - Desulfurisation of Arylthioethers

Computational mechanistic studies revealed the reason for the difference in reactivity of the dibenzofurans and dibenzothiophenes.[7] It was proposed by Grubbs and Houk that triethylsilyl radicals are involved in this chemistry, due to the detection of a TEMPO-$SiEt_3$ adduct when TEMPO was added to the reaction. Their calculations used trimethylsilyl radicals (rather than triethylsilyl radicals) due to the smaller computational cost associated with the trimethylsilyl radical. The initiating trialkylsilyl radical has been proposed to form by trace amounts of oxygen in solution,[92] or via an electron transfer process. 4,6-Dimethyldibenzofuran **171** and 4,6-dimethyldibenzothiophene **166** were used as model substrates for this calculation, and it was found that addition of a trialkylsilyl radical into the *ipso*-position was possible in both the C-O bond and C-S bond cleavages, affording **172** (Scheme 47, Pathway A). Rearomatisation and C-X bond cleavage affords intermediate **173**, before transfer of the silyl group onto the heteroatom affords intermediate **174**. In the desulfurisation pathway, this same intermediate can be reached by direct attack of the trimethylsilyl radical onto the sulfur (Pathway B) – this pathway is not accessible for the C-O bond cleavage. Radical intermediate **174** can be quenched by hydrogen atom abstraction from trimethylsilane. The resulting compound **175** cannot react further when X=O, and is hydrolysed upon work-up to phenol **176**. However, the silyl thioether **175** (X=S) can be further attacked by another trimethylsilyl radical to afford radical **177**, which can be quenched to the biphenyl product **178** by hydrogen atom transfer from trimethylsilane. However, it is not clear why the model substrate used in this study contains two *ortho*-methyl groups, when substrates without these *ortho*-methyl groups are also found to undergo C-X bond cleavages. Indeed, unpublished computational studies within the Murphy group show that when these methyl groups are not

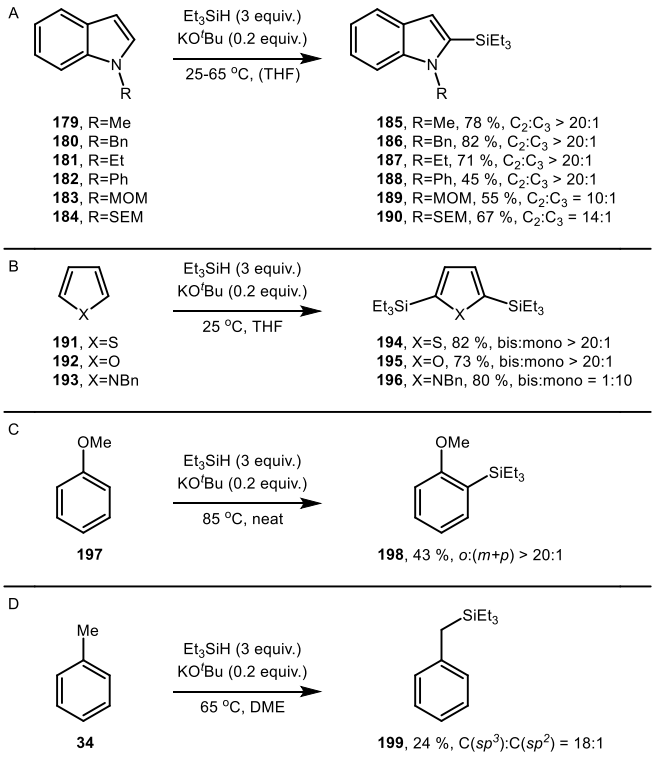
present, the preferred site of attack for a trimethylsilyl radical is in the *ortho*-position. These results suggest that although the mechanism proposed by Grubbs and Houk is feasible for substrates **166** and **171**, an alternative mechanism may be taking place other than the *ipso*-addition of a trimethylsilyl radical when the *ortho*-position is not alkylated.[93]



Scheme 47 – Proposed Mechanism for C-S Bond Cleavage

The Et_3SiH/KO^tBu system has also been shown to facilitate the regioselective silylation of arenes and heteroarenes.[2,3] This is an attractive procedure, as silylated compounds are of interest in the fields of organic electronics,[94] drug discovery,[95] nuclear medicine,[96] and in complex molecule syntheses.[97–99] Traditional methods of silylation generally involve transition metal-catalysis in the presence of hydrogen acceptors.[100] A variety of electron-rich and electron-neutral heterocycles *e.g.* **179**-**184** were silylated using Et_3SiH/KO^tBu in solvent-free conditions (although THF can be used), in high yields and with excellent regioselectivity in the 2-position (forming **185-190**), whereas electron-deficient heterocycles were generally unreactive (Scheme 48A). The authors say that the poor reactivity of electron-deficient heterocycles suggests that a silyl radical substitution mechanism is unlikely (although they later propose a silyl radical substitution mechanism). Sulfur-containing heterocycles were more reactive than oxygen-containing heterocycles, which were in turn more reactive than nitrogen-containing heterocycles (*e.g.* in the conversion of **191**-**193** to **194**-**196**, Scheme 48B). This result provides complementary reactivity to Minisci-type reactions, and to electrophilic substitutions. Further studies on arenes such as anisole **197** and toluene **34** showed that the preferred site of silylation in anisole **197** was in the *ortho*-position, whereas the preferred site of silylation of toluene **34** was on the methyl group, allowing for the formation of compounds **198** and **199** (Scheme 48C and D, respectively). Again, replacement of KO^tBu with NaO^tBu or LiO^tBu resulted in no product formation, and the use of other potassium bases such as KOMe (<5 %), KOEt (0 %), KH (0 %) or KHMDS (44 %) resulted in a decrease in yield for the silylation of *N*-methylindole **179**. Complexation of the potassium

cation with 18-crown-6 also saw a decrease in yield for *N*-benzylindole **180**, down from 82 % to 22 %.

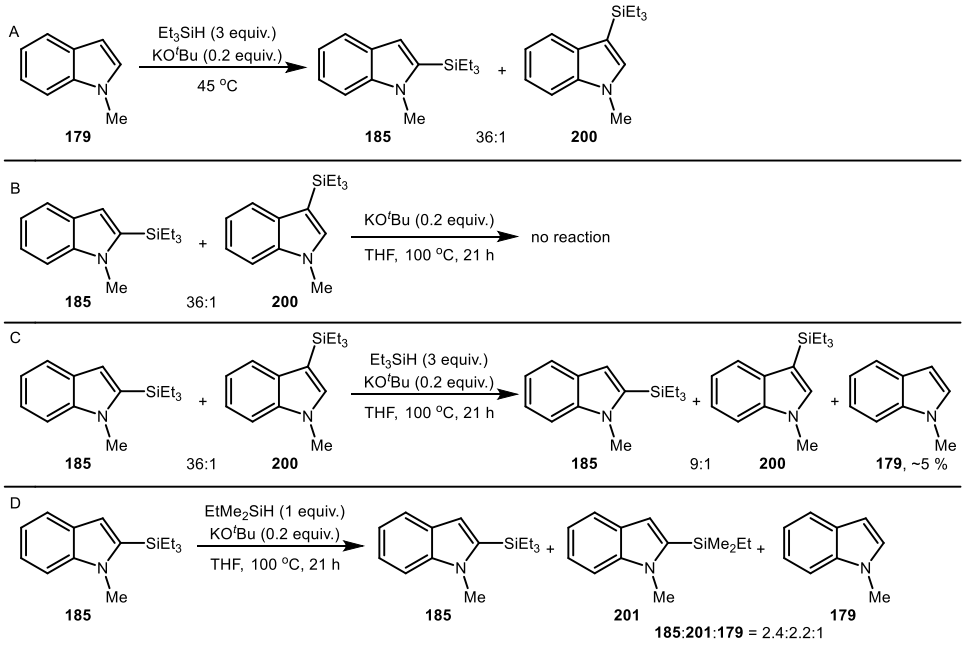


Scheme 48 - Silylation of Arenes and Heteroarenes using Et_3SiH/KO^tBu

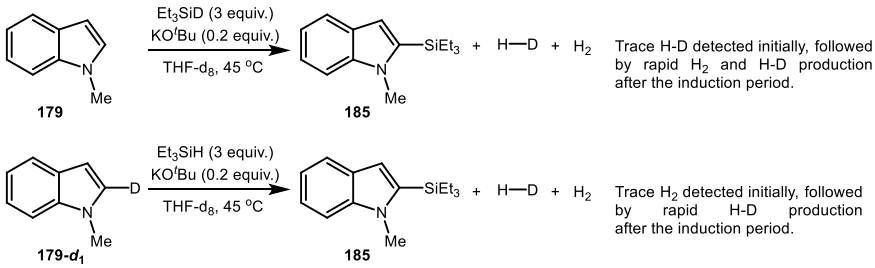
A large amount of computational and experimental studies were carried out to try to determine the mechanism of the silylation reactions.[4,5] In the first mechanistic study, the group looked into the evidence that the silylation proceeds via a radical mechanism.[4] They found in these studies that cations with larger ionic radii were also compatible with the silylation chemistry, albeit in lower yields relative to the potassium cation, *e.g.* KO^tBu (88 %) *vs.* $CsOH.H_2O$ (64 %) and $RbOH.H_2O$ (38 %). They also found that although the C2 silylation of *N*-methylindole (**179**→**185**) was the major product under their standard conditions (Scheme 49A), an increase in the reaction time and temperature resulted in C3 silylation product **200** becoming the major product. This is consistent with the C2 silylation being the kinetic process, and C3 silylation being the thermodynamic process. Base alone was not sufficient to bring about this isomerisation of **185** to **200** (Scheme 49B), but the combination of Et_3SiH/KO^tBu facilitated the isomerisation (Scheme 49C). Therefore, the conversion of **185** to **200** must be occurring intermolecularly rather than intramolecularly (*i.e.* loss of the silyl group to reform a pentavalent silicate, followed by another silylation of **179**). This reversibility was further evidenced by the crossover reaction, where **185** was converted to a mixture of **185**, **201** and **179** (Scheme 49D).

Further studies showed the formation of hydrogen gas in the reaction. A trace amount of hydrogen gas was detected during the induction period of the reaction, followed by a large increase in the volume of hydrogen gas produced as the silylation proceeded. H-D gas was detected by proton NMR in the induction period upon carrying out the reaction with Et_3SiD and **179**, however, H-D

was only detected after the silylation began upon carrying out the reaction of **179-d_1** with Et_3SiH (Scheme 50). This suggests that the hydrogen is formed by a cross-dehydrogenative pathway from the indole C2 position and the silane. The hydrogen produced in the induction period was proposed to be formed by either the reaction of the silane with a trace amount of water, or by the formation of an active radical intermediate.



Scheme 49 - Reversibility of the Silylation Reactions

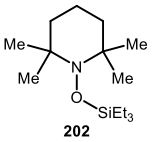


Scheme 50 - Formation of Hydrogen Gas

Evidence of a radical intermediate was given by the addition of TEMPO to the reaction mixture. The addition of 6 mol % of TEMPO led to an immediate bleaching of the reaction mixture from dark purple to light yellow, with the dark purple colour returning over time. The addition of stoichiometric TEMPO led to the detection of a TEMPO-$SiEt_3$ adduct (**202**, Scheme 51) by GC-MS. The reaction mixture of Et_3SiH/KO^{t}Bu in THF at 45 °C was also found to be EPR active, indicating the formation of a radical species. Carrying out the silylation reaction in the dark led to a similar yield of product as when the reaction was carried out in light, which rules out a light-mediated silyl-radical formation.

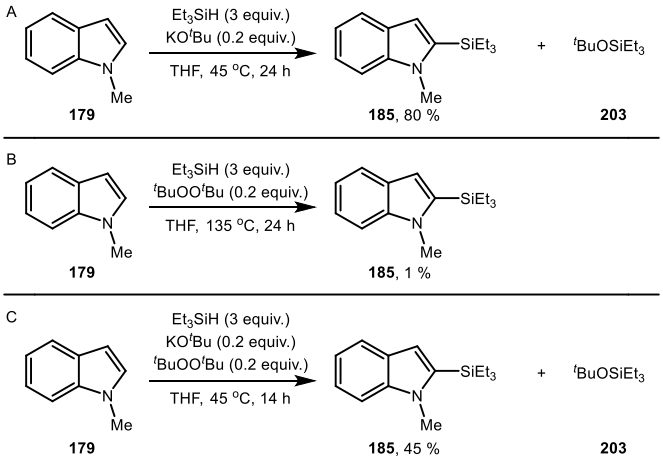
Replacing KO^{t}Bu with radical initiators such as di-*tert*-butyl peroxide afforded only a trace amount of product, suggesting that *tert*-butoxyl radicals are not involved in the transformation (Scheme

52). It is known that *tert*-butoxyl radicals decompose to acetone and methyl radicals, so it is likely that this is what would happen if a *tert*-butoxyl radical formed from KO^{t}Bu.[101,102] Moreover, a by-product of the standard reaction conditions is the silyl ether ^{t}BuOSiEt$_3$ **203** (Scheme 52A), which is not produced with ^{t}BuOO^{t}Bu and Et$_3$SiH (Scheme 52B), which is further evidence that *tert*-butoxyl radicals are not involved in the silylation chemistry. The combination of Et$_3$SiH, KO^{t}Bu and ^{t}BuOO^{t}Bu allowed silylation to occur (Scheme 52C). However, it is not clear how comparable these results are with each other, with the reactions being carried out at different temperatures and for different reaction times – *e.g.* the silylation with Et$_3$SiH and KO^{t}Bu (Scheme 52A) is carried out at 45 °C, whereas the ^{t}BuOO^{t}Bu experiment is carried out at the higher temperature of 135 °C (Scheme 52B). Also, it is not clear if the addition of ^{t}BuOO^{t}Bu to Et$_3$SiH and KO^{t}Bu has hindered the silylation reaction (Scheme 52C), or if the yields would be comparable had the reaction been left for the same length of time as in Scheme 52A (24 h vs. 14 h).



202

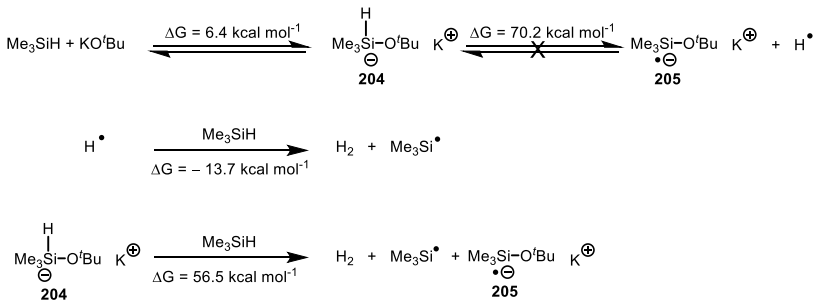
*Scheme 51 - Structure of the Detected TEMPO-SiEt$_3$ Adduct **202***



Scheme 52 - Effect of tert-Butoxyl Radicals on the Silylation

It was also proposed that pentavalent silicates may be formed from the combination of Et$_3$SiH and KO^{t}Bu. Isolation and characterisation of any pentavalent silicate species by NMR was not possible, but evidence for the formation of a new silicate species was obtained from infrared spectroscopy. By using ReactIR, a new Si-H stretch was visible at 2056 cm^{-1} adjacent to the Et$_3$Si-H stretch at 2100 cm^{-1}. This shift is consistent with an elongated, weaker Si-H bond as would be expected in the formation of a pentavalent silicate.[103,104] The formation of this new peak correlated with the product formation – silylation only begins once the new IR peak reached a steady state. This new peak remained visible throughout the course of the reaction. Furthermore, only bases which were able to carry out the silylation even in low yield (KO^{t}Bu, CsOH, KOEt etc.) showed the formation of a new peak in the absence of substrate, whereas bases that were not effective in the silylation (e.g. NaO^{t}Bu or LiO^{t}Bu) did not exhibit any new Si-H stretch in the infrared spectrum, suggesting a different interaction between these bases and the silane. This suggests

that it is highly likely that the formation of a pentavalent silicate is necessary for the silylation to occur.

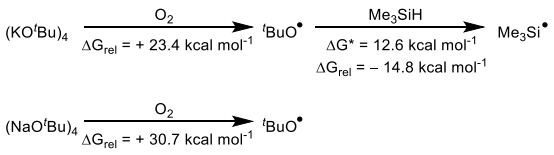


Scheme 53 - Computational Studies on the Formation of Trimethylsilyl Radicals. Trimethylsilane is used in calculations for simplicity.[c]

Attention was then focussed on the initiation pathway and the formation of silyl radicals in the reaction mixture. Formation of pentavalent silicate **204** was found to be possible, with a relative energy for this step of + 6.4 kcal, mol^{-1} (Scheme 53). Direct homolysis of the Si-H bond in the pentavalent silicate **204** to generate radical anion **205** and a hydrogen atom was considered unlikely due to the high energy of + 70.2 kcal, mol^{-1} calculated by computational analysis. It was proposed that if the hydrogen atom was generated then it could form hydrogen gas by abstraction of a hydrogen atom from Me_3SiH, which was energetically favoured at – 13.7 kcal, mol^{-1}. Direct combination of the pentavalent silicate **204** with trimethylsilane to form hydrogen gas, radical anion **205** and a trimethylsilyl radical was also found to be disfavoured computationally, with a relative energy of + 56.5 kcal, mol^{-1} for this process.

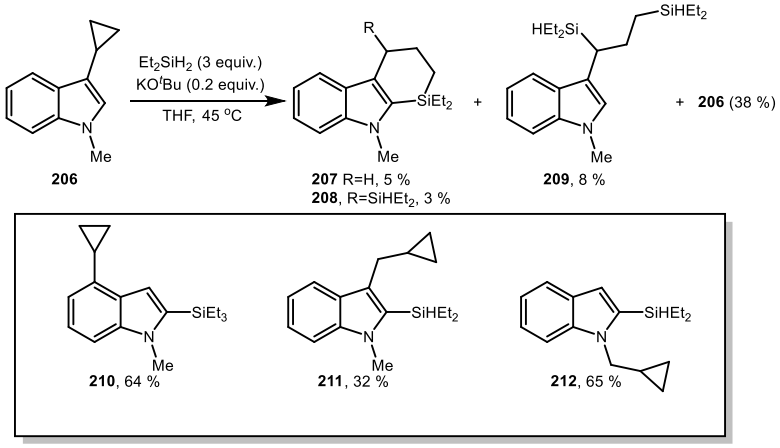
Since potassium *tert*-butoxide is known to exist as a tetramer $(KO^tBu)_4$ rather than a monomer,[105] and the dissociation of the tetramer to the trimer and the monomer was unfavourable computationally (ΔG = + 15.3 kcal, mol^{-1}), the tetramer was considered for future calculations.[c] It was proposed that the initiation step may involve electron transfer from potassium *tert*-butoxide tetramer to a trace amount of molecular oxygen in the system, allowing for formation of a *tert*-butoxyl radical (although they earlier ruled out the involvement of *tert*-butoxyl radicals by the addition of ^{t}BuOO^{t}Bu as a radical initiator) (Scheme 54). The barrier for this electron transfer process was found to be 23.4 kcal, mol^{-1} for KO^{t}Bu, and 30.7 kcal, mol^{-1} for the analogous sodium case, which the authors suggest may be a reason why NaO^{t}Bu is not effective for the silylation reactions. Once the *tert*-butoxyl radical is formed, it could abstract a hydrogen atom from the silane to afford the trimethylsilyl radical. Although this process is endergonic, only a trace amount of radicals may be needed to initiate the reaction.

[c] Geometry optimisation and energy calculations were performed with the B3LYP method using the 6-31G(d) basis set for all atoms. Single point energies were calculated at the M06-2X6 /6-311+G(d,p) level with solvent effects (solvent = THF) modelled using the CPCM solvation model.



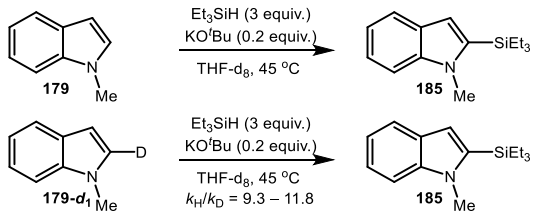
Scheme 54 - Generation of Trimethylsilyl Radicals from (MO^{t}Bu)$_4$ + Me$_3$SiH

A range of cyclopropyl-containing substrates was also prepared and used as radical probes. Only **206** was found to undergo ring-opening, supporting the hypothesis of a radical intermediate centred at C3 (Scheme 55). Compounds **207** and **208** are evidence of a silyl radical addition into C2, whereas compound **209** is evidence of a hydrogen atom addition into C2. Compounds **210**-**212** were formed in moderate yields without ring-opening of the cyclopropanes.

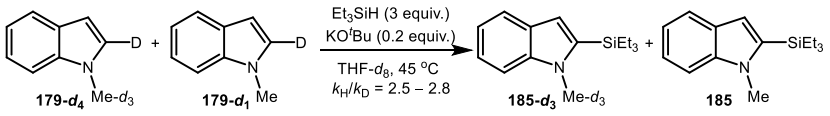


Scheme 55 - Cyclopropanes as Radical Probes

To determine if a β-C-H bond cleavage from a C3-centred radical was the rate-determining step for the silylation reactions, deuterated substrate **179-*d*$_1$** was reacted in parallel with the non-deuterated analogue **179** (Scheme 56). A significant kinetic isotope effect (KIE) was observed for this process (k_H/k_D = 9.3–11.8). Similarly, a mixture of substrates **179-*d*$_1$** and **179-*d*$_4$** were treated under the silylation conditions, and a KIE was observed (k_H/k_D=2.5–2.8, Scheme 57). These results indicate that the breaking of the C-H bond is observed in the rate-determining step. When Et$_3$SiH was replaced with Et$_3$SiD, a longer induction period for the reaction was observed, and a decrease in reaction rate was observed. This is consistent with the higher energy required to cleave the Si-D bond.

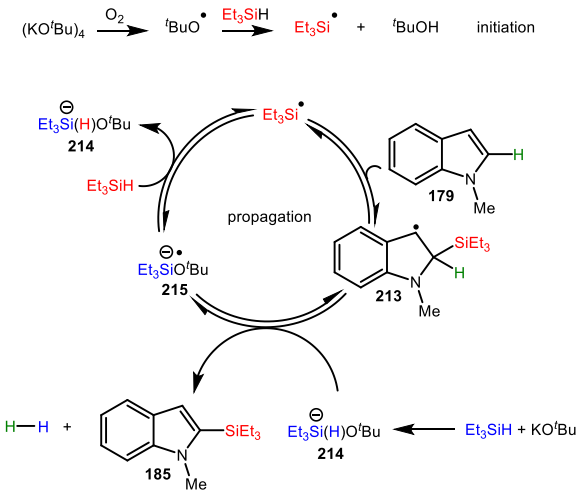


Scheme 56 - Kinetic Isotope Effect Studies



Scheme 57 - Further Kinetic Isotope Effect Studies

Based on all of the evidence above, and in collaboration with computational chemists, two possible radical mechanisms for the silylation were proposed - one based on a pentavalent silicate, and one based on tetrameric KO^{t}Bu. In the first of these proposals (Scheme 58), radical initiation firstly occurs upon reaction between (KO^{t}Bu)$_4$ and a trace amount of oxygen to form a *tert*-butoxyl radical, which abstracts a hydrogen atom from triethylsilane to form a triethylsilyl radical as discussed previously. This radical adds to the C2-position of the indole **179** to form benzylic radical **213**. Rearomatisation then occurs, with the expulsion of hydrogen gas originating from the hydrogen atom from C2 in **213** and the hydrogen atom on pentavalent silicate **214**, allowing for the formation of the silylated product **185** and radical anion **215**. This radical anion **215** can then abstract a hydrogen atom from triethylsilane to regenerate **214** and a triethylsilyl radical, which propagates the chain. The observed reversibility of the reaction can be explained by the addition of a hydrogen atom to the silylated product **185** to regenerate intermediate **213**, which could undergo β-scission of the C-Si bond rather than the C-H bond, resulting in desilylation and reformation of indole **179** and a triethylsilyl radical.

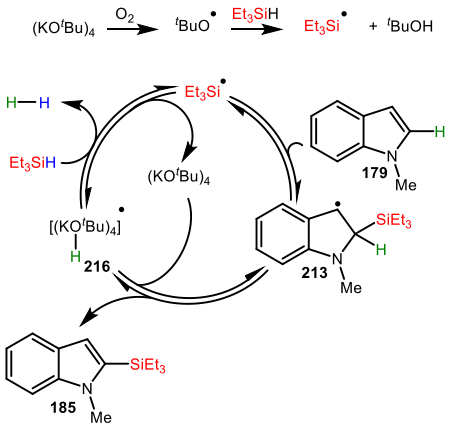


Scheme 58 - Proposed Radical Mechanism with a Pentavalent Silicate

Alternatively, (KO^{t}Bu)$_4$ could play a role in the chain process instead of radical anion **215**. Addition of the triethylsilyl radical to the 2-position of the indole would result in **213** as before (Scheme 59). This intermediate could then transfer a hydrogen atom to (KO^{t}Bu)$_4$, generating silylated product **185** and radical **216**. This radical can then react with another molecule of triethylsilane to produce hydrogen gas, and regenerate (KO^{t}Bu)$_4$ and the triethylsilyl radical which propagates the chain.

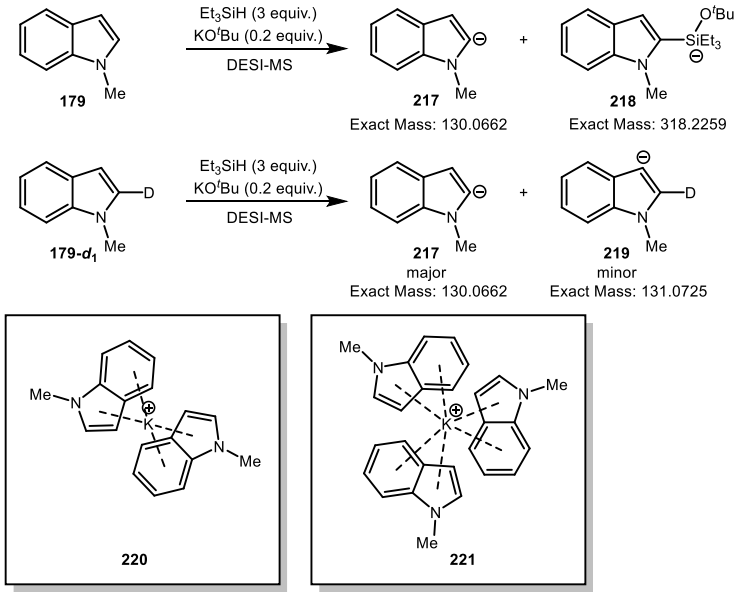
Grubbs, Zare *et al.* also published a paper where they considered non-radical mechanisms.[5] They used desorption ionisation mass spectrometry (DESI-MS) to detect reaction intermediates that form under the reaction conditions (Scheme 60). Upon treatment of **179** under the reaction

conditions, the anion of this species (*i.e.* **217**) was detected (*m/z* = 130.0663). By comparing the pK_a of the C2 and C3 proton (37 and 42 in THF respectively),[106] it would be expected that the C2 position would be selectively deprotonated by treatment with a strong base. This was verified as when substrate **179-*d*$_1$** was treated under the reaction conditions, abstraction of the deuterium occurred and anion **217** (*m/z* = 130.0663) was observed as the major product, and proton abstraction to form anion **219** (*m/z* = 131.0749) was observed as the minor product. This is in agreement with the C2-silylation being the major product from the silylation chemistry. However, the reported mass of **219** (131.0749) represents an 18 ppm error from the calculated mass (131.0725), so it is not clear if this is the correct identity of the species which has been detected. These species were not detected when KO^{t}Bu was replaced with either NaO^{t}Bu or LiO^{t}Bu, which is consistent with the silylation not occurring with these bases. Also detected in the reaction mixture was a signal with *m/z* = 318.2288, which was proposed to be **218**. This product did not form in a control reaction where 2-silylated product **185** was treated with KO^{t}Bu, suggesting that **218** is a reaction intermediate. Again, the reported mass of 318.2288 represents a 9 ppm error from the calculated mass of 318.2259, so it is unclear if this is the correct structure of the intermediate formed.



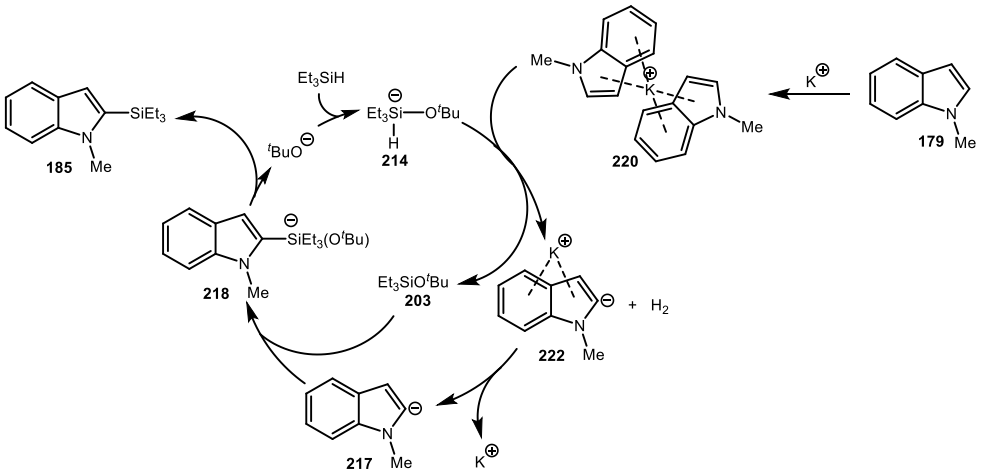
Scheme 59 - Proposed Radical Mechanism with (KO^{t}Bu)$_4$

Also detected by electrospray ionisation mass spectrometry (ESI-MS) was the presence of cation-π complexes **220** and **221** (Scheme 60). The corresponding lithium and sodium complexes were also detected when KO^{t}Bu was replaced with LiO^{t}Bu or NaO^{t}Bu. Further evidence for an anionic mechanism comes from the rate of reactivity for heterocycles (thiophene>furan>1-methylpyrrole) following the trend of p*K*a for the C2 proton of each of these heterocycles (33, 36, and 40 respectively). Conductivity measurements showed that the resistance of the mixture containing **179**/Et$_3$SiH/KO^{t}Bu/THF decreased over time, suggesting that the concentration of ions in solution was increasing. This shows that (KO^{t}Bu)$_4$ is able to dissociate over time, likely aided by the formation of cation-π complexes such as **220** or **221**.



Scheme 60 - Species Detected by DESI-MS and ESI-MS

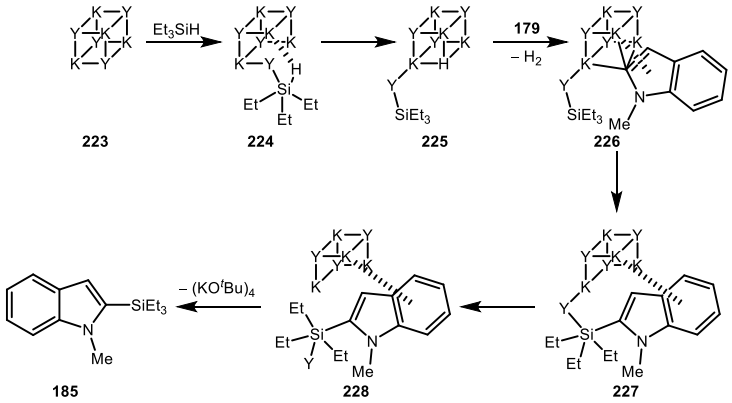
On the basis of these observations, and supported by computational chemists, an anionic mechanism was proposed for the silylation (Scheme 61). Formation of cation-π complex **220** from 1-methylindole **179** occurs, which is deprotonated by the hydride of pentavalent silicate **214** (formed by the combination of triethylsilane and a *tert*-butoxide anion) to form potassium complexed anion **222** and hydrogen gas. It is not clear if this hydride is first displaced from **214** to form a free hydride anion, or if it reacts as part of the complex. Dissociation of the potassium cation affords naked anion **217**, which could nucleophillically attack the silyl ether **203**, forming pentavalent silicate **218** (which was detected by ESI-MS). This pentavalent silicate **218** could then dissociate to silylated product **185** and regenerate the *tert*-butoxide anion to propagate the chain.



Scheme 61 - Anionic Mechanism of Silylation, (shown for C2 silylation)

Another mechanism was proposed that does not involve dissociation of the $(KO^tBu)_4$ tetramer (Scheme 62). This mechanism is similar to the anionic pathway, but with neutral intermediates. In this mechanism, $(KO^tBu)_4$ **223** reacts with Et_3SiH to form an Si-O bond in species **224**. This species **224** can then undergo heterolysis with formation of a hydride, which is incorporated into one corner of the cubic structure, forming intermediate **225**. This intermediate then co-ordinates

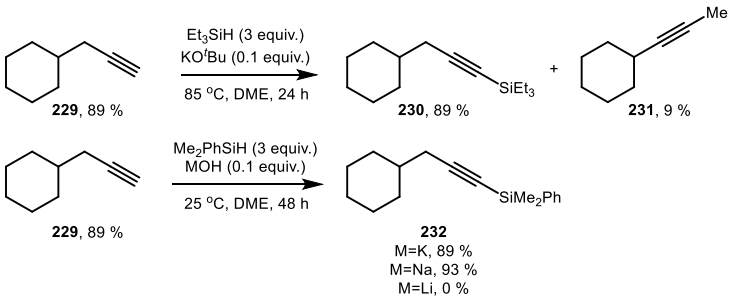
to the substrate **179** and deprotonates in the 2-position, forming **226** and hydrogen gas. An intramolecular C-Si bond formation then occurs, forming **227**, which undergoes pseudorotation to **228**, followed by dissociation to form the product **185**.



Scheme 62 - Neutral Mechanism for Silylation. Y=O^{t}Bu (omitted for clarity).

All of the mechanisms proposed by Grubbs and Stoltz for the silylation chemistry, as well as for the reductive cleavage or C-O and C-S bonds discussed previously, exemplify the large number of possible reaction pathways that the Et_3SiH/KO^tBu could be taking, and highlights the potential for further study into this system.

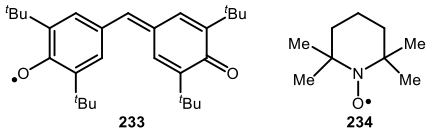
Grubbs and Stoltz also published the mild silylation of alkynes mediated by silanes and alkali metal hydroxides (NaOH and KOH, Scheme 63).[6] The Et_3SiH/KO^tBu system was found to be effective for the silylation of **229**, affording **230** in 89 % yield, alongside isomer **231**. However, upon changing to the milder bases NaOH or KOH, and lowering the temperature from 85 °C to 25 °C, the yield of **232** was found to be comparable to the KO^{t}Bu case, and no isomerised by-product was formed. No products were formed when LiOH was used as the base. This methodology was found to be applicable to a wide range of hydrosilanes and alkynes. The mechanism has not been extensively studied at this point, but some preliminary mechanistic studies were carried out.



Scheme 63 - R_3SiH/MOH Mediated Silylation of Alkynes (M=Na or K).

Firstly, addition of galvinoxyl **233** (10 mol %) or TEMPO **234** (300 mol %) inhibited the silylation, although no adducts were detected (Scheme 64). It is therefore unclear if the reaction is proceeding via a radical or an ionic mechanism. The sodium or potassium cation was found to be

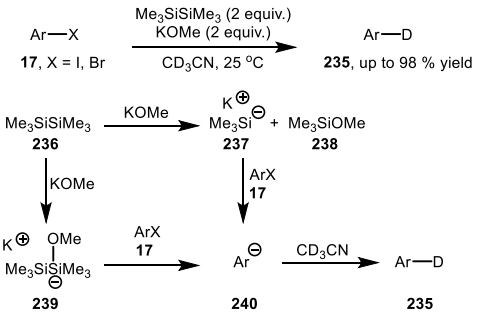
unimportant in the silylation, as no effect in yield was observed when 15-crown-5 or 18-crown-6 was added as sodium or potassium chelators in the silylation with Et_3SiH/NaOH or Et_3SiH/KO^{t}Bu respectively. The sodium ion was only found to be necessary when the silane used was $(EtO)_3SiH$, where no silylation occurred with the addition of 15-crown-5 (*cf.* 99 % silylation with no crown ether). However, in the case of $(EtO)_3SiH$/KOH, silylation does not occur with or without 18-crown-6 as a potassium chelator. It is unclear what role the sodium ion is playing in the silylation of alkynes with this particular silane, and further mechanistic studies are ongoing.



233 **234**

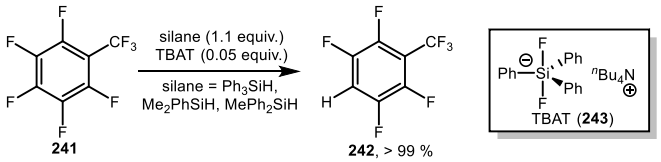
*Scheme 64 - Structure of Galvinoxyl Radical **233** and TEMPO Radical **234***

A further use of silane-alkoxide systems was reported by Liu *et al*., who carried out the reductive dehalogenation of aryl bromides and iodides **17** mediated by $Me_3SiSiMe_3$ and KOMe to form deuterated arenes **235** (Scheme 65).[107] The addition of TEMPO **234** had little effect on the yield of deuterated products. The mechanism was therefore proposed to proceed via the slow formation of either silyl anions **237** or via formation of a hypervalent silicate **239**, either of which abstracts the halide from the substrate **17** to form a carbanion **240**. This carbanion can then deprotonate CD_3CN to afford deuterated product **235**.

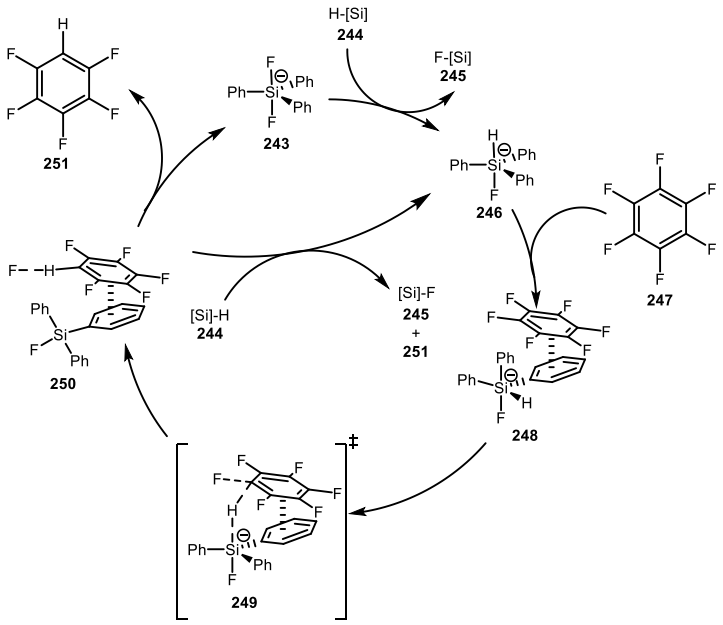


Scheme 65 - Deuterodehalogenation of Aryl Halides

Ogoshi *et al*. have reported the hydrodefluorination of polyfluoroarenes with hydrosilicates *e.g.* **241→242** (Scheme 66).[108] The authors propose that the combination of the silane and tetrabutylammonium difluorotriphenylsilicate (TBAT) **243** forms a highly reactive hypervalent silicate which delivers a hydride to the perfluoroarene via concerted nucleophilic aromatic substitution (cS_NAr – this will be discussed in Chapter 5, and was recently reviewed by Murphy and Chiba *et al.*).[109] Two alternative mechanisms were proposed in collaboration with computational chemists. The first mechanism (Scheme 67) involves generation of **246** from TBAT **243** and the hydrosilane **244**. This can then co-ordinate to the polyfluoroarene **247** via π-π stacking, affording **248**. The cS_NAr step can then occur with hydride from the silicate displacing a fluoride in the transition state **249**. The eliminated fluoride can then either be trapped intramolecularly by a fluorosilane or intermolecularly by a hydrosilane to regenerate **243** or **246** respectively.



Scheme 66 - Hydrodefluorination of Perfluoroarenes

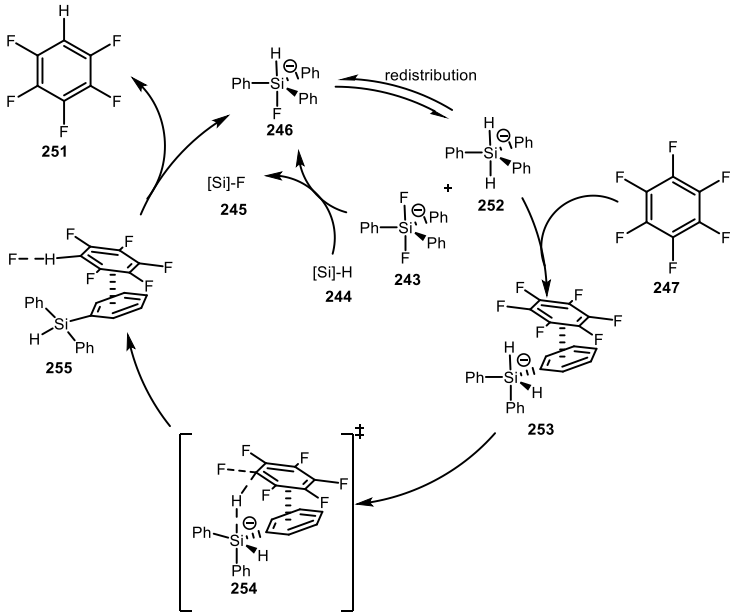


Scheme 67 - Hydrodefluorination of Perfluoroarenes A

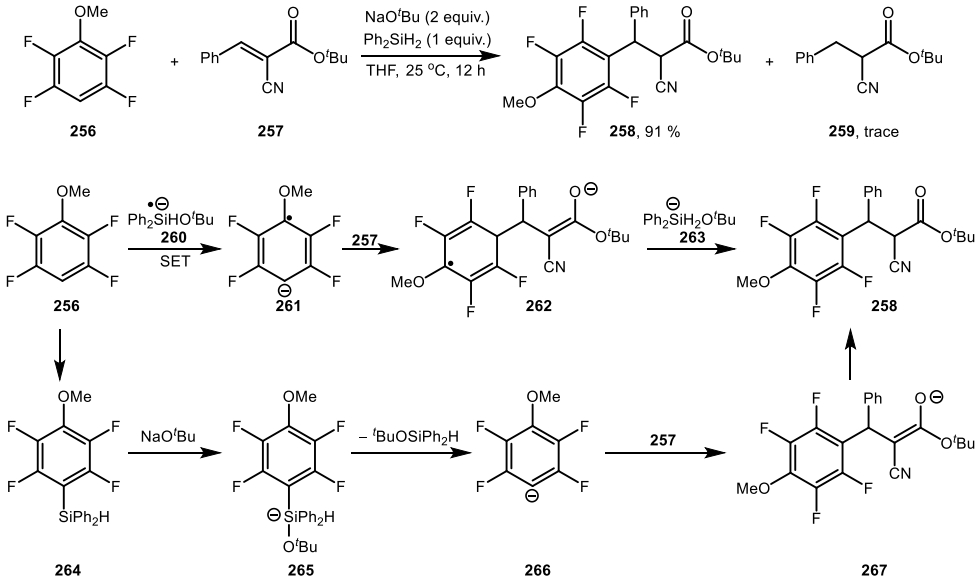
The alternative mechanism involves dihydrosilicate **252** as an intermediate, which can be formed by redistribution of **246** (Scheme 68). Hydride transfer from **252** via complex **253** displaces a fluoride from the polyfluoroarene via transition state **254**. The displaced fluoride can then be trapped by the hydrosilane to regenerate **246**. Computational data for the mechanisms in Scheme 67 and Scheme 68 show that the energy barriers are 79.4 kJ, mol^{-1} and 45.0 kJ, mol^{-1} respectively, indicating that the pathway in Scheme 68 is the more likely of the two. Meisenheimer intermediates were not detected for either pathway, indicative of cS_NAr reactivity.

Chang *et al*. have also shown the conjugate addition of perfluoroarenes to α,β–unsaturated carbonyl compounds using Ph_2SiH_2 and NaO^{t}Bu.[110] Perfluoroarene **256** was efficiently coupled to **257** using the silane-alkoxide system. It was found that the cation (Na>K>Li) and the anion (^{t}BuO>MeO) were important for the reactivity of the alkoxide. The reaction mixture was found to be EPR active, indicating that a radical species was present. Similarly, the addition of radical scavengers led to a decreased yield of **258**. In collaboration with computational chemists, they were able to propose a series of mechanisms. Firstly, they proposed that electron transfer to the perfluoroarene from the silane-alkoxide mixture could occur (likely from radical anion **260** – see results and discussion of this thesis for the formation of this species) to form radical anion **261**, which could then undergo conjugate addition to **257** followed by loss of H_2 (mediated by the pentavalent silicate **263**) and protonation upon work-up to form product **258**. Alternatively, a

radical silylation of **256** could occur, similar to the Grubbs and Stoltz chemistry previously discussed, forming **264**. This species could then desilylate under the excess NaO^{t}Bu used in the reaction to form anion **266**, which could undergo conjugate addition to **257** and form **267** and ultimately the product **258** after protonation upon work-up.



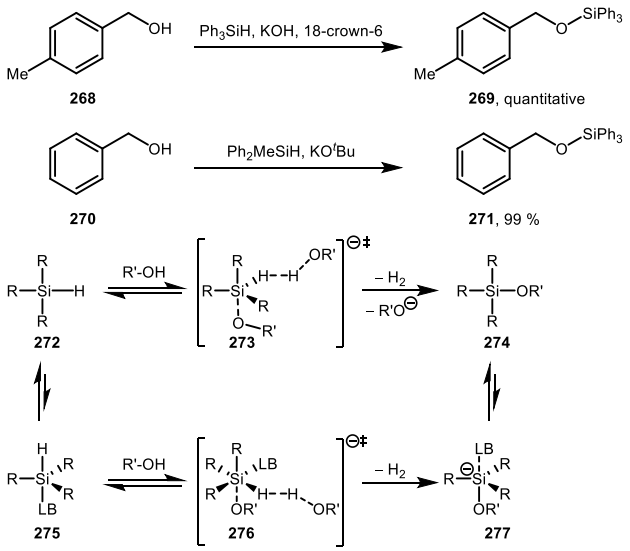
Scheme 68 - Hydrodefluorination of Perfluoroarenes B



Scheme 69 - Conjugate Addition of Perfluoroarenes to α,β-Unsaturated Carbonyl Compounds

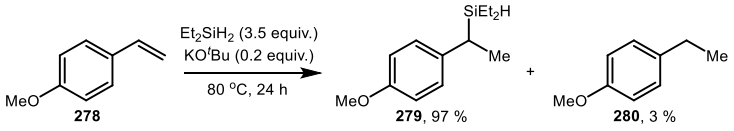
Oestreich *et al*., Bideau *et al*., and Grubbs *et al.* have reported the dehydrogenative coupling of hydrosilanes and alcohols mediated by oxide bases (Scheme 70).[111–113] The mechanism likely involves complexation of either the alcohol directly to the silane **272** to form **274** (via loss of hydrogen gas through transition state **273**), or via complexation of the Lewis base (LB = NaOH, KOH or KO^{t}Bu) firstly to form **275**, followed by complexation of the alcohol with loss of hydrogen

gas via transition state **276**, leading to **277** which can undergo dissociation of the Lewis base to form the product **274**.



Scheme 70 - Dehydrogenative Coupling of Alcohols and Hydrosilanes

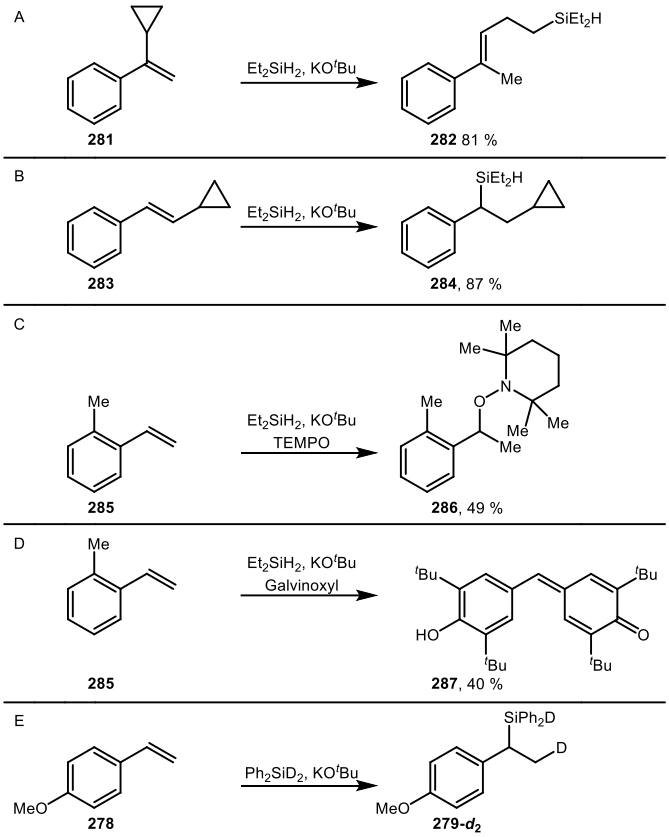
Jeon *et al.* have recently reported that the combination of dihydrosilanes and potassium bases was able to carry out the hydrosilylation of styrenes by hydrogen atom transfer (HAT).[114] They reported that the counterion is important in this chemistry, as different results are seen for potassium bases relative to sodium or lithium bases. When styrene **278** was treated with Et_2SiH_2 and KO^{t}Bu, hydrosilylation product **279** was formed in 97 % yield, along with reduced product **280** in 3 % yield (Scheme 71). High yields of **279** were also observed for other potassium bases, such as KH (87 %), KOH (93 %), KOEt (91 %), or KOTMS (95 %). However, comparison of KOH (93 %) with LiOH (0 %) or NaOH (2 %) resulted in significantly decreased yields of hydrosilylation product **279** being observed in the sodium and lithium cases, with starting material **278** being recovered (100 % and 95 % for LiOH and NaOH respectively). When 18-crown-6 was added as a potassium chelator, polymerisation was found to occur as the sole outcome from this reaction. It was therefore proposed that the metal counterion is key to affording the reactivity seen through cation-π interactions.



Scheme 71 - Hydrosilylation of Styrenes via HAT

The use of radical probes **281** (Scheme 72A) and **283** (Scheme 72B) revealed that ring-opening of the cyclopropane occurs only for substrate **281**, affording ring-opened product **282**. Substrate **283** does not afford any ring-opened products under the reaction conditions, suggesting that a benzylic radical is formed regioselectively under the reaction conditions. The addition of TEMPO to the reaction mixture also led to the isolation of **286** in 49 % yield (Scheme 72C), providing further evidence for the formation of a benzylic radical. Addition of galvinoxyl as a radical trap also afforded the trapping of a hydrogen atom by isolation of **287**, providing evidence of hydrogen

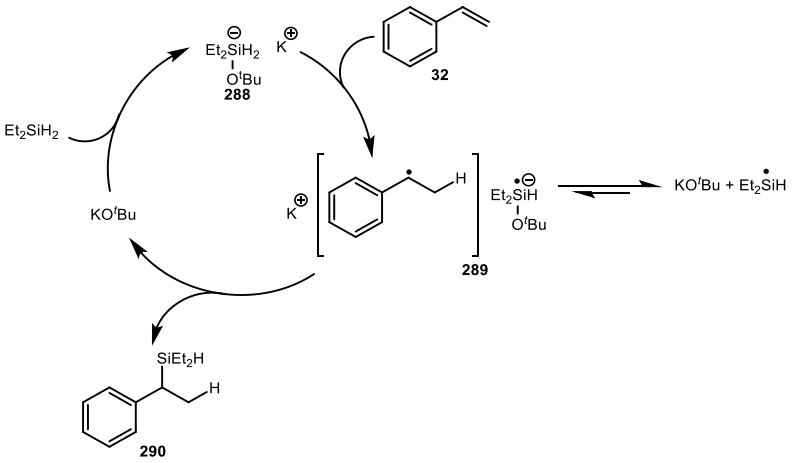
atom transfer (Scheme 72D). Furthermore, the comparative studies with Ph_2SiH_2 and Ph_2SiD_2 showed a KIE of ~2.3, showing that Si-H bond cleavage is involved in the rate-determining step of the reaction. Deuterium atom transfer was observed to occur regioselectively to **278** to form only product **279-d_2** (Scheme 72E).



Scheme 72 - Mechanistic Studies for the Hydrosilylation of Styrenes

This evidence led to a mechanistic proposal (Scheme 73). KO^{t}Bu and Et_2SiH_2 combine to form pentavalent silicate **288**, which can undergo hydrogen atom transfer to styrene **32** to form species **289**, which is described as an intimate radical-radical anion pair. This allows for the slow release of silyl radicals and KO^{t}Bu, and therefore the species can then undergo radical-radical combination to afford silylated product **290**. The liberated KO^{t}Bu can then combine with another molecule of silane to continue the chain mechanism.

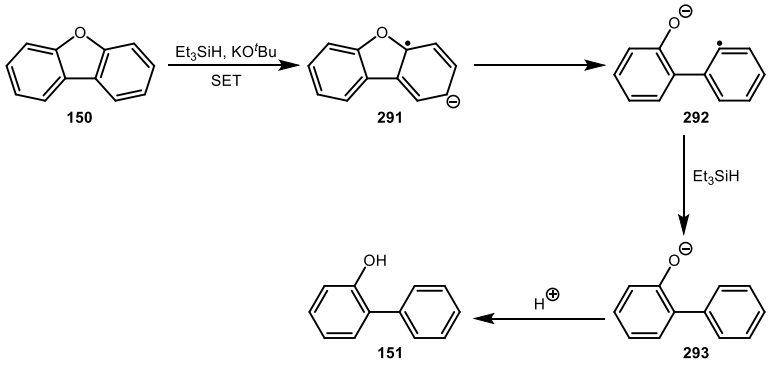
In conclusion, a number of synthetically useful transformations have been reported to be mediated by the simple combination of hydrosilanes and alkoxide bases. A large number of mechanistic studies have been carried out on this system, with pathways involving silyl radicals, hydrogen atom transfer and hydride transfer being proposed. It is likely that these transformations proceed via the formation of pentavalent silicates, but further studies are required to determine the mechanistic possibilities of this combination of reagents.



Scheme 73 - Mechanism for the Hydrosilylation of Styrenes

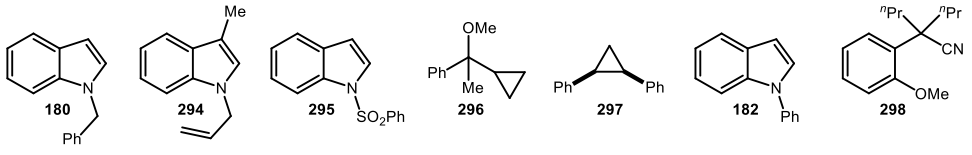
2: Project Overview

Recent interest in the literature has focussed on the combination of small molecules with potassium *tert*-butoxide as electron donors. As there is some literature precedence for single electron transfer chemistry from pentavalent silicates,[115,116] we wondered if the combination of triethylsilane with potassium *tert*-butoxide, as reported by Grubbs and Stoltz, might be capable of forming *in situ* electron donors. Although pentavalent silicates were discussed by Grubbs and Stoltz, SET reactivity was not considered, and so the first aim was to determine if it was possible to show SET reactivity within the system. The second aim was to find out what novel transformations might be carried out by the Et_3SiH/KO^tBu system. Particularly, the major product obtained from the reductive cleavage of C-O bonds by Grubbs appears as though it could be a product from electron transfer chemistry (**150**→**151**).[1]



Scheme 74 - Proposed Reductive Cleavage of C-O Bonds via SET

N-benzylindoles have been shown in the literature to undergo reductive cleavage under single electron transfer conditions to afford the parent indoles in good yields.[117,118] Therefore, the first step was to treat *N*-benzylindoles under the Et_3SiH/KO^tBu system to determine if debenzylation would occur which might be an indication of single electron transfer reactivity (Scheme 75). Other substrates which have been shown in the literature to undergo reduction with SET conditions were then also treated under the Et_3SiH/KO^tBu system to determine how powerful any electron donor that forms would be (**294**-**297**). Following on from this work, results obtained during the course of this thesis led to the discovery that *N*-phenylindole **182** and nitriles such as **298** may lead to novel chemistry, and so the final aims were to determine how these substrates behaved under the Et_3SiH/KO^tBu system and to determine the mechanism of any novel transformations which would occur.



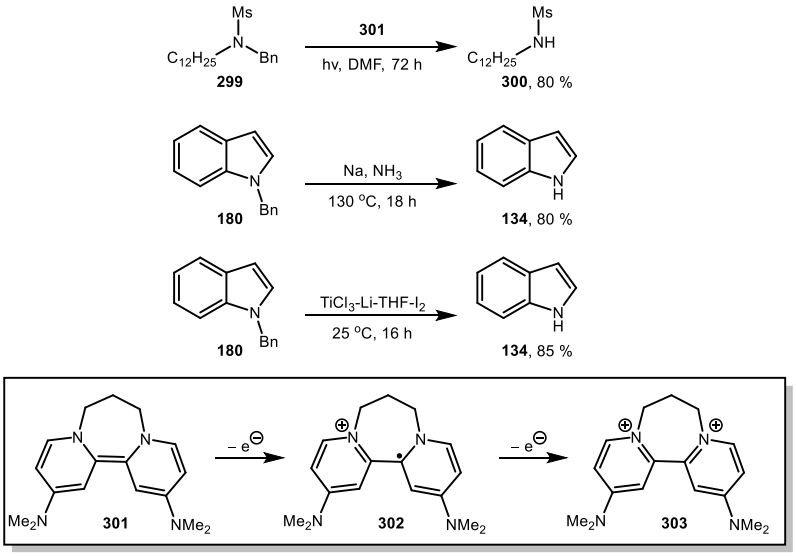
Scheme 75 – Substrates to be Treated with Et_3SiH/KO^tBu

3: Single Electron Transfer Reactions Mediated by Et_3SiH/KO^tBu

3.1: Introduction

As reviewed in Chapter 1, recent interest within the literature has focussed on the combination of small molecules with alkoxide bases (usually KO^tBu) to form *in situ* electron donors.[9,31,33,46] As the cleavage of Grubbs' diaryl ethers[1] and diaryl thioethers[7] could be products from electron transfer chemistry, it was proposed that the combination of Et_3SiH and KO^tBu may lead to the formation of *in situ* electron donors. The aim of this project was to test whether single electron transfer from the Et_3SiH/KO^tBu system could occur, and if so, to gauge the reducing power of the electron donor which forms.

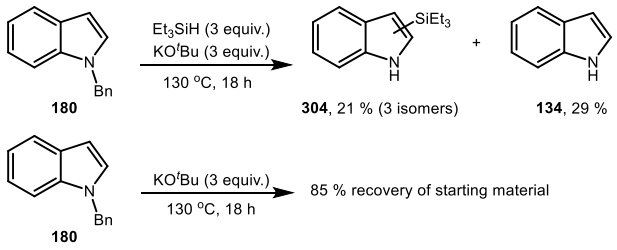
Debenzylation of amines has been shown to occur under electron transfer conditions within the Murphy group by debenzylation of **299** with electron donor **301**, affording the parent amine **300** in 80 % yield (Scheme 76).[119] Electron donor **301** has been shown to have an oxidation potential of −1.13 V and works by donating two electrons to become **303**.[120] There is an aromatic driving force for the oxidation of this compound. It has also been previously shown in the literature that *N*-benzylindoles *e.g.* **180** can undergo cleavage to the parent indole **134** in good yields under single electron transfer using Birch conditions,[117] or from low-valent titanium species.[118]



Scheme 76 - Previously Reported Debenzylations of Amines

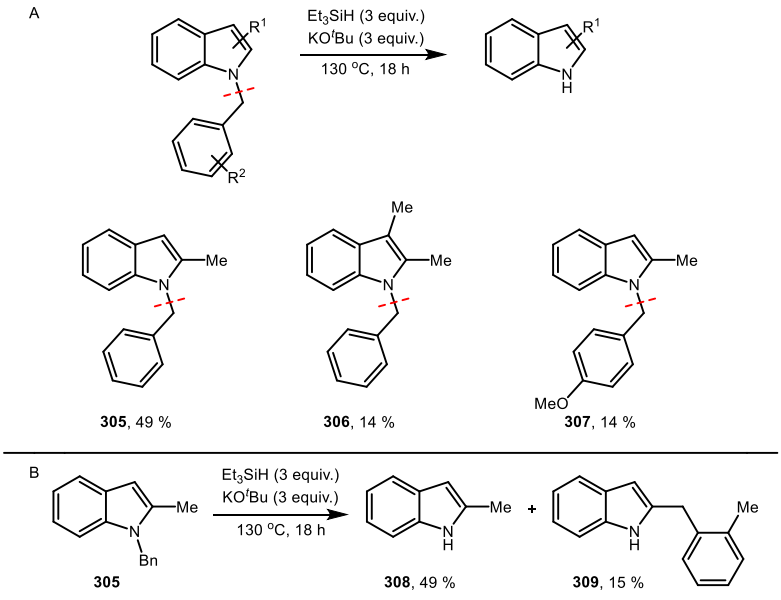
3.2: Results and Discussion

As a starting point, *N*-benzylindole **180** was prepared and treated under Et_3SiH/KO^tBu conditions. Debenzylation was seen in this case to afford **134** in 29 % yield, alongside a complex mixture which included three isomers of silylated indole **304** (Scheme 77). Upon treatment of **180** with KO^tBu alone, no reaction took place and starting material **180** was recovered in 85 % yield.



*Scheme 77 - Debenzylation of N-benzylindole **180** with Et_3SiH/KO^tBu*

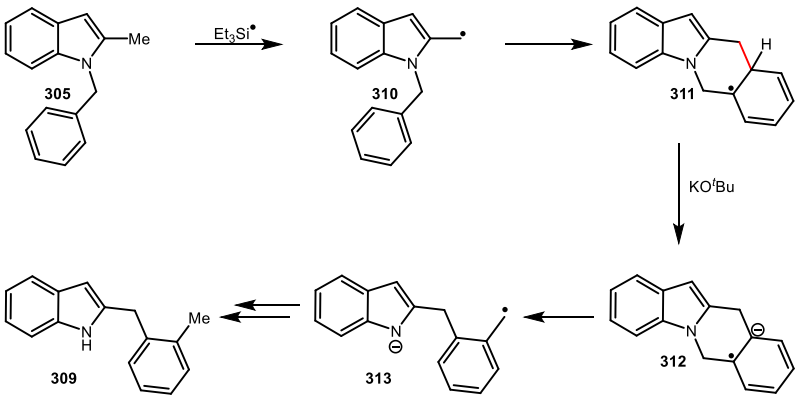
Due to the detection of small amounts of a number of isomers of silylated compounds (**304**) from the reaction of *N*-benzylindole **180** under these conditions, a range of substrates with substituents in the 2-position was prepared and tested under the reaction conditions (**305**-**307**). Debenzylation was again observed, albeit still in low yield (Scheme 78A). The complex nature of these reactions is exemplified by the isolation of rearranged compound **309** (Scheme 78B), which is proposed to occur via the mechanism shown in Scheme 79 (or a closely related mechanism). Firstly, hydrogen atom abstraction of an α-hydrogen atom by a triethylsilyl radical occurs, forming **310**. This radical can then undergo a 6-*endo*-trig cyclisation to **311**, followed by deprotonation to **312**. Cleavage of the C-N bond to **313**, followed by abstraction of a hydrogen atom and a proton would lead to rearranged product **309**. Substrates **305**-**307** were all treated in side-by-side reactions with the Et_3SiH/KO^tBu system, and with KO^tBu alone. No reaction was observed for any of these substrates in the absence of the silane, with starting material being recovered in high yields in all cases.



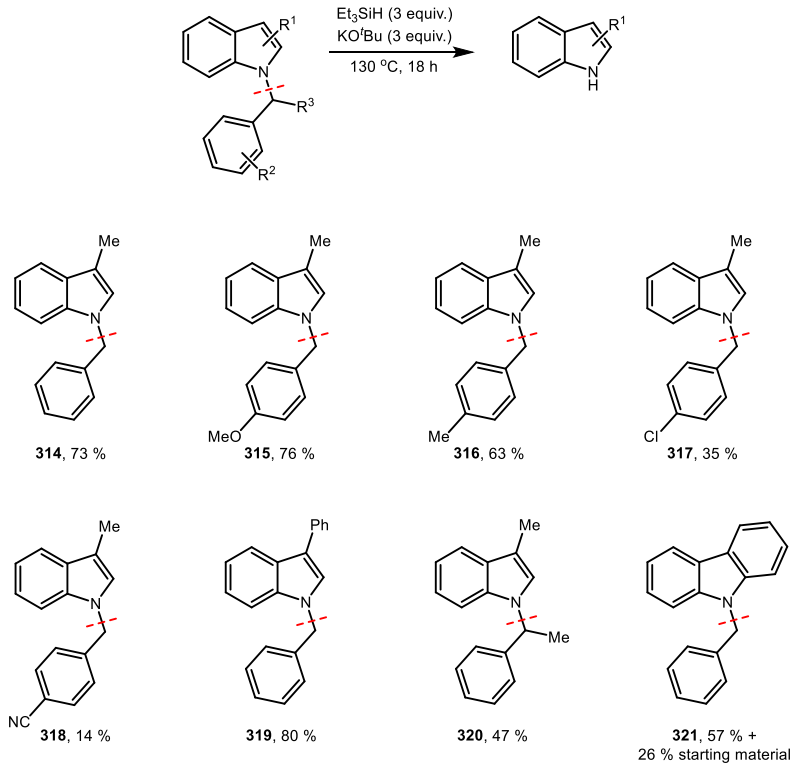
Scheme 78 - Debenzylation of 2-Substituted N-Benzylindoles using Et_3SiH/KO^tBu. Yields refer only to the indole portion of the molecule, with compounds derived from the benzyl portion being too volatile to isolate.

To try to prevent either rearrangement or silylation from occurring, a range of 3-substituted *N*-benzylindoles were prepared and treated under the reaction conditions (**314**-**321**, Scheme 80). The idea was that the 3-substituted indoles should not undergo a rearrangement similar to that in Scheme 79, and the substituents may also provide sufficient steric hindrance to prevent the silylation reaction at the 2-position. This was indeed the case, with generally much greater yields

of debenzylated indoles being isolated from substrates **314**-**321**. Substrate **317** likely has a decreased yield relative to the other 3-substituted indoles due to the formation of benzyne by-products from this reaction. Similarly, the electron-deficient substrate **318** may have a largely decreased yield due to alteration of the site of the electron transfer (see later on for details on the site of electron transfer).



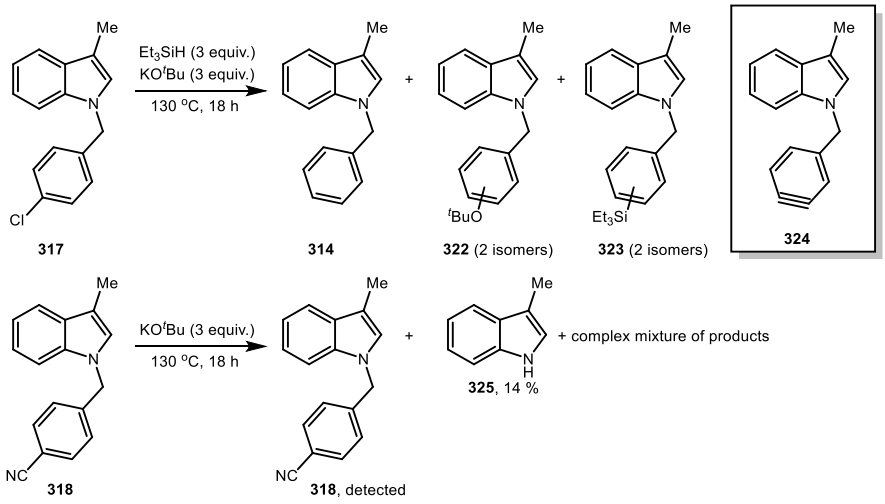
*Scheme 79 - Proposed Mechanism for the Rearrangement of **305** to **309***



Scheme 80 - Debenzylation of 3-Substituted N-Benzylindoles using Et_3SiH/KO^tBu. Yields refer only to the indole portion of the molecule, with compounds derived from the benzyl portion being too volatile to isolate.

All of the substrates in Scheme 80 were unreactive when treated with KO^tBu alone (*i.e.* in the absence of silane) apart from **317** and **318**. When **317** was treated with KO^tBu alone, an inseparable mixture of starting material **317**, **322** and **323** was observed (Scheme 81). The isomers of compound **322** are consistent with the trapping of benzyne **324** with *tert*-butoxide anions. Importantly, no debenzylation was observed, showing that the silane is necessary for the C-N bond cleavage to occur in this case. However, when **318** was treated with KO^tBu alone,

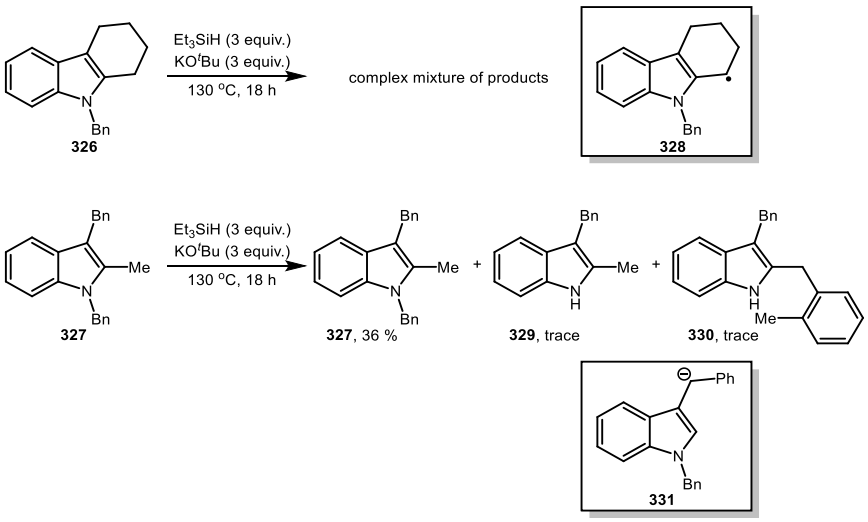
debenzylation was observed in 9 % yield, along with 9 % remaining starting material. No other products could be identified from the complex reaction mixture. It is unclear exactly how debenzylation has occurred in the case of **318** with KO^{t}Bu alone.



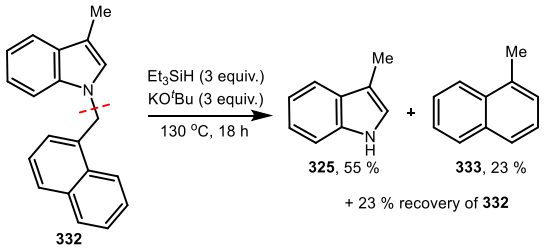
*Scheme 81 - Treatment of **317** and **318** with KO^{t}Bu alone*

Some indole substrates which were less successful in the debenzylation chemistry were **326** and **327** (Scheme 82). It is likely that **326** could behave in a similar way to the other 2-substituted indoles previously discussed, where hydrogen atom abstraction in the 2-position could occur to form **328**, and this could lead to other products arising from cyclisation onto the benzyl group. Substrate **326** was unreactive when treated with KO^{t}Bu alone, indicating that the complex nature of the reaction is not due to heating with the strong base. Similarly, **327** also produced a complex mixture of products when treated under the Et$_3$SiH/KO^{t}Bu conditions, with a trace amount of debenzylated **329** and rearranged **330** detected alongside 36 % of starting material **327**. If deprotonation occurred in the benzylic position to afford anion **331**, the indole might become too electron-rich to receive another electron from the Et$_3$SiH/KO^{t}Bu system and the electron transfer may occur to the benzyl portion of the molecule instead (see later for justification of the site of electron transfer). Therefore, different reactivity may be observed. Alternatively, hydrogen atom abstraction from the 2-position may occur as before, leading to other complex products. Substrate **327** also does not react when treated with KO^{t}Bu alone.

From all of the substrates tested so far, the benzyl portion of the fragmented molecule has proved too volatile to isolate under the standard work-up procedure. To determine the fate of the benzyl portion of the molecule, substrate **332** was tested under the reaction conditions, and indeed 1-methylnaphthalene **333** was isolated albeit in low yield (23 %), along with **325** in 55 % yield and 23 % recovery of **332** (Scheme 83).

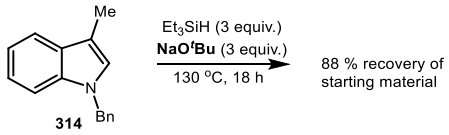


*Scheme 82 - Treatment of Substrates **326** and **327** under the Et_3SiH/KO^tBu System*



*Scheme 83 - Isolation of 1-Methylnaphthalene **333** from Substrate **332***

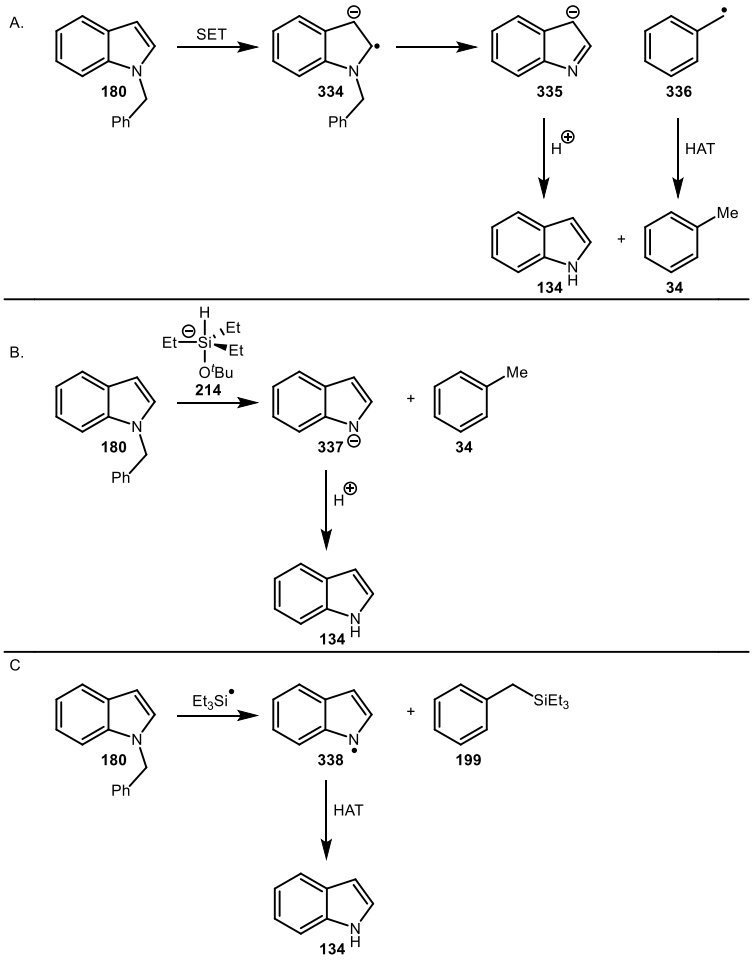
An interesting observation from this chemistry is that potassium *tert*-butoxide appears to be necessary for the debenzylation to occur. When this was replaced with sodium *tert*-butoxide, no debenzylation took place and the starting material **314** was recovered in 88 % yield (Scheme 84). This is consistent with both the work of Grubbs and Stoltz,[1–5,7] and also with many other electron transfer reactions in the literature, as reviewed in Chapter 1, where potassium *tert*-butoxide is the necessary base in the formation of *in situ* electron donors. Of course, there are examples in the literature where electron donors are proposed to form *in situ* using sodium *tert*-butoxide,[23,25] but these are much less frequent. The reason for this is unclear, but work is on-going within the group to determine the reason for this interesting cation effect.



*Scheme 84 - Treatment of **314** with Et_3SiH/NaO^tBu*

At this time, three possible mechanistic pathways appear possible. The first of these involves single electron transfer, whereby an electron donor could form *in situ* and donate an electron to the *N*-benzylindole **180** (Scheme 85A). The resulting radical anion **334** could then fragment to yield anion **335** (which would protonate upon work-up to afford **134**), and tolyl radical **336**, which could become toluene **34** after hydrogen atom abstraction. Alternatively, the hydride transfer capability of pentavalent silicates has previously been demonstrated.[115,121–125] Therefore, it is

logical that a pentavalent silicate such as **214** could undergo hydride transfer to the benzylic position of **180** (Scheme 85B), affording anion **337** and toluene **34** via an S_N2 process. Anion **337** could protonate upon work-up to afford indole **134**. The final mechanistic possibility that presents itself is an S_H2 displacement of indolyl radical **338** by a triethylsilyl radical (Scheme 85C). Radical **338** could then abstract a hydrogen atom from a suitable source (likely Et_3SiH) to afford indole **134**. This mechanism is unlikely, as S_H2 reactions on tetrahedral carbons are rare, and it is likely that the product from silylation of the benzyl portion of the molecule would be detected by NMR spectroscopy or GC-MS of the crude reaction mixture (*e.g.* compound **199** has a reported boiling point of 267-269 °C at atmospheric pressure, and would be unlikely to evaporate upon concentration of the reaction mixture after work-up).[126]

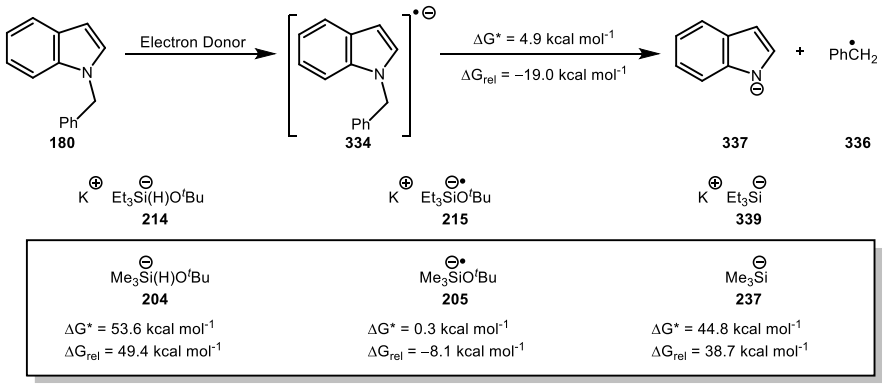


*Scheme 85 - Possible Mechanisms for the Debenzylation of N-benzylindole **180***

To aid the understanding of the mechanism of the debenzylation reactions, collaboration with computational chemists was required.[d] The three different mechanisms were computationally modelled. Firstly, electron transfer was modelled using three potential electron donors that may form under the reaction conditions (Scheme 86). Two of these (**214** and **215**) have already been

[d] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modelled using the CPCM solvation model.

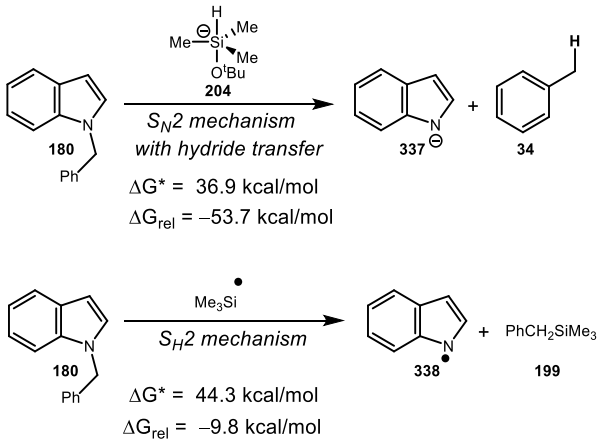
proposed as intermediates (although not as electron donors) by Grubbs, whereas the third (**339**) was added by our group. The radical anion **215** would appear to be an excellent candidate electron donor due to the highly reducing power of radical anions.[30] Pentavalent silicate **214** would also be an excellent candidate electron donor due to the literature precedents of single electron transfer from pentavalent silicates.[115,116] It has also been shown that the combination of hydrosilanes and base can lead to the formation of trivalent silyl anions.[127] Triethylsilyl anion **339** was therefore also considered as a potential electron donor. Calculations found that if the radical anion **334** formed, then the fragmentation to indole anion **337** and tolyl radical **336** has a surmountable barrier, with more stabilised products relative to the starting materials. Modelling each of the three potential electron donors in turn found that only **215** (modelled as **205** for simplicity) could act as an electron donor under the conditions of the reaction, and that the barrier for the electron transfer was 0.3 kcal, mol^{-1}, *cf.* 53.6 and 44.8 kcal, mol^{-1} for species **214** and **339** (modelled as **204** and **237** respectively). Therefore, if SET is occurring, then the most likely candidate for the electron donor species is radical anion **215**. Once the electron transfer occurs, fragmentation of radical anion **334** to **336** and **337** is facile, with an energy barrier of 4.9 kcal, mol^{-1}.



Scheme 86 - Computational Modelling of Electron Donor Candidates.[d] Trimethylsilyl groups replace triethylsilyl groups in calculations for simplicity. ΔG^* represents the energy barrier, whereas ΔG_{rel} represents the change in energy relative to the starting materials.

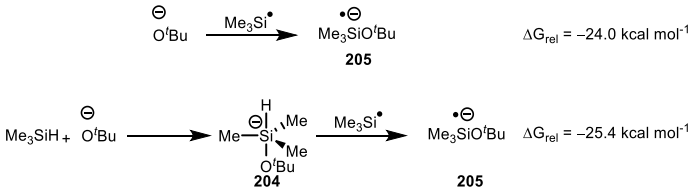
The remaining two mechanisms were also modelled computationally (Scheme 87).[ed] The S_N2 reaction (where a hydride delivery from **204** to the benzylic position of **180** occurs) was found to have an insurmountable energy barrier at 36.9 kcal, mol^{-1}. Similarly, the S_H2 mechanism (with attack of a trimethylsilyl radical onto the benzylic carbon and homolysis of the C-N bond) was found to have a barrier of 44.3 kcal, mol^{-1}, which is again insurmountable under the reaction conditions. Therefore, it can be concluded that SET was the most likely mechanism of those computed for the debenzylation of *N*-benzylindoles.

[d] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modelled using the CPCM solvation model.



Scheme 87 - S_N2 and S_H2 Mechanisms. Trimethylsilyl groups replace triethylsilyl groups in calculations for simplicity. ΔG^* represents the energy barrier, whereas ΔG_{rel} represents the change in relative energy.[d]

The next calculations considered how electron donor **205** may form. From the previous results from Grubbs and Stoltz, it was shown that triethylsilyl radicals are formed when Et_3SiH and KO^{t}Bu are combined.[1,2] They confirmed the presence of triethylsilyl radicals by the addition of TEMPO to the reaction, and isolated the TEMPO-$SiEt_3$ adduct. Therefore, triethylsilyl radicals may be involved in the formation of the electron donor **205**. Two methods of formation of **205** that are possible by computational chemistry are the direct combination of a *tert*-butoxide anion with a trimethylsilyl radical (ΔG_{rel} = –24.0 kcal, mol^{-1}), or firstly formation of pentacoordinate silicate **204**, before hydrogen atom abstraction with a trimethylsilyl radical occurs to form electron donor **205** (ΔG_{rel} = –25.4 kcal, mol^{-1}).[d]



*Scheme 88 - Methods of Forming Electron Donor **205**.[d] Trimethylsilyl groups replace triethylsilyl groups in calculations for simplicity.*

Computational modelling of the site of electron transfer was also conducted.[d] It was found that the LUMO of **314**, and the SOMO of radical anion **340** were located on the electron-rich indole portion of the molecule, and not on the less electron-rich benzyl group as might be expected (Figure 1). This is explained by the unpaired electron having greater delocalisation in the bicyclic indole portion of the molecule, and therefore the resulting radical anion being more stabilised.

[d] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modelled using the CPCM solvation model.

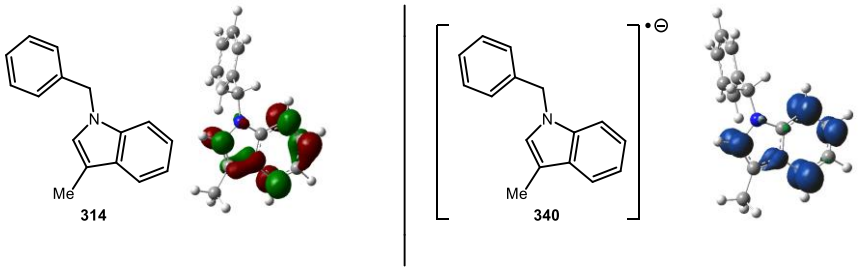


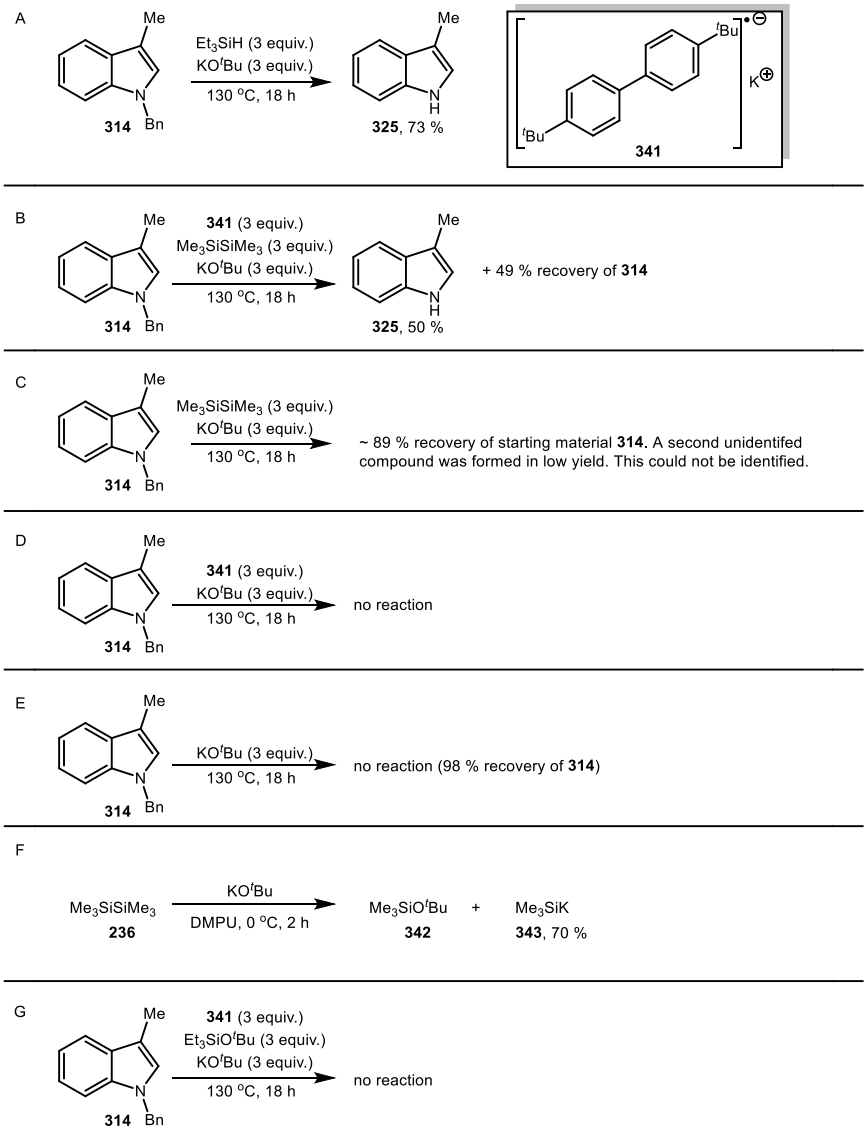
*Figure 1 - Computational Modelling of the LUMO of **314** (left) and the SOMO of **340** (right).*[d]

To add further experimental evidence to the hypothesis that electron transfer was occurring in these reactions, substrate **314** was treated with an authentic electron donor – namely **341** (Scheme 89). It was found that in the presence of a silyl source that is not able to act as a hydride donor (hexamethyldisilane) and the radical anion **341**, the same reductive cleavage of the benzyl group occurred (Scheme 89B), albeit in lower yield that with the Et_3SiH/KO^tBu conditions (Scheme 89A). In the absence of **341**, no debenzylation was detected, and the major component of the crude reaction mixture was recovered starting material **314** (Scheme 89C). A small amount of a second product was detected with ^1H NMR signals that closely mirrored the signals of **314**. However, no separation of this second component could be achieved by TLC, and GC-MS showed only a single peak which corresponded to the starting material **314**. Therefore, it is not clear what this second component may be. In the absence of the disilane, no reaction occurred and only starting material **314** and 4,4'-di-*tert*-butylbiphenyl were detected by crude NMR, TLC and GC-MS (Scheme 89D). As previously mentioned, no reaction occurs with KO^tBu alone, with starting material being recovered in 98 % yield (Scheme 89E). Previous research has shown that silicon-silicon bonds can undergo cleavage upon treatment with nucleophiles to generate silyl anions (Scheme 89F).[128] However, it is not known how the silicon-silicon bond might react under electron transfer conditions. If cleavage of this bond occurred to produce a silyl anion and a silyl radical, then we envisage that the generated trimethylsilyl radical could then combine with the *tert*-butoxide anion to generate the methyl analogue of our powerful electron donor *i.e.* **205**, which can then carry out the debenzylation chemistry as before. Interestingly, the use of Et_3SiO^tBu as the silyl source (Scheme 89G) did not afford any debenzylation products. This is likely due to the electron donor **205** being calculated as being more reducing (E_{ox} = – 3.74 V vs. SCE) than potassium metal.[d] This suggests that potassium metal (or **341**) is not capable of reducing the silyl ether Et_3SiO^tBu and generating the powerful electron donor.

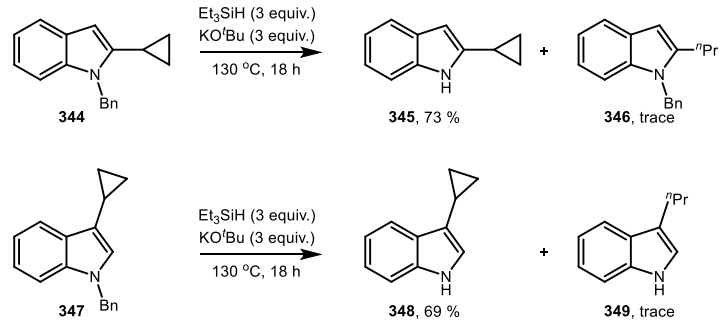
Experimental evidence of a radical mechanism may also be provided by the ring-opening of the cyclopropyl-containing substrates **344** and **347** as radical probes (Scheme 90). Preparation and treatment of these substrates under the reaction conditions provided predominantly the

[d] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modelled using the CPCM solvation model.

ring-closed species **345** and **348** in 73 % and 69 % yields respectively, alongside trace amounts (<1 mg) of ring-opened products **346** and **349**. Albeit in trace amounts, the detection of these ring-opened products may be evidence of a radical process, where there is radical character in both the 2- and 3-positions of the indole.

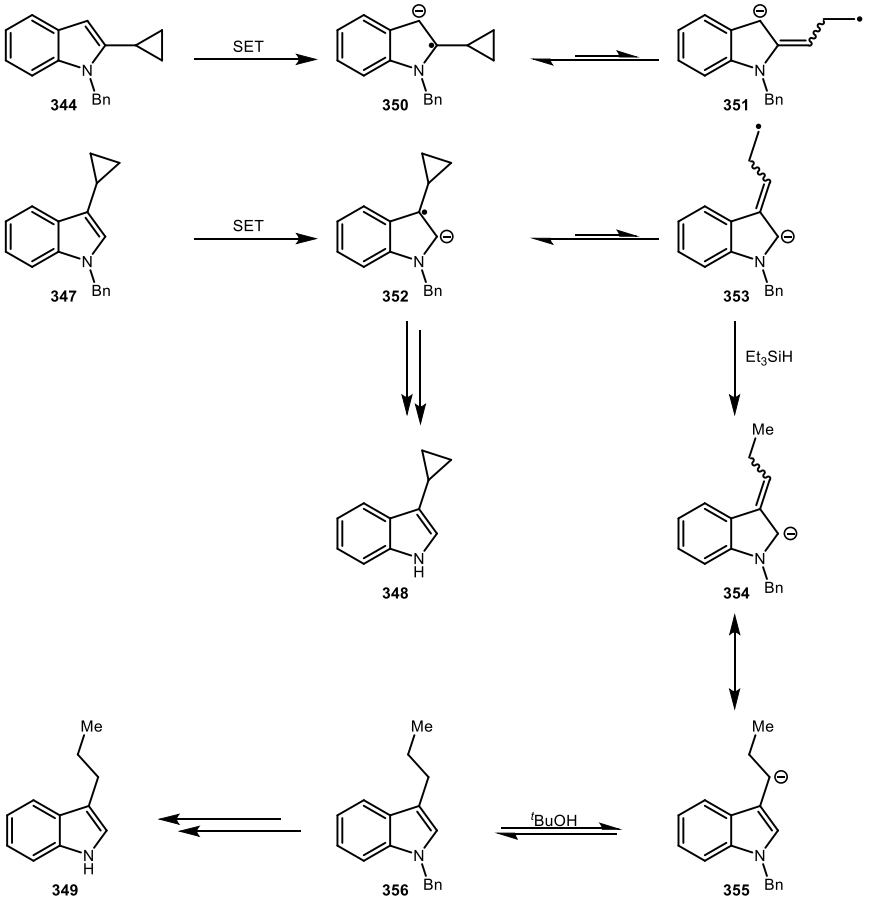


*Scheme 89 - Mechanistic Study of the Debenzylation of Substrate **314***

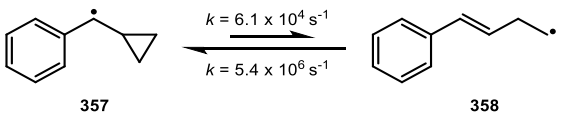


*Scheme 90 - Ring-opening of Cyclopropanes in **344** and **347***

The relative amounts of ring-opened versus ring-closed products would depend on the kinetics of the reactive intermediates, and whether the opening of the cyclopropane or debenzylation would occur more rapidly. Here, it may be that the debenzylation occurs much faster than the cyclopropane can open, thus explaining the detection of only trace amounts of ring-opened products. Alternatively, the kinetics may favour the ring-closed cyclopropane species due to the greater stabilisation of the radical anion **350**, or radical anion **352**. The reactivity of benzylic radicals adjacent to cyclopropanes has been studied by Ingold and by Newcomb who determined that this is indeed the case, with the equilibrium lying towards the side of the cyclopropyl species **357** rather than ring-opened species **358** (Scheme 92).[129–131] Radical anions **350** and **352** can be processed as previously to afford debenzylated products **345** and **348**. Alternatively, the disfavoured ring-opened radical anions **351** and **353** can be quenched by abstraction of a hydrogen atom from triethylsilane to afford an intermediate such as **354** (shown only for the 3-cyclopropylindole). Anion **354** is a resonance form of **355**, which could protonate to **356**. This could then receive another electron from the Et_3SiH/KO^tBu system to ultimately afford ring-opened species **349**.

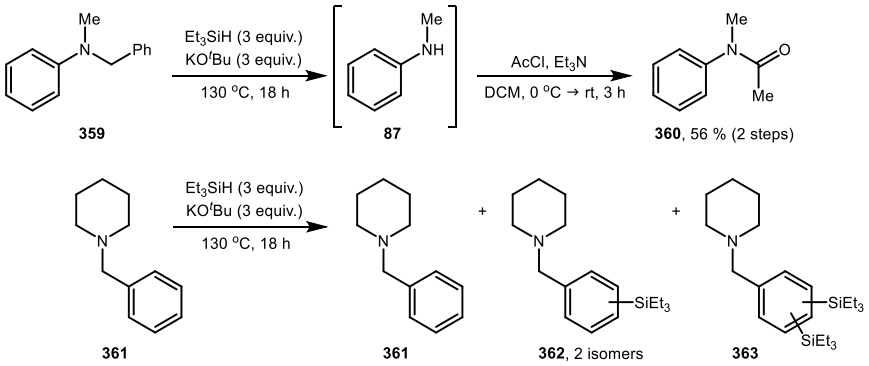


*Scheme 91 – Treatment of Cyclopropyl-containing Substrates **344** and **347** under Et_3SiH/KO^tBu*



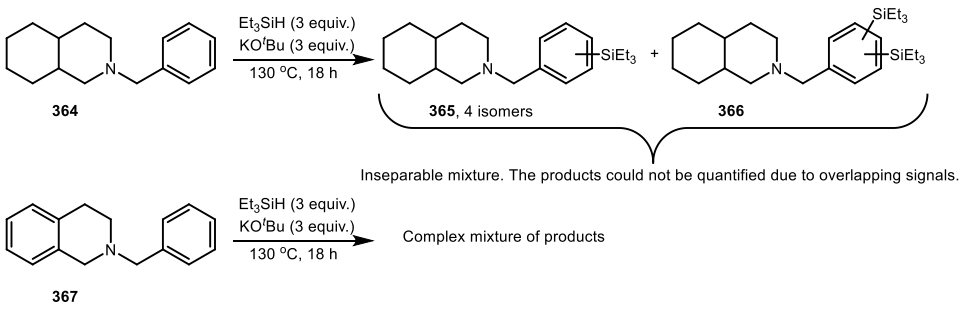
*Scheme 92 - Rate Constants for Ring-Opening and Ring-Closing of Radicals **357** and **358***

Further debenzylation reactions were also attempted. Since *N*-benzylindoles (*i.e.* aromatic amines) were efficiently debenzylated under the reaction conditions, the next steps were to determine if *N*-benzylanilines (*i.e.* amines adjacent to aromatic systems) or *N*-benzylpiperidines (*i.e.* aliphatic amines) could also be debenzylated under the reaction conditions. From **359**, debenzylation to **87** was observed, although the volatility of this compound made isolation difficult (Scheme 93). The reaction was therefore repeated, and the crude material was acetylated. Amide **360** was isolated in 56 % yield across the two steps (a proton NMR with an internal standard suggested that the yield of **87** in the crude mixture was 65 %). Substrate **359** is unreactive in the absence of Et_3SiH, with starting material being recovered in 97 % yield. With **361**, only starting material and silylated products **362**-**363** were observed.



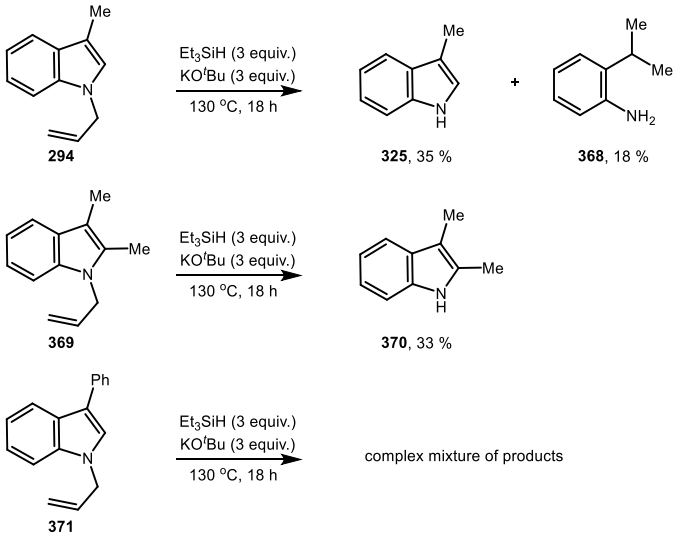
*Scheme 93 - Debenzylation of **359** and **361** under Et_3SiH/KO^tBu*

It was thought that one reason for no debenzylation being detected under the Et_3SiH/KO^tBu conditions may be due to the relative volatility of the expected products (piperidine and toluene). To counteract this, substrate **364 (**mixture of *cis*- and *trans*- isomers) was prepared and tested under the Et_3SiH/KO^tBu conditions. This substrate produced a complex mixture of products from which **365**-**366** could be detected by GC-MS. These compounds could not be isolated, and could not be quantified due to overlapping NMR signals. Therefore, it may be beneficial to test an aliphatic amine that is not volatile and does not have such a complex NMR spectrum. Therefore, compound **367** was tested under the reaction conditions, and this time a complex mixture of products was again observed, but no silylation products were detected. It is likely that in the case of the aliphatic amines, there is no electron transfer into the amine-containing portion of the molecule due to the absence of a π-system, and any electron transfer therefore occurs into the benzyl portion of the molecule, leading to different chemistry occurring. Only starting material was recovered when **364** or **367** were treated with KO^tBu alone, in 48 % and 87 % yield respectively. This is in contrast to **361**, from which no products could be detected when this was treated with KO^tBu alone. It is not clear what happened to the rest of the material upon treatment of **361** or **364** with KO^tBu alone.



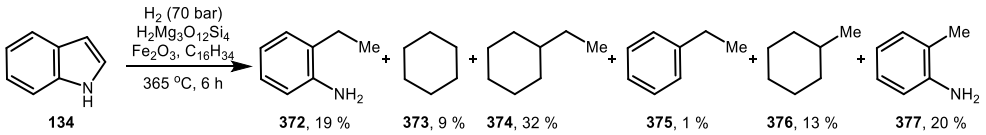
Scheme 94 - Attempted Debenzylation of Aliphatic Amines

As electron transfer was occurring into the indole portion of the *N*-benzylindoles and not into the benzyl group, it was thought that it might also be possible to carry out deallylation reactions under the same conditions. Substrates **294**, **369**, and **371** were prepared and tested under the Et_3SiH/KO^tBu conditions, and indeed deallylated compounds **325** and **370** were isolated in 35 % and 33 % yields from **294** and **369** respectively (Scheme 95). From substrate **371**, a complex mixture of products was produced from which nothing could be isolated (although <1 % of 3-phenylindole was detected). The allyl group allows for other side-reactions to occur, and the wide range of side-reactions possible was exemplified by the isolation of 2-*iso*-propylaniline **368** in 18 % yield.

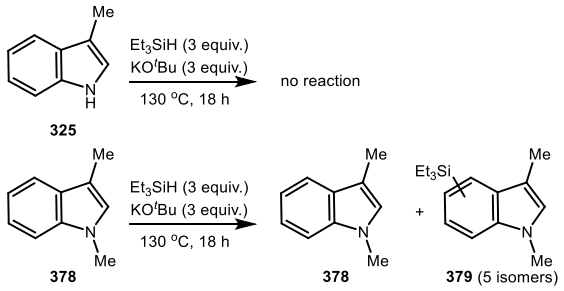


Scheme 95 - Deallylation of N-allylindoles under Et_3SiH/KO^tBu

This type of indole reduction had at this time only been previously reported under high temperatures (> 225 °C) and high pressures of hydrogen gas (> 15 bar), generally over transition metal catalysts.[132–135] An example of this type of reduction is shown in Scheme 96.[136] To probe the mechanism of this ring-opening, compounds **325** and **378** were treated under the reaction conditions (Scheme 97). No ring-opening was observed in either case, with only starting material being returned from compound **325**, and a complex mixture of starting material and silylated products **379** being obtained from **378**. Compounds **378** and **379** could not be isolated, and could not be quantified due to overlapping NMR signals. Further mechanistic studies on a similar C-N bond cleavage in *N*-phenylindoles will be discussed in Chapter 4.

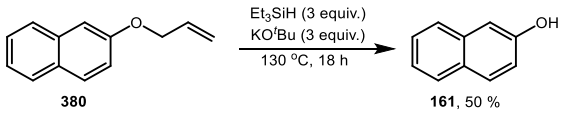


Scheme 96 - Reduction of Indoles



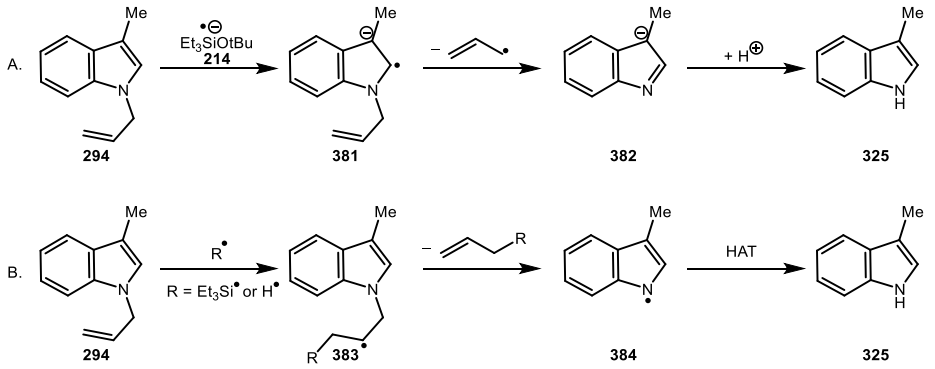
Scheme 97 - Probing the Mechanism of the Ring-opening of Indoles

Following on from the deallylation of indole derivatives, we wondered if deallylation of *O*-allyl groups was also possible. To test this, **380** was prepared and treated under the silyl conditions, and 2-naphthol **161** was isolated in 50 % yield (Scheme 98).

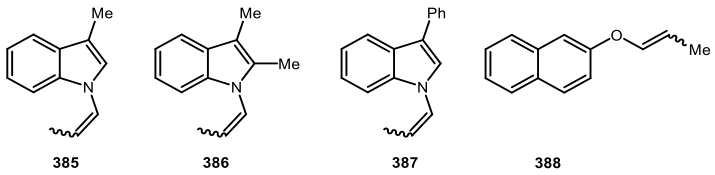


*Scheme 98 - Deallylation of **380***

It is possible that these deallylation reactions may be occurring via electron transfer, but this is inconclusive. If an electron is again transferred to the indole portion of **294** forming **381**, deallylation to **382** followed by isomerisation to **325** can occur to produce the parent indole (Scheme 99A). Alternatively, addition of a triethylsilyl radical or a hydrogen atom may occur to the allyl group forming radical **383**. Deallylation could then occur, forming indolyl radical **384**, which can abstract a hydrogen atom (likely from triethylsilane) to produce the parent indole **325**. In the absence of Et_3SiH (*i.e.* treatment of **294**, **369**, **371** and **380** with KO*t*Bu alone), no deallylation occurred, and isomerisation of the starting materials was observed in each case, forming **385**-**388** (Scheme 100).

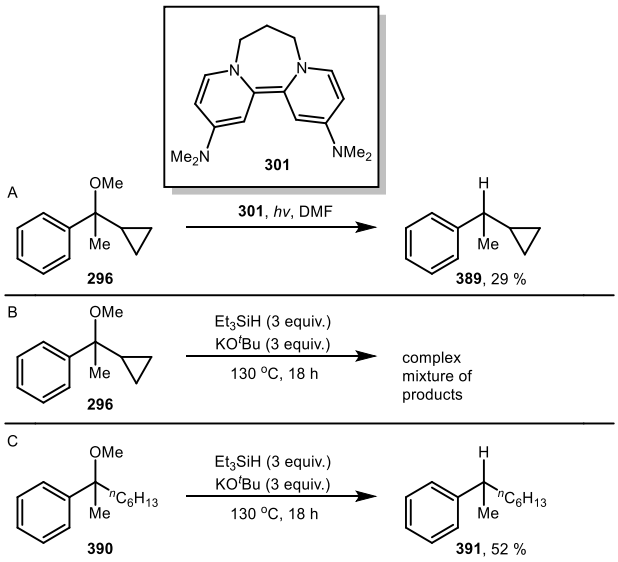


Scheme 99 - Some Possible Mechanisms for Deallylation Reactions



*Scheme 100 - Isomerisation of **294**, **369**, **371** and **380** to **385**-**388** Respectively upon Treatment with KO^{t}Bu Alone*

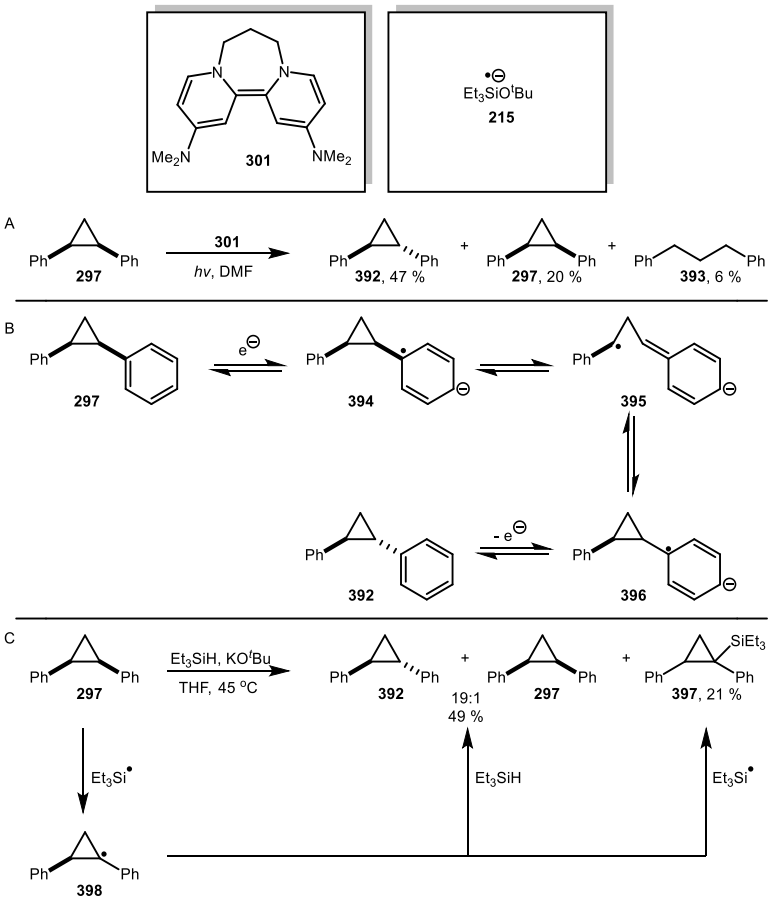
Other substrates in the literature which have previously been shown to react under electron transfer conditions include benzylic ethers such as **296** which receives two electrons from electron donor **301** to afford **389** in 29 % yield (Scheme 101A).[137] Upon preparing and testing substrate **296** under the Et_3SiH/KO^tBu conditions, a complex mixture of products was obtained from which nothing could be isolated (Scheme 101B). However, the mass of **389** was detected in a complex GC-MS spectrum. Compound **296** did not react when treated with KO^{t}Bu alone, with starting material being recovered in 73 % yield. A less-complex substrate **390** was prepared and treated under the Et_3SiH/KO^tBu conditions, and this was able to afford the parent hydrocarbon **391** after cleavage of the C-O bond (Scheme 101C). This result provides further evidence of electron transfer chemistry mediated by Et_3SiH/KO^tBu. No other products were detected when **390** was treated with KO^{t}Bu alone, however starting material was recovered in only 62 % yield.



Scheme 101 - Cleavage of Benzylic Ethers under Silyl Conditions

It has also been shown in the literature that unactivated arenes can be reduced using an organic electron donor (Scheme 102A).[138] This is generally considered to be a challenging reduction to carry out due to the high reduction potential of benzene (– 3.42 V vs. SCE). This means that this type of reduction has historically been carried out using highly reactive alkali metals such as sodium or lithium dissolved in liquid ammonia.[139] Treatment of *cis*-1,2-diphenylcyclopropane **297** with electron donor **301** forms the radical anion **394**, which can reversibly open the cyclopropane to **495** (Scheme 102B). Ring-closing of the cyclopropane again afforded the *trans*-isomer of the radical anion **396** for steric reasons, before back-electron transfer provided isomerised starting material **392**. This could previously only be achieved under photoactivation of the organic electron donor **301**. However, treatment of **397** with Et_3SiH/KO^tBu under thermal conditions afforded the

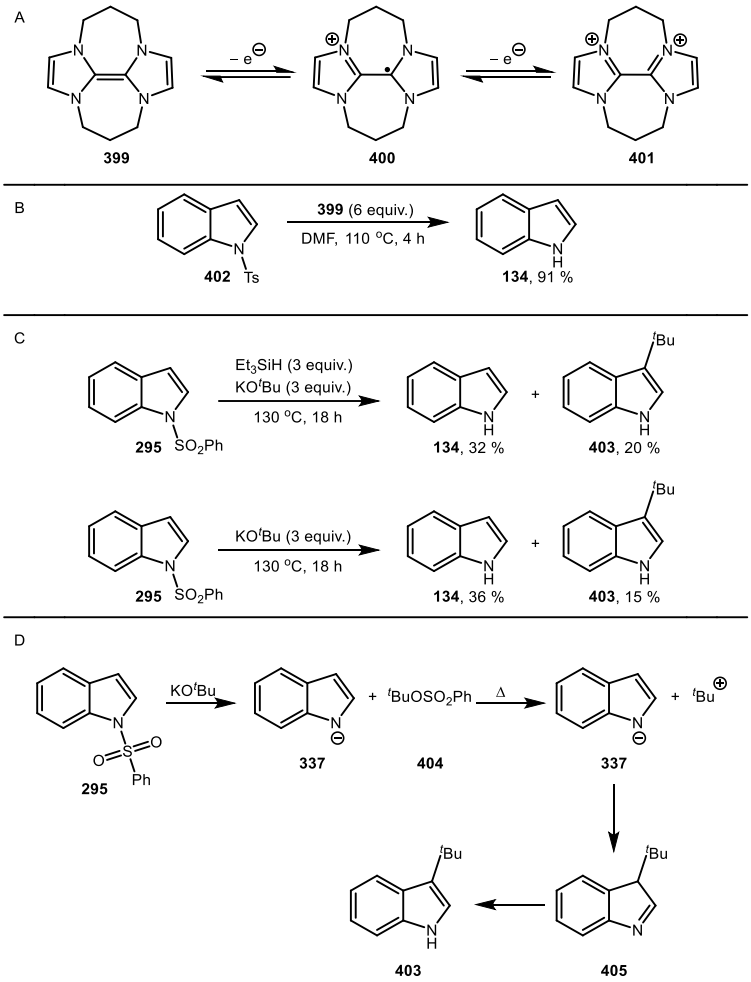
trans-isomer **392** at only 45 °C (Scheme 102C). This may be further evidence of electron transfer from a powerful electron donor derived from Et_3SiH/KO^tBu (*i.e.* **215**) – however, the isolation of **397** detracts confidence from this result. If triethylsilyl radicals were formed in the reaction mixture, then one of these radicals could abstract a hydrogen atom from **297**, forming radical **398**. If radical **398** then abstracted another hydrogen atom from triethylsilane, it would likely occur so that the two phenyl groups are kept in *trans*-stereochemistry. Alternatively, radical recombination between **398** and a triethylsilyl radical could afford **397**.



*Scheme 102 - Isomerisation of cis-1,2-diphenylcyclopropane **297** to trans-1,2-diphenylcyclopropane **392***

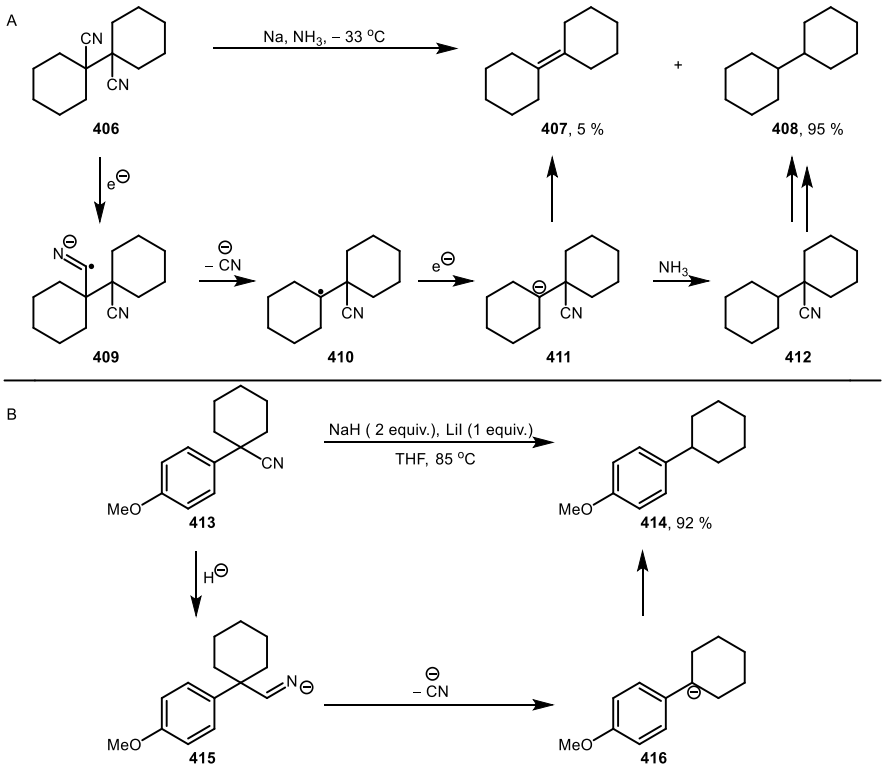
Sulfonamides have also been previously shown to be reductively cleaved under electron transfer conditions.[140] This has been carried out by electron donor **399**, which works by donating two electrons to become aromatic species **401** (via radical cation **400**, Scheme 103A).[141] Upon treatment of sulfonamide **402** with electron donor **399**, cleavage of the S-N bond was observed with the parent indole **134** being isolated in 91 % yield (Scheme 103B).[140] Upon treatment of sulfonamide **295** under the Et_3SiH/KO^tBu conditions, cleavage of the S-N bond was observed to afford parent indole **134** in 32 % yield, alongside indole **403** in 20 % yield (Scheme 103C). However, when **295** was treated with KO^tBu alone (*i.e.* in the absence of silane) cleavage of the S-N bond was also observed and compounds **134** and **403** were again isolated in 36 % and 15 % yield respectively. It is therefore likely that this cleavage is not due to electron transfer in this case, and that nucleophilic attack of the *tert*-butoxide anion on **295** affords indole anion **337** and **404**. Compound **404** could then undergo loss of the SO_3Ph anion to afford a *tert*-butyl cation, which

could be trapped by the indole anion **337** to afford **405**. This ultimately will isomerise to the aromatic species **403**.



Scheme 103 - Cleavage of Sulfonamides

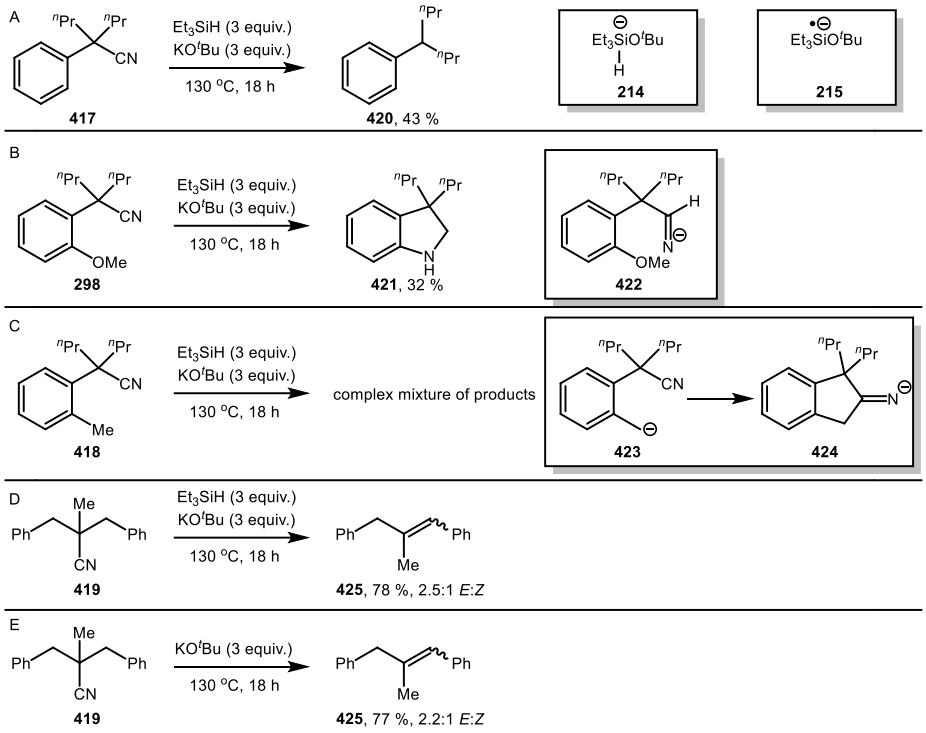
Another reaction which was tested under the Et_3SiH/KO^tBu conditions was the reductive decyanation of nitriles.[142] This has been shown in the literature to proceed via either electron transfer or via hydride transfer. Substrate **406** (Scheme 104A) has been shown to undergo reductive decyanation by electron transfer from sodium metal.[143] This proceeds via electron transfer to **406** to generate **409**, which then undergoes elimination of cyanide to afford **410**. This radical can then undergo a second electron transfer to afford anion **411**. This anion can then either eliminate a second molecule of cyanide to afford alkene **407**, or it can protonate to afford **412**, which will ultimately undergo a second reductive decyanation to alkane **408**. Alternatively, substrate **413** has been shown to undergo reductive decyanation by hydridic reagents such as $LiAlH_4$,[144] $NaBH_4$,[145] or a NaH.LiI composite.[146,147] Whilst $LiAlH_4$ and $NaBH_4$ mediated reductive decyanation of nitriles have been proposed to proceed via single electron transfer, the reduction by a NaH.LiI composite has been proposed to proceed via hydride transfer (Scheme 104B). Hydride transfer to the nitrile results in anion **413**, which could undergo decyanation to afford anion **416**. Protonation of this anion would afford the product **414**.



Scheme 104 – Literature Reductive Decyanation of Nitriles

Nitriles **417**, **298**, **418** and **419** were prepared and treated under the Et_3SiH/KO^tBu conditions. Substrates **298**, **417** and **418** were found to have restricted rotation around the propyl groups, with diastereotopic protons observed for the CH_2 groups in the ^1H NMR spectra of these compounds. Substrate **417** underwent reductive decyanation to afford **420** in 43 % yield (Scheme 105A). Upon treatment of this substrate with KO^tBu alone, no decyanation was observed, and starting material **417** was recovered in quantitative yield. It is possible that this reductive decyanation could have occurred either by electron transfer from radical anion **215**, or by hydride transfer from pentavalent silicate **214**. Substrate **298** was found to undergo cyclisation to afford indoline **421** in 32 % yield, with no decyanation products observed (Scheme 105B). Compound **421** was also found to contain diastereotopic protons for the propyl CH_2 groups in the ^1H NMR spectrum due to restricted rotation. Around the time of this experiment being carried out, Chiba *et al.* published their paper which showed a similar cyclisation occurring using their NaH.LiI composite, which they propose to occur via a concerted nucleophilic aromatic substitution via intermediate **422**.[148] This type of cyclisation will be discussed in more detail in Chapter 5. Upon treatment of **298** with KO^tBu alone, no cyclisation was observed, and starting material was recovered in 42 % yield, alongside a complex mixture of products. Nitrile **418** was also treated under the Et_3SiH/KO^tBu conditions, and was found to produce a complex mixture of products (Scheme 105C). Similarly, a complex mixture of products was also observed when **418** was treated with KO^tBu alone. It is likely that under the reaction conditions, deprotonation of the methyl groups occurs to afford anion **423**, which could undergo cyclisation onto the nitrile to afford **424**. The products obtained from this reaction are likely to include derivatives of this species. An aliphatic nitrile **419** was also tested under the Et_3SiH/KO^tBu conditions to see if decyanation was possible without the nitrile being in a benzylic position (Scheme 105D). This was found to undergo

elimination to **425** both under the Et_3SiH/KO^tBu conditions, and in the presence of KO^tBu alone (Scheme 105E), suggesting that this reaction does not proceed via electron transfer, and is instead a base-mediated E2 type process.

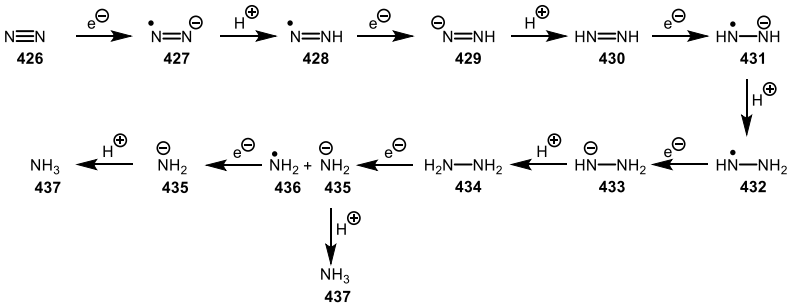


Scheme 105 - Treatment of Nitriles under Et_3SiH/KO^tBu Conditions

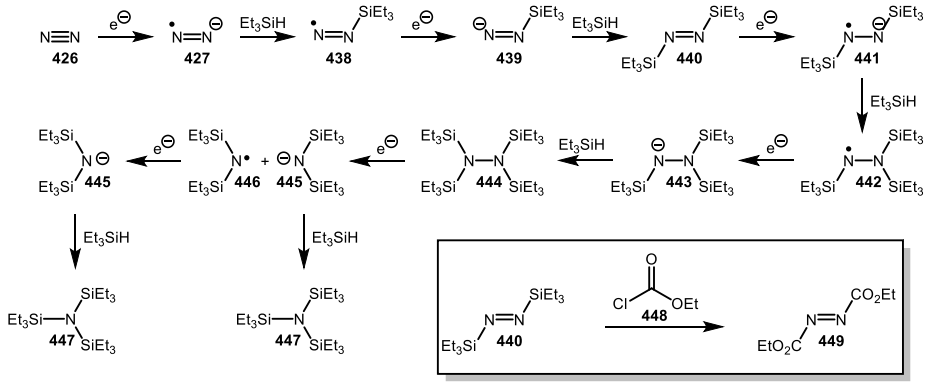
Due to the highly reducing ability of the Et_3SiH/KO^tBu system, it was thought that nitrogen reduction might be possible. Nitrogen reduction to ammonia via the Haber-Bosch process is an extremely important reaction to produce enough fertiliser to sustain crop growth to feed the world's ever-increasing population.[149] However, some drawbacks of the Haber-Bosch process are the use of non-renewable sources of hydrogen, and the high energy intensity of the process (the Haber-Bosch process is responsible for 1 % of the world's total annual energy consumption, and is responsible for the emission of 300 million tonnes of carbon dioxide per year). Therefore, it is not sustainable to continue this process long-term, and new greener alternatives must be found. In its simplest form, nitrogen reduction requires the transfer of a total of six electrons and six protons to dinitrogen (Scheme 106).[150] Electrochemical,[151] photochemical,[152] and enzymatic[153] methods of nitrogen reduction have been recently reviewed.

Without a proton source, it is unlikely that complete reduction of dinitrogen to ammonia would occur in the presence of Et_3SiH/KO^tBu, and that masking of the forming anions via silylation may be necessary. The silylation of amines using Et_3SiH/KO^tBu has been shown in the group previously,[154] and therefore it was not unreasonable to assume that if dinitrogen could be reduced to the radical anion **427**, trapping of this radical anion by a silyl group could occur forming radical **438**. This radical could then receive another electron to afford anion **439**, which could again silylate to afford **440**. Further electron transfer and silylation steps might then allow for the

reduction of dinitrogen to occur. The idea was that any nucleophilic nitrogen species produced by the reduction of dinitrogen could be trapped by the addition of an electrophile. Ethyl chloroformate **448** was added to the crude mixture at the end of the reaction to attempt to trap any nucleophilic nitrogen species which would have been produced through the reduction of nitrogen. Therefore, DEAD **449** was prepared independently, and the data used as a reference to see if this compound could be detected when dinitrogen was treated with Et_3SiH/KO^tBu and quenched by the addition of ethyl chloroformate **448**. Only a small set of conditions were attempted. Under our standard Et_3SiH/KO^tBu reduction conditions (Table 1, entry 1) no reduction products were detected. Upon decreasing the number of equivalents of base (entry 2), no reduction products were detected – using 0.2 equivalents of base was successful for the silylation of amines, which is why these conditions were chosen. Increasing the reaction temperature (entries 3 and 4) also led to no reduction products being detected by ^1H NMR in either case. It is likely that under the high temperature of the reaction that even if a species such as **440** could form, the reaction would be reversible and dinitrogen would be regenerated thermally by a homolysis mechanism.

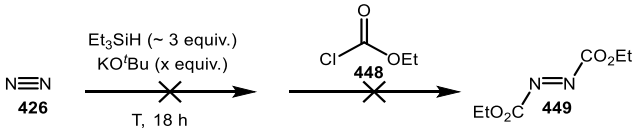


Scheme 106 - Mechanism for the Reduction of Dinitrogen to Ammonia



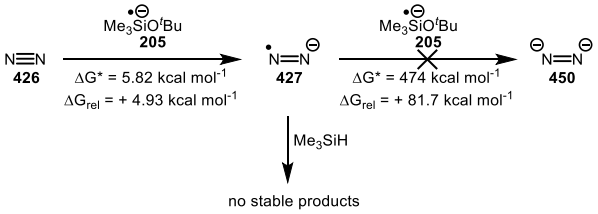
Scheme 107 - Possible Reduction of Dinitrogen with Et_3SiH/KO^tBu

Table 1 - Attempted Reduction of Nitrogen



Entry	X	T/ °C	**449**
1	~ 3	130	0
2	~ 0.2	130	0
3	~ 3	150	0
4	~ 3	180	0

Computational analysis showed that the reduction of dinitrogen to the radical anion **427** was possible, however, the formation of the dianion **450** was not possible, with energy barriers 5.82 kcal, mol^{-1} and 474 kcal, mol^{-1} respectively (Scheme 108).[e] Also, the trapping of radical anion **427** did not lead to the formation of any stable products. Therefore, it is unlikely that these reaction conditions are likely to lead to the formation of any reduction products from dinitrogen.



Scheme 108 - Computational Analysis of Nitrogen Reduction.[e] ΔG represents the energy barrier, whereas ΔG_{rel} represents the change in relative energy.*

3.3: Conclusions and Future Work

In conclusion, *N*-benzylindole derivatives have been shown in the literature to undergo debenzylation under electron transfer conditions. Upon preparing a range of *N*-benzylindoles and treating these with the combination of Et_3SiH and KO^{t}Bu, debenzylation was observed in up to 80 % yield. Computational chemistry was useful to identify potential electron donors which could be forming from this combination of reagents, and identified the *tert*-butoxytriethylsilyl radical anion **215** as a good candidate for the active electron donor in these reactions (Figure 2). Further computational analysis revealed that the oxidation potential of radical anion **215** was – 3.74 V (vs. SCE in MeCN), which is more powerful an electron donor than alkali metals.[93] Further reductive cleavages were also explored, including the reductive cleavage of *N*-allylindoles, which were shown to be facilitated by the combination of Et_3SiH and KO^{t}Bu. The potential mechanisms for the cleavage of the C2-N bond in this chemistry will be further explored in Chapter 4.

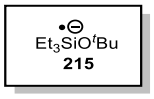


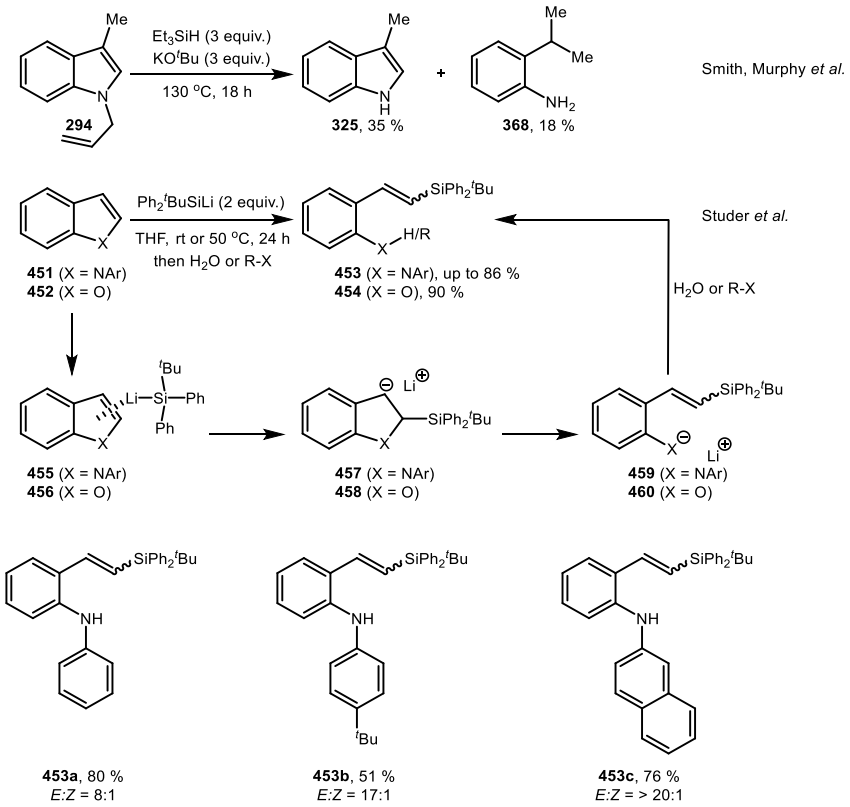
*Figure 2 - Structure of Electron Donor **215***

[e] These calculations were carried out by Simon Rohrbach, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-311++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modelled using the CPCM solvation model.

4: Ring-opening and Cyclisation of *N*-phenylindoles to 9,10-Dihydroacridines Mediated by Et_3SiH/KO^tBu

4.1: Introduction

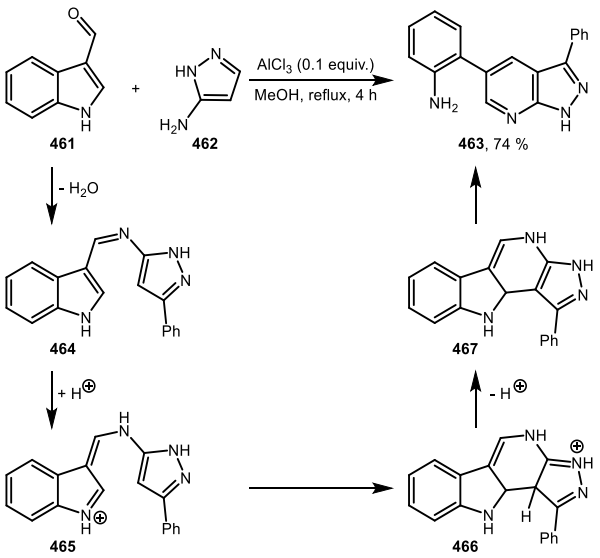
During our study into the debenzylation of *N*-benzylindoles, it was shown that deallylation of **294** was also possible, affording both the deallylated indole **325**, and ring-opened 2-*iso*-propylaniline **368** in low yields. After publication of this work,[155] Studer *et al.* also reported on a similar C-N bond cleavage in *N*-arylindoles **451** (and benzofurans **452**) using silyl anions, affording vinyl silanes **453**-**454** in excellent yields.[156] Through DFT calculations, the mechanism was proposed to involve firstly complexation of the silyllithium reagent to the heterocycle to afford intermediate **455** or **456**. Nucleophilic attack of the anion into the 2-position of the indole then occurs, resulting in anion **457** or **458**. This anion can then fragment, leading to the formation of anion **459** or **460**, which can be quenched with water or other electrophiles to form the products **453** or **454**. In the case of indoles, the *N*-aryl group was found to be important, as when *N*-methylindoles were tested under the same conditions, no ring-opening occurred. Whilst similar C-O bond cleavages have previously been reported,[1,157–164] this type of bond cleavage for indoles was rare at this time, with no examples of C_2-N bond cleavage of unactivated indoles.



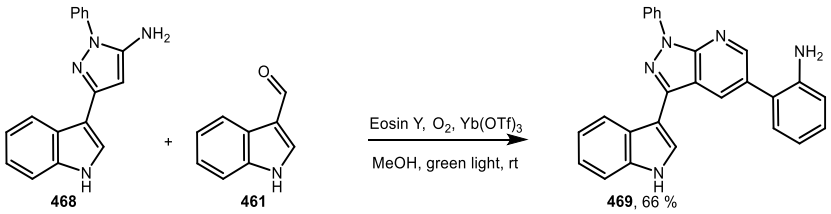
Scheme 109 - C_2-N Bond Cleavage in Indole Derivatives

In terms of other published methods involving indole cleavage, Park *et al.* reported in 2009 that the C_2-N bond of indoles could be cleaved in the synthesis of pyrazolopyridines **463**.[165] The authors propose that this occurs via condensation of **461** with **462** under Lewis acid catalysis to form intermediate **464**. Protonation of this intermediate would afford **465**, which could undergo

ring-closure to **466**. This intermediate can then be deprotonated to afford **467**, which aromatised by ring-opening of the indolenine, affording the product **463** in 74 % yield. Yadav *et al*. have also recently reported on the ring-opening of indoles via cleavage of the C_2-N bond under photocatalysis to afford a similar pyrazolopyridine skeleton **469** (Scheme 111).[166]



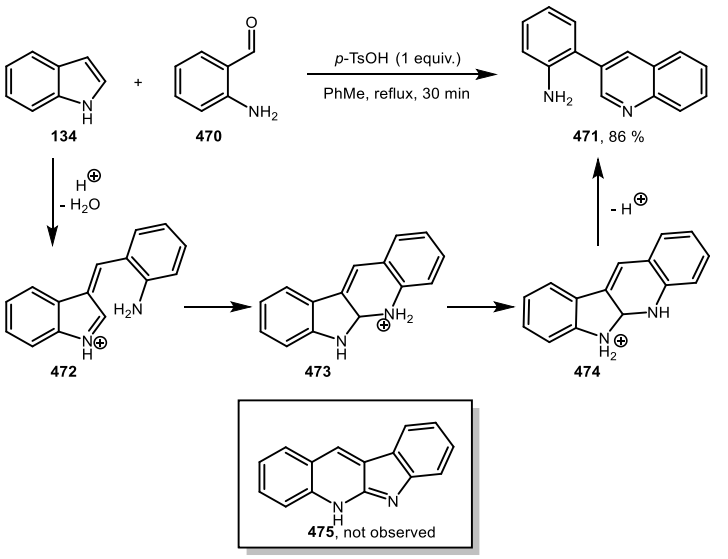
Scheme 110 - Ring-opening of Indoles by Park[165]



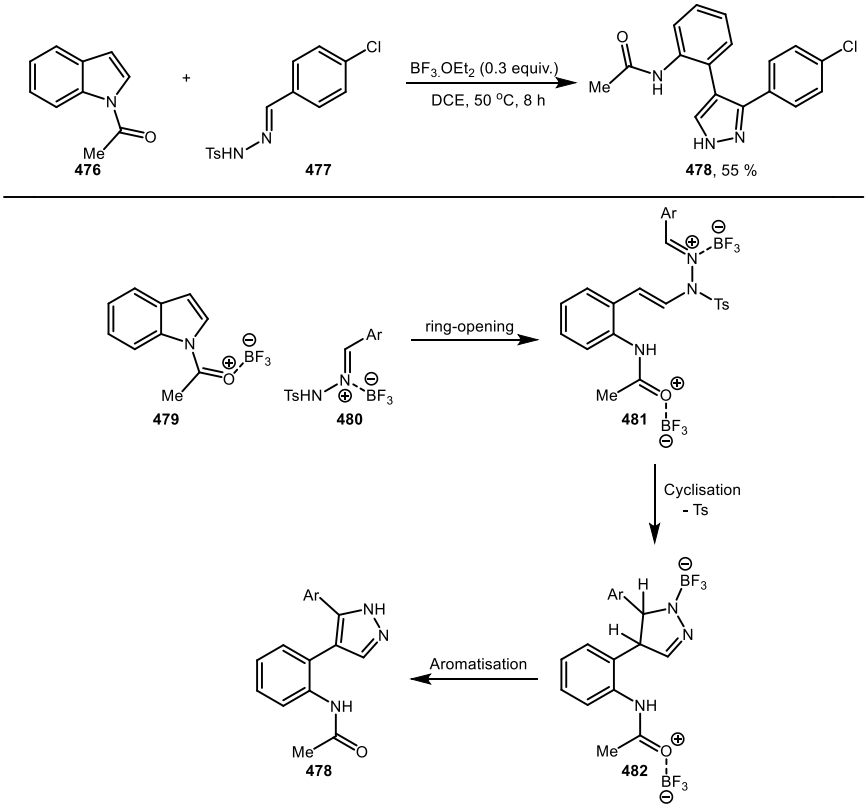
Scheme 111 - Photocatalytic Ring-opening of Indoles by Yadav[166]

In 2011, Seidel *et al.* reported that the condensation of indole **134** with aminobenzaldehyde **470** did not result in the expected product **475**, but instead resulted in quinoline **471** with cleavage of the C_2-N bond in the indole (Scheme 112).[167] It was proposed that this transformation occurs by condensation of the indole **134** with aminobenzaldehyde **470** to afford intermediate **472**. Ring-closure provides intermediate **473**, followed by proton transfer to afford **474**. This intermediate can then aromatise to the quinoline **471** with cleavage of the indole C_2-N bond occurring in this step.

Manna *et al.* have reported on the conversion of indoles **476** to pyrazoles **478** under Lewis acid catalysis (Scheme 113).[168] This is proposed to occur by complexation of the Lewis acid to both reaction partners to afford **479** and **480**. These two species can then react, with nucleophilic attack of **480** into the 2-position of the indole **479** to afford **481**. This species can then undergo cyclisation with loss of the tosyl group to afford **482**, which can aromatise to the product **478**.

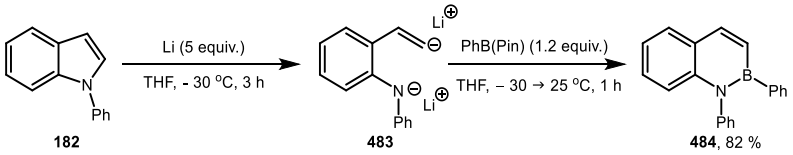


Scheme 112 - Ring-opening of Indoles Reported by Seidel[167]



Scheme 113 - Ring-opening of Indoles by Manna[168]

A final example on the ring-opening of indoles was reported by Yorimitsu in 2019 (Scheme 114).[169] This involves the reductive ring-opening of the indole **182** along the C_2-N bond to afford dianionic intermediate **483**, which could then be trapped with boron electrophiles to afford benzoazaborins **484**. Again, the *N*-aryl group was essential, as replacement of this aryl group with alkyl or benzyl groups did not lead to the formation of any ring-opened products. Dianion **483** is proposed to form via electron transfer from lithium metal.

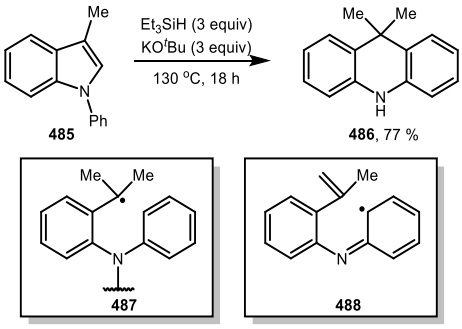


Scheme 114 - Ring-opening of Indoles by Yorimitsu[169]

The emergence of the Studer publication led us to study how *N*-arylindoles, similar to those reported to ring-open by his group, might behave under our reducing conditions, and if cleavage of the C_2-N bond would also occur.

4.2: Results and Discussion

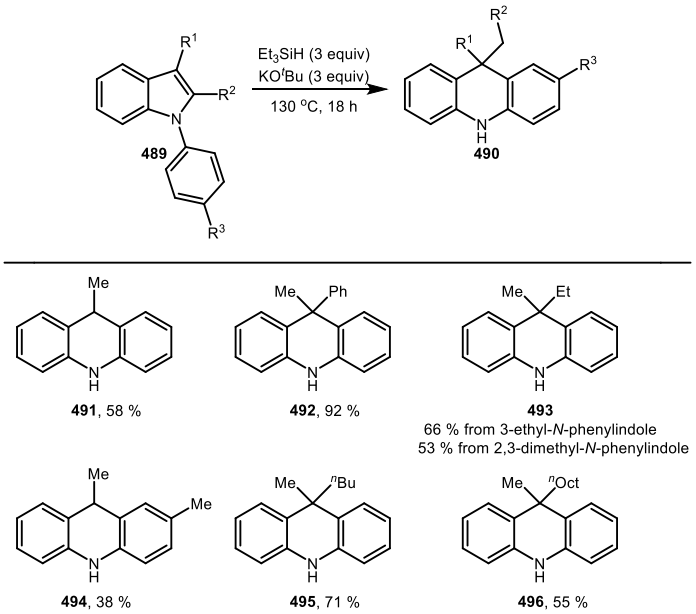
As a starting point, 3-methyl-*N*-phenylindole **485** was prepared and treated under the Et_3SiH/KO^tBu conditions. This was found to undergo ring-opening of the indole portion of the molecule, followed by cyclisation with the phenyl portion of the molecule via a 6-*exo*-trig transition state, to produce 9,9-dimethyl-9,10-dihydroacridine **486**, presumably via an intermediate such as **487** or **488**, where the nitrogen atom on **487** is a radical, an anion, or an N-$SiEt_3$ group (Scheme 115). Detailed mechanistic studies of this reaction will be discussed throughout this chapter.



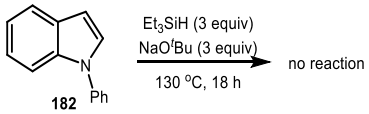
*Scheme 115 – Ring-Opening and Cyclisation of 3-Methyl-N-phenylindole **485***

A range of *N*-arylindoles were then prepared and treated under the reaction conditions to afford a range of 9,10-dihydroacridines **491**-**496** in moderate to excellent yields. Alkyl and aryl substituents were tolerated in the 2- and 3-positions of the indoles, as well as on the *N*-aryl portion. Again, the conversion of **182** into **491** was not successful when KO^tBu was replaced by NaO^tBu (Scheme 117).

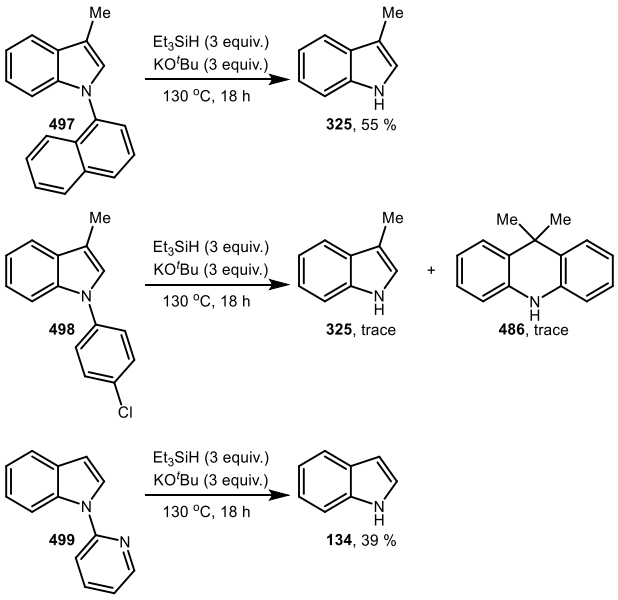
N-arylindole substrates which did not transform to the corresponding dihydroacridines in good yields are shown in Scheme 118. Substrate **497** underwent cleavage of the N-aryl bond to afford 3-methylindole **325** in 55 % yield. Substrate **498** produced a complex mixture of products likely due to benzyne formation, however, **325** and **486** were detected, albeit in low yield. Further work within our group showed the cleavage of the N-aryl bond in *N*-pyridylindole **499** to afford indole **134** in 39 % yield.



Scheme 116 - Substrate Scope



Scheme 117 - No Reaction Occurs when KO^{t}Bu is Replaced by NaO^{t}Bu



Scheme 118 - N-Arylindoles Which Were Less Successful

To understand the cleavage of the N-aryl bond in electron-deficient substrates **497**-**499**, computational modelling was undertaken.[f] When the SOMO of the radical anion **500** (which would result from single electron reduction of **485**) was modelled computationally, the data showed that

[f] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modeled using the CPCM solvation model.

if the transformation proceeds via single electron transfer, then the single electron resides principally in the indole portion of the molecule (Figure 3). The electron transfer to the more electron-rich indole portion of the molecule rather than the less electron-rich phenyl portion is rationalised by the radical anion being delocalised across the bicyclic system of the indole, rather than the monocyclic phenyl group, allowing for greater stabilisation. When *N*-naphthylindole substrate **497** was prepared and tested under the reaction conditions, cleavage of the Ar-N bond occurred and 3-methylindole **325** was isolated in 55 % yield. This time, electron transfer could occur to either the bicyclic indole portion of the substrate or to the bicyclic naphthyl group. Computational modelling shows that electron transfer occurs to the more electron-deficient naphthyl group in this case, forming radical anion **501**, which can expel the anion of indole. Subsequent protonation upon aqueous work-up affords the product **325**. Other electron-deficient aryl groups which did not afford any dihydroacridine products such as **499** could also be explained by the electron transfer occurring to the more electron-deficient aryl group in this cases, with fragmentation of the indole anion occurring.

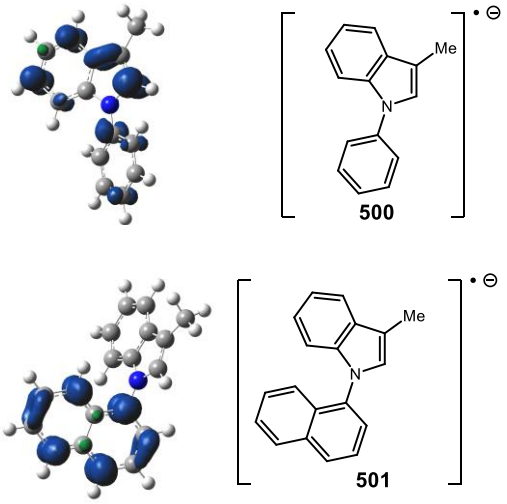
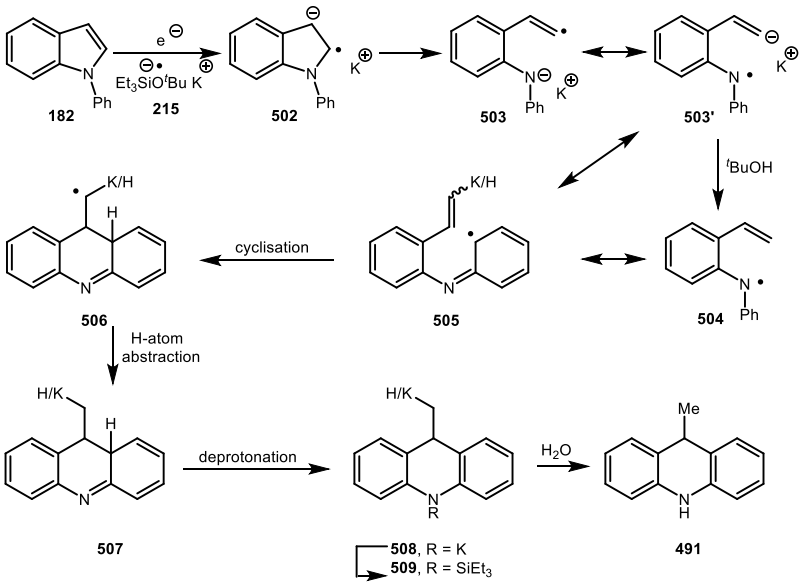


*Figure 3 - Computational Modelling of the SOMO of Radical Anions **500** and **501**[f]*

As we had previously published that Et_3SiH and KO^{t}Bu are able to form an *in situ* electron donor in radical anion **215**,[155] our first mechanistic proposal involved electron transfer from **215** to the *N*-arylindole **182** to form radical anion **502** (Scheme 119). This radical anion could then undergo fragmentation of the N-C_2 bond to form the radical anion **503**, which is a resonance form of **503'**. Protonation of **503'** may occur if a suitable proton source (*e.g. tert*-butanol) formed *in situ* to afford **504**, or the vinyl potassium species could remain. These potential species are drawn as **505**. Cyclisation via a 6-*exo*-trig transition state affords radical **506**, which can be quenched by hydrogen atom abstraction from a suitable source of H-atoms (likely Et_3SiH, or $Et_3Si(H)OtBu$

[f] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modeled using the CPCM solvation model.

anion), affording **507**. Deprotonation of **507** affords **508**, which may silylate under the reaction conditions to afford **509**. Silylation of various amines with Et_3SiH/KO^tBu has been shown within our group in unpublished work.[154] Hydrolysis upon aqueous work-up would then afford the product **491**.



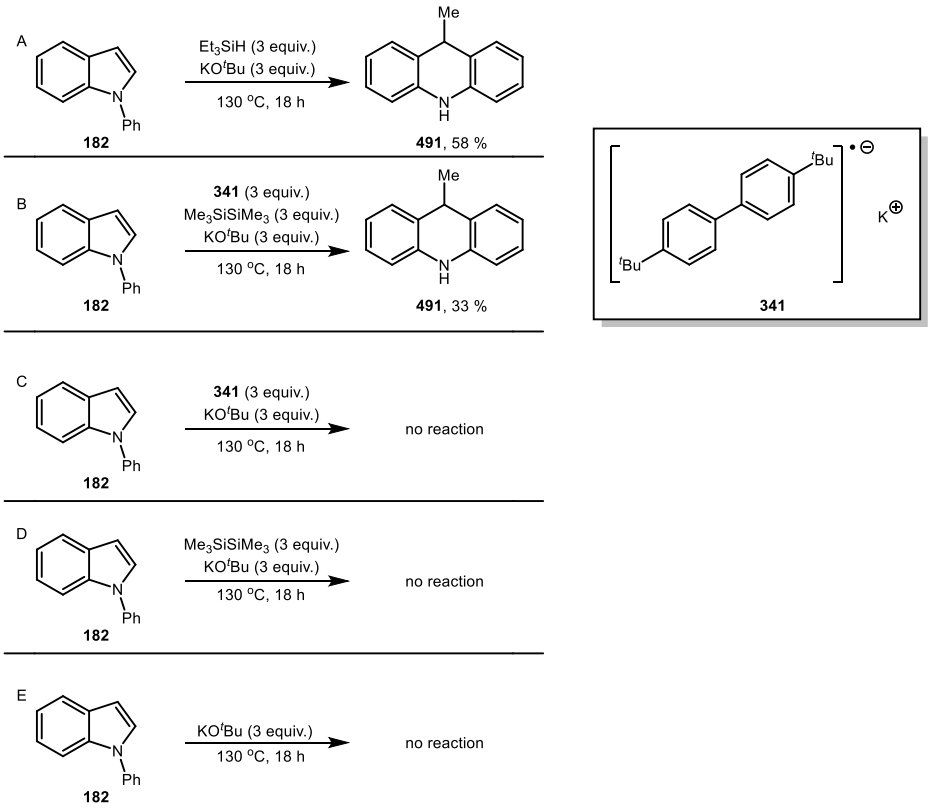
*Scheme 119 - Mechanism for the Conversion of N-phenylindole **182** to 9,10-Dihydroacridine **491**.*

Evidence for SET reactivity was obtained by the use of electron transfer conditions from radical anion **341** in combination of a silyl source which cannot undergo hydride transfer or hydrogen atom transfer (*i.e.* $Me_3SiSiMe_3$), and KO^tBu. Under the Et_3SiH/KO^tBu system, transformation of **182** to **491** occurred in 58 % yield (Scheme 120A). Upon treatment of **182** with **341**, $Me_3SiSiMe_3$ and KO^tBu, dihydroacridine **491** was isolated in 33 % yield (Scheme 120B). In the absence of the silyl source (Scheme 120C), the absence of the radical anion **341** (Scheme 120D), or with KO^tBu alone (Scheme 120E), no conversion of **182** was observed by ^1H NMR, GC-MS, or TLC analysis. These results provide evidence that electron transfer conditions and the silyl source are necessary for the conversion of *N*-arylindoles to the corresponding dihydroacridines. Similar to Chapter 3, it is likely that electron transfer to $Me_3SiSiMe_3$ could occur, resulting in the formation of trimethylsilyl radicals and trimethylsilyl anions. Combination of a trimethylsilyl radical with a *tert*-butoxide anion could result in the formation of electron donor **205** which could allow for the reactivity seen.

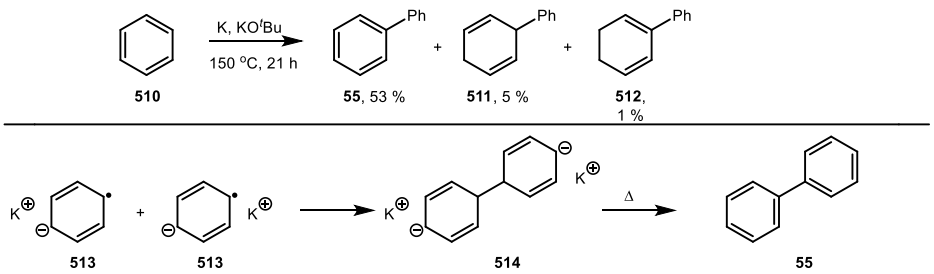
Further evidence of electron transfer was obtained within the group by the treatment of **515** with potassium and potassium *tert*-butoxide.[g] This combination of reagents has previously been shown to facilitate the homocoupling of benzene **510** to afford biphenyl **55**, and dihydrobiphenyls **511** and **512** through electron transfer conditions (through the dimerisation of radical anions **513** followed by expulsion of hydride from **514** upon heating) (Scheme 121).[170] Replacement of either

[g] These reactions were carried out by Krystian Kolodziejczak, University of Strathclyde

potassium reagent with the sodium equivalent results in no reaction taking place (*i.e.* no reaction occurs with Na/KO^{t}Bu or with K/NaO^{t}Bu, and only takes place with K/KO^{t}Bu).



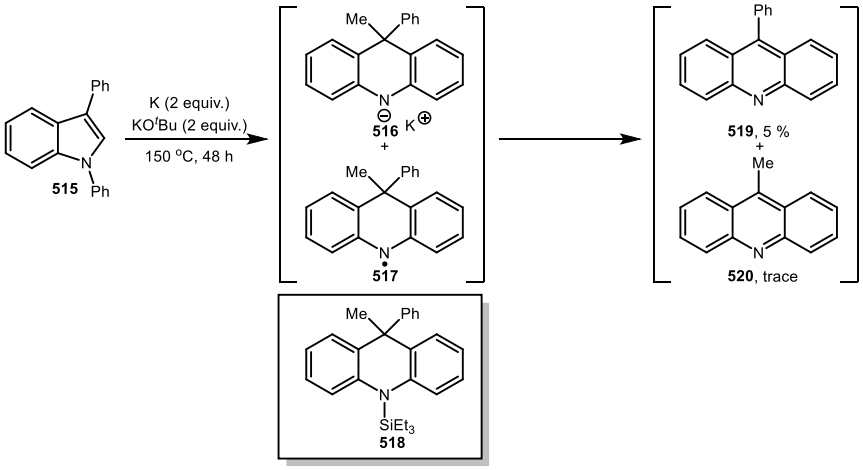
*Scheme 120 - Electron Transfer From **341***



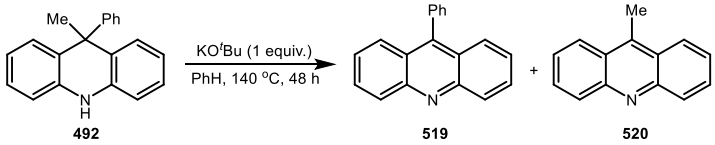
Scheme 121 - Homocoupling of Benzene Mediated by K/KO^{t}Bu

When **515** was treated under the K/KO^{t}Bu conditions, **519** and **520** were isolated from the reaction mixture, albeit in low yields (Scheme 122). These products are likely oxidation products from dihydroacridine **516** or **517**, where loss of a phenyl or a methyl group occurs upon oxidation. These groups are generally not considered to be good leaving groups, but some recent literature has suggested that an aromatic driving force is sufficient to cause bad leaving groups to leave if aromaticity can be gained.[171] No oxidation to acridine products is observed for the disubstituted dihydroacridines shown in Scheme 115 or Scheme 116. Therefore, it is likely that if the formation of the dihydroacridines proceeds via electron transfer under the Et$_3$SiH/KO^{t}Bu conditions, that the silylation of the anionic or radical intermediate to afford **518** (also shown in the mechanism in Scheme 119) prevents the oxidation to the corresponding acridines. Upon treating **492** with

KO^{t}Bu, compounds **519** and **520** were detected in small amounts in the crude reaction mixture by GC-MS, indicating that the silyl group in **518** may be providing some stability (Scheme 123).[g]



*Scheme 122 - Conversion of **515** to **519** and **520** with K/KO^{t}Bu[g]*



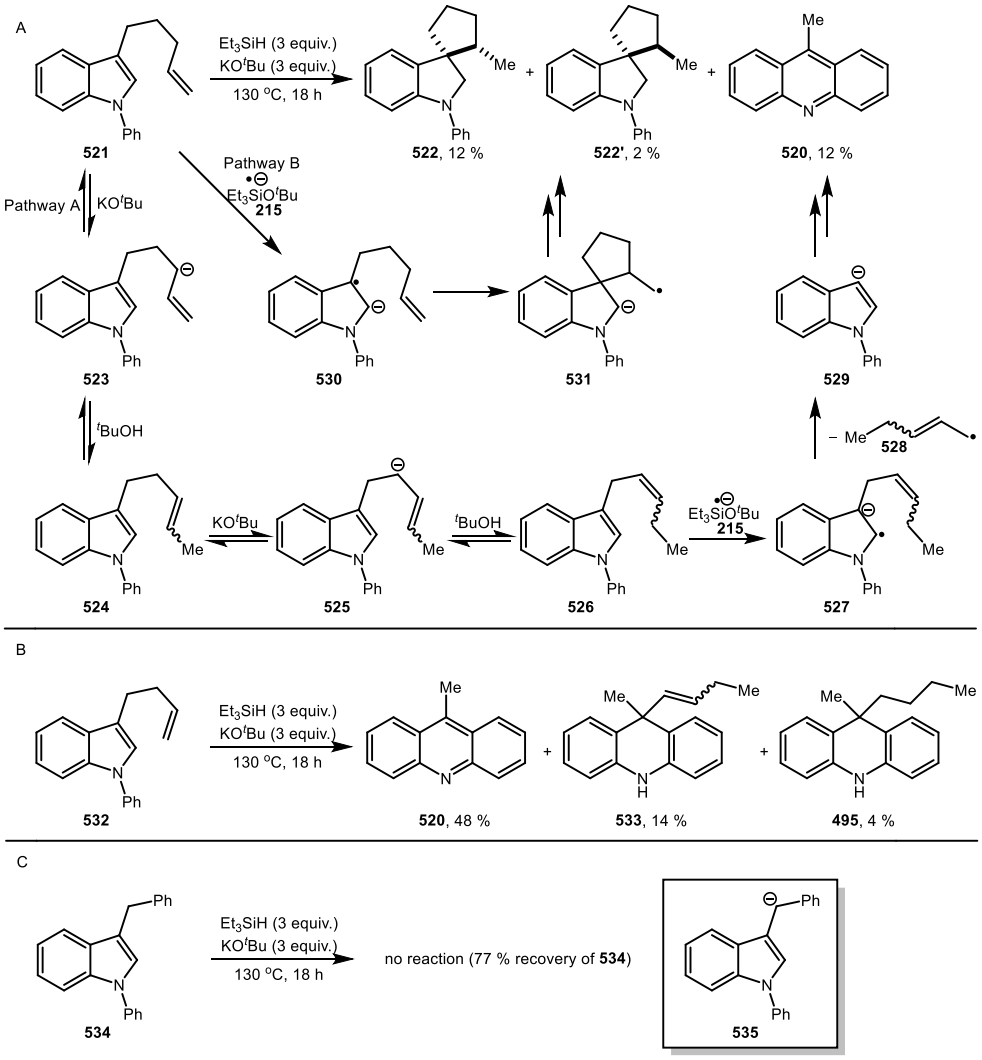
*Scheme 123 - Oxidation of **492** with KO^{t}Bu[g]*

To obtain evidence of radical intermediates being involved in the ring-opening of the *N*-arylindoles, substrate **521** was prepared and treated under the Et$_3$SiH/KO^{t}Bu conditions (Scheme 124A). It was found that the expected cyclised products **522** and **522'** were produced in the reaction mixture, providing evidence of radical intermediates. However, unexpectedly, acridine **520** was also isolated from the reaction mixture (the corresponding dihydroacridine was initially produced, but was intentionally oxidised in air to facilitate purification). It is likely that upon heating with KO^{t}Bu, the alkenyl side-chain in **521** can deprotonate to afford anion **523** (Pathway A). Protonation from the generated *tert*-butanol can afford isomerised alkene **524**. Another isomerisation step via anion **525** can afford alkene **526**. Single electron transfer from radical anion **215** could then occur, allowing for the formation of radical anion **527**. The isomerisation of the alkenyl side-chain could then provide stabilisation for cleavage of the side-chain by loss of allyl radical **528**. The resulting indole anion **529** could protonate and react as discussed previously to ultimately afford acridine **520** (after oxidation).

Alternatively, substrate **521** could receive an electron from radical anion **215** before isomerisation of the side-chain occurs (Pathway B). The resulting radical anion **530** could then cyclise onto the alkene via a 5-*exo*-trig cyclisation to afford radical anion **531**. Protonation and hydrogen atom abstraction would ultimately afford diastereomers **522** and **522'**. In contrast, *N*-phenylindoles with long-chain alkyl side-chains such as butyl or octyl did not undergo any cleavage of the side-chain

[g] These reactions were carried out by Krystian Kolodziejczak, University of Strathclyde

upon conversion to their corresponding dihydroacridines (*i.e.* **495** and **496** discussed in Scheme 116). To confirm that the alkenyl group was necessary for the cleavage of the side-chain, substrate **532** was also treated under the Et_3SiH/KO^tBu conditions (Scheme 124B). Again, cleavage of the side-chain was observed as the major product to afford **520** in 48 % yield (again, aerial oxidation of the initial dihydroacridine to afford **520** was allowed to aid purification). Without cyclisation affording complex by-products in this case, dihydroacridines **533** and **495** were also isolated as a mixture from this reaction, albeit in lower yield. Substrates **531** and **532** were also treated with KO^tBu alone and isomerisation of the side-chain was indeed observed to afford a mixture of isomers. This gives confidence in the alkene-isomerisation pathway occurring and being responsible for the stabilisation of the leaving group.



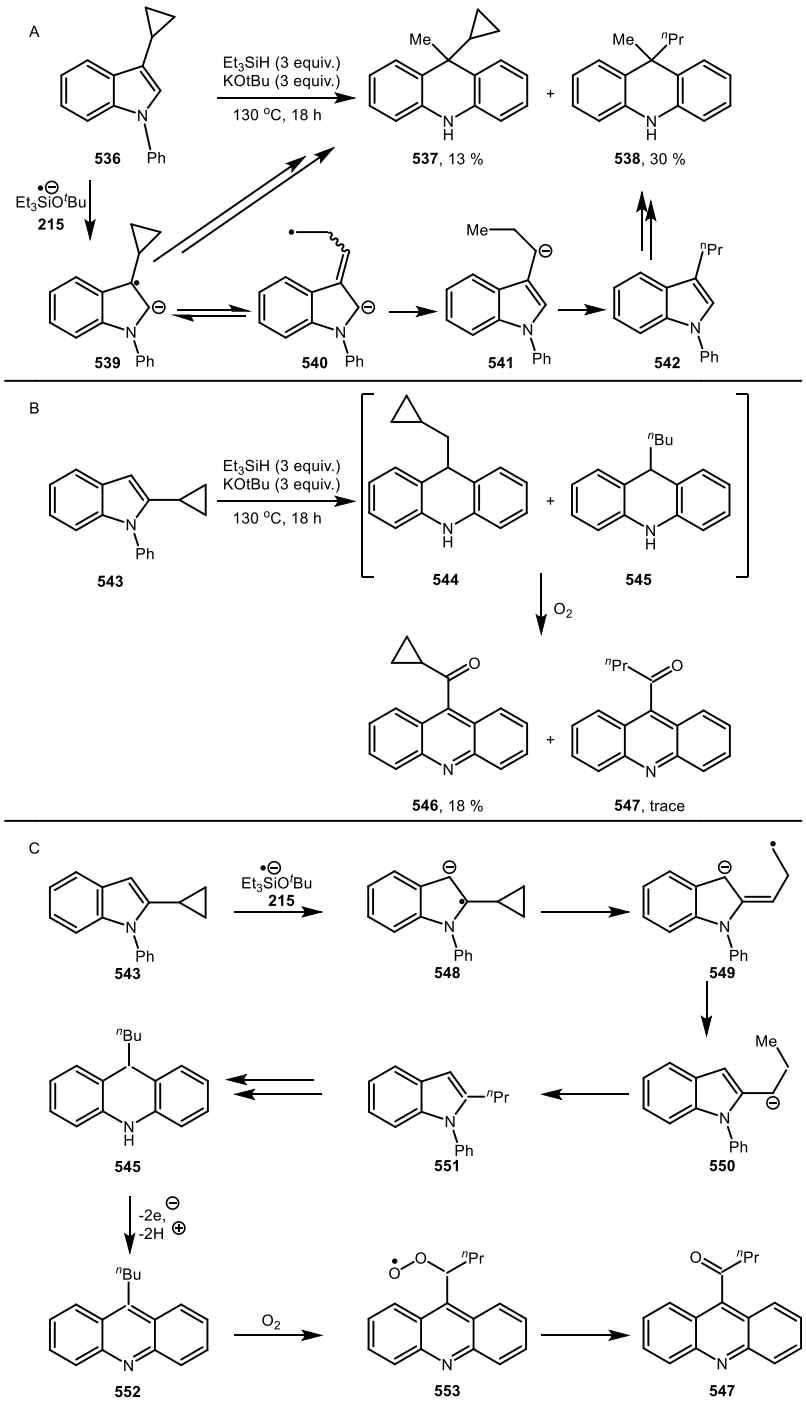
Scheme 124 - Evidence of Radical Intermediates and Loss of Alkenyl Groups

It was thought that if an alkenyl group could stabilise cleavage of the side-chain, then perhaps a benzyl group could also afford such stabilisation. Therefore, substrate **534** was prepared and treated under the Et_3SiH/KO^tBu conditions (Scheme 124C). No reaction was found to occur in this case, with starting material being recovered in 77 % yield. It is likely that in this case, deprotonation of the benzylic position may occur to afford anion **535**. This anion may be too

electron-rich to receive another electron from the Et_3SiH/KO^tBu system, and therefore no reaction occurs.

Further evidence of radical intermediates was obtained by the preparation and use of cyclopropyl substrates **536** and **543** as radical probes (Scheme 125). Substrate **536** was found to afford an inseparable mixture of ring-closed and ring-opened products **537** and **538** (Scheme 125A). This could be consistent with the electron transfer pathway, as electron transfer from **215** would afford intermediate **539**. This could then either be processed directly via the mechanism already discussed to afford **537**, or could undergo ring-opening of the cyclopropane to afford **540**. The ring-opening of the cyclopropane in this case would be expected to be reversible due to the stabilisation afforded to the radical anion **539**, so mixtures of ring-opened and ring-closed products would be expected.[129–131] Hydrogen atom abstraction to afford **541**, followed by protonation would allow for the formation of **542**. This can then be processed by the same mechanism as the other substrates to afford ring-opened product **538**. However, a result which contradicts the proposal of an electron transfer-mediated reaction was obtained from the use of **543** (Scheme 125B). Upon treatment of **543** under the Et_3SiH/KO^tBu system, ring-opening of the cyclopropane (*i.e.* product **545**) was observed in trace amount, with the major product being ring-closed species **544**. These dihydroacridines could not be purified, so were allowed to undergo aerial oxidation. Interestingly, oxidation to the ketones **546** and **547** was observed. The formation of the ring-opened products **545** and **547** would fit with the electron transfer mechanism previously discussed. Electron transfer from **215** to afford radical anion **548** could occur, followed by ring-opening of the cyclopropane to afford radical anion **549** (Scheme 125C). Abstraction of a hydrogen atom (likely from Et_3SiH) would afford anion **550**, and protonation would afford **551**. Indole **551** could then be processed as previously discussed to afford dihydroacridine **545**. Subsequent oxidation in air could afford firstly acridine **552**. Hydrogen atom abstraction at the benzylic position followed by recombination with a peroxyl radical would afford intermediate **553** en route to ketone **547**.[172]

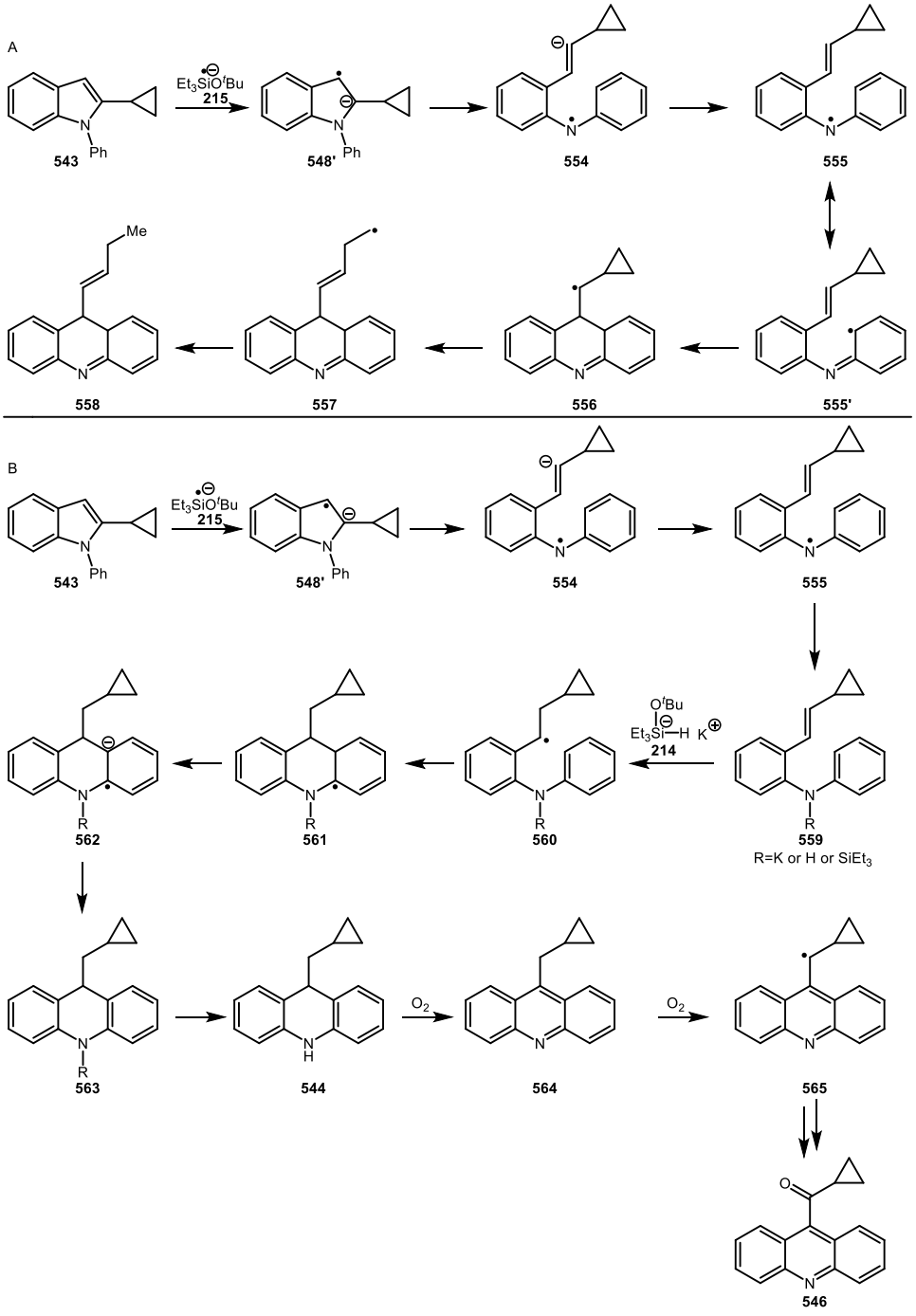
However, ring-closed acridine **546** cannot be the product from an electron transfer reaction. Electron transfer to substrate **543** would be expected to afford radical anion **548'**, which could fragment to **554** (Scheme 126A). Protonation of **554** would afford radical **555**, which is a resonance form of **555'**. Cyclisation onto the alkene via a 6-*exo*-trig transition state would afford radical **556**. This radical has no benzylic stabilisation and would therefore behave as a normal secondary radical, undergoing essentially irreversible ring-opening to **557**. Hydrogen atom abstraction would lead to **558**, and essentially no ring-closed compounds would remain. This result is a clear contradiction of the electron transfer pathway previously discussed, and therefore it is likely that an alternative or additional mechanism is taking place.



*Scheme 125 - Use of Cyclopropyl Substrates **536** and **543** as Radical Probes*

Substrate **543** could undergo electron transfer, C-N bond cleavage, and protonation as before to afford **555**, but at this stage alternatively undergo quenching of the nitrogen-centred radical to afford **559** (Scheme 126B). The quenching of the nitrogen-centred radical in **555** could take place either by reduction to the anion, hydrogen atom abstraction, or by silylation. This styrene could then undergo hydrogen atom addition from pentavalent silicate **214**, similar to the work of Jeon.[114] This would allow for the formation of radical **560** and allow the cyclopropane to remain intact. Next, 6-*endo*-trig cyclisation would afford radical **561**. Deprotonation of this species would afford radical anion **562**, which could either lose an electron *in situ* or upon exposure to oxygen at the end of the reaction to afford **563** (an interesting observation is the rapid colour change from pink

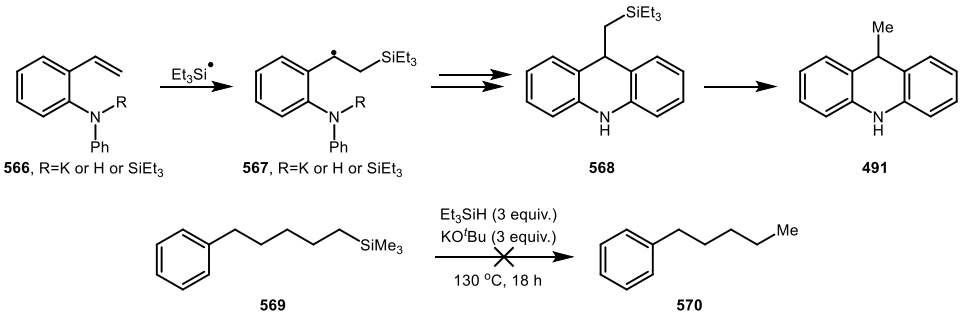
to brown upon exposing the reaction mixtures to oxygen). Conversion of the N-R group to N-H via either protonation or hydrolysis of the silylated amine would afford the dihydroacridine **544**. This dihydroacridine could then undergo aerial oxidation to firstly acridine **564**, followed by hydrogen atom abstraction by more oxygen to afford benzylic radical **565**. Although this radical could cause ring-opening of the cyclopropane, the equilibrium would now favour the ring-closed species due to the benzylic stabilisation afforded to this radical.[129–131] Further reaction of this radical with a peroxyl radical or with molecular oxygen would ultimately afford the product **546**.



*Scheme 126 - Expected Reactivity of **543** under (A) SET Conditions and (B) under HAT Conditions*

It is not clear how the reactions mentioned above with radical anion **341** or with K/KO^{t}Bu (Scheme 120 and Scheme 122) occur if not by electron transfer. It may be that both SET and HAT pathways are possible, but in the absence of a suitable HAT reagent (*e.g.* when K/KOtBu is used) the entire mechanism proceeds via SET instead. A remaining mechanistic question is whether the initial ring-opening of the indole (*i.e.* the conversion of **543** to **555**) is due to electron transfer, or if this could also be due to hydrogen atom transfer.

An alternative mechanism could involve triethylsilyl radicals, as was proposed by Grubbs and Stoltz in their reactions.[1–5,7] A benzylic radical such as **567** could also form if silyl radicals were to add to a styrene intermediate such as **566** (Scheme 127). As the major products from the conversion of *N*-phenylindoles to dihydroacridines are not silylated (*e.g*. **491**), then desilylation of intermediates such as **568** must occur either during the reaction or upon work-up if the reaction proceeds via silyl radical addition. To determine if this was likely, alkyl silane **569** was prepared and treated under the Et$_3$SiH/KO^{t}Bu conditions, followed by a standard work-up. No desilylation was found to have occurred under these conditions, meaning that silyl radical addition is unlikely to play a role in the conversion of *N*-phenylindoles to the corresponding dihydroacridines.

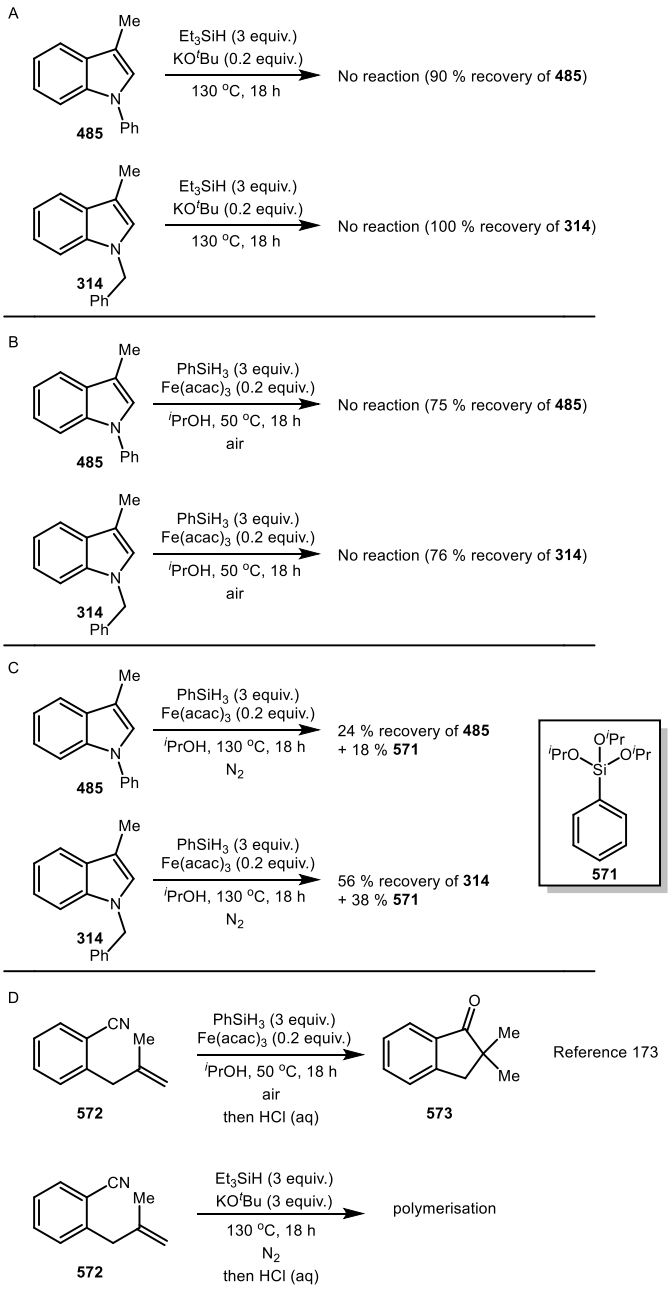


Scheme 127 - Silyl Radical Addition to Styrene Intermediates

To determine if HAT was occurring in the mechanism, substrate **485** was treated under the Et$_3$SiH/KO^{t}Bu system using substoichiometric base, as was previously published by Jeon (Scheme 128A).[114] This did not lead to any formation of product, with starting material being recovered in 90 % yield. At this stage, we reconsidered the mechanism for the debenzylation of indoles (Chapter 3). Substrate **314** was also treated with substoichiometric base, and no reaction was found to occur, with 100 % of starting material being recovered.

Substrates **485** and **314** were also treated under iron-catalysed HAT conditions recently published by our group (Scheme 128B).[173] No reaction was found to take place for either substrate, with 75 % and 76 % of starting material recovered for **485** and **314** respectively. It was thought that the difference in temperature (50 °C vs 130 °C), or the presence of air in the reaction mixture under the literature HAT conditions may be affecting the reactions. Therefore, the reactions were repeated at 130 °C under nitrogen (Scheme 128C). Only starting materials (**485** or **314**) and by-product **571** were detected in the reaction mixture. The yields of recovered starting material

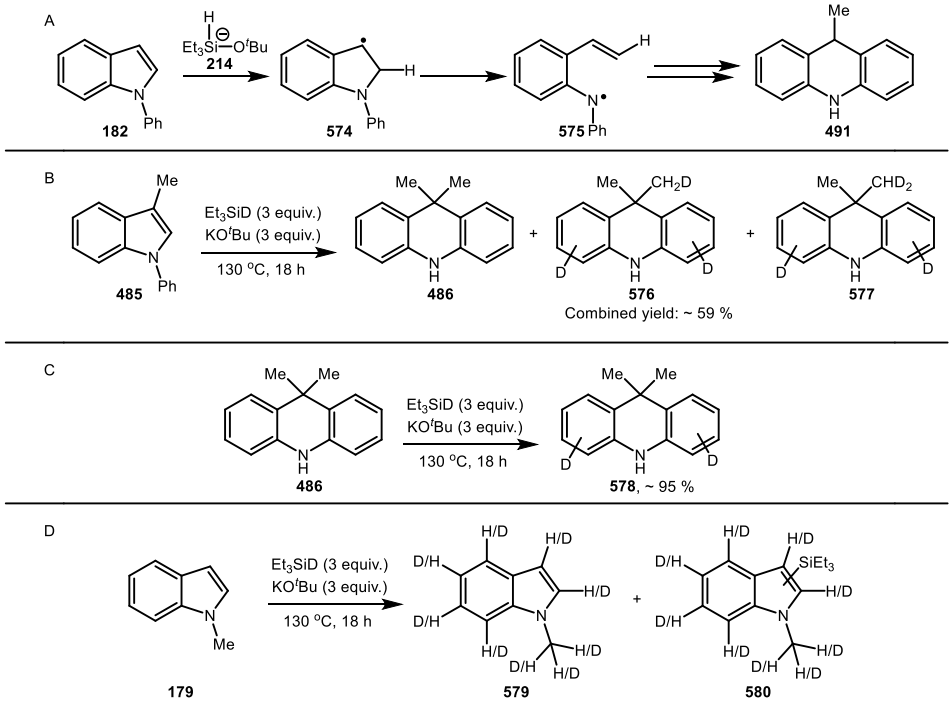
were low (24 % and 56 %), but it is not clear what has happened to the rest of this material as no other products were detected. It may be that the presence of the iron cation does not allow for HAT to occur, and a potassium counterion may be necessary, similar to the proposal by Jeon.[114]



Scheme 128 - Mechanistic Study for HAT Reactivity

Substrate **572**, which was successfully cyclised to **573** under the iron-catalysed HAT conditions,[173] was then treated under the Et_3SiH/KO^tBu system (Scheme 128D). Polymerisation was found to occur, which was diagnosed by the presence of broad peaks in the ^1H NMR spectrum, with no cyclised products detected. All of this evidence seems to suggest that HAT may not be responsible for the initial ring-opening of the indole, but no firm conclusion can be made at this stage.

If the initial ring-opening of the indole were occurring by hydrogen atom transfer to the indole skeleton, then it is likely that this hydrogen atom transfer would occur to the 2-position to afford benzylic radical **574** (Scheme 129A). This radical could then cause fragmentation of the C_2-N bond to afford **575**, which could then continue to the dihydroacridine product **491**. To determine if this was occurring in our mechanism, substrate **485** was treated with Et_3SiD/KO^tBu (Scheme 129B).[d] If deuterium atom transfer was occurring in this case, deuteration would be expected on only one methyl group in the product (*i.e.* the methyl group that originated as the C_2-position of the indole). Two deuterium atom additions would be possible in this position if HAT occurred both to ring-open the indole and to add to the styrene. Products **486**, **576** and **577** were formed from this experiment, and feature zero, one and two deuterium atoms in one of the methyl groups respectively, as determined by the presence of a singlet, a triplet, and a quintet in the ^{13}C NMR. This may be evidence for HAT occurring, with the CH_2D group resulting in the generation of Et_3SiH *in situ* (if the formation of triethylsilyl radicals occurred from Et_3SiD, then these radicals could abstract a hydrogen atom from somewhere to become Et_3SiH). It is likely that only one deuterium atom would be present on the methyl group of the dihydroacridines produced if the SET pathway was followed (Scheme 119). Deuterium atom transfer was observed to the aromatic rings, with some H/D exchange occurring in the formation of **576** and **577**.



Scheme 129 - HAT to N-phenylindoles

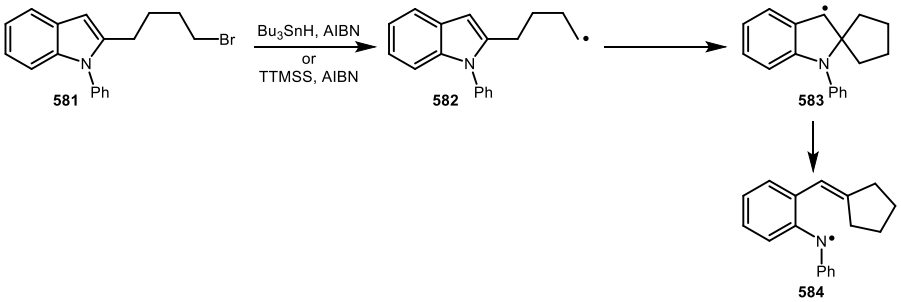
Compound **486** was then treated under the Et_3SiD/KO^tBu conditions (Scheme 129C).[h] Again, deuterium incorporation was observed in the previously unlabelled aromatic rings, but importantly, no deuteration of the methyl groups was observed by NMR. This is consistent with the deuteration of the methyl groups occurring during the course of the reaction mechanism, and not through

[h] This reaction was carried out by Daniela Dimitrova, University of Strathclyde

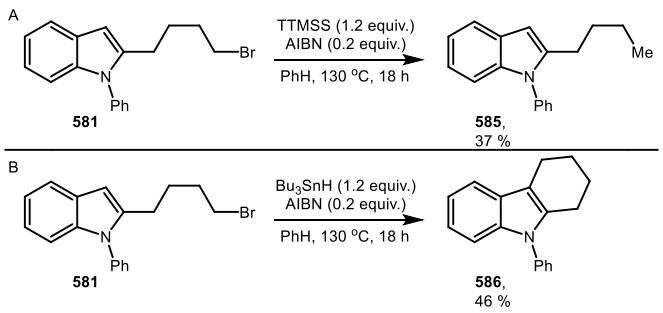
indiscriminate H/D exchange of the product. However, it is still possible that triethylsilyl radicals may abstract a hydrogen atom from the methyl group of **485**, and this resulting radical could then abstract a deuterium atom from Et_3SiD, and so this experiment is inconclusive.

Further evidence of H/D exchange was obtained from treatment of **179** under the Et_3SiD/KO^tBu conditions (Scheme 129D). A complex mixture of deuterated and silylated products was obtained from this reaction, which included varying levels of deuteration in all positions including the *N*-methyl group. Overall, the results in Scheme 129 do not clearly point to either the SET or HAT mechanism for the ring-opening of the indole.

To determine if HAT could be responsible for the initial ring-opening of the indole, substrate **581** was prepared (Scheme 130). Abstraction of the bromine atom from **581** with tin or silicon radicals could afford radical **582**, which could add into the 2-position of the indole to afford radical **583** (similar to how a hydrogen atom would add to the indole). Radical **583** could then cause fragmentation of the C_2-N bond. However, upon treatment of **581** with tris(trimethylsilyl)silane (TTMSS) and AIBN or with Bu_3SnH and AIBN, no ring-opening of the indole was detected in either case. From TTMSS/AIBN, reduced product **585** was isolated in 37 % yield (Scheme 131A), whereas from Bu_3SnH/AIBN, compound **586** was isolated in 46 % yield (Scheme 131B). These results suggest that with TTMSS/AIBN, radical **582** is fast to abstract a hydrogen atom from TTMSS, and no cyclisation is observed. When Bu_3SnH/AIBN is used, hydrogen atom abstraction is slower and cyclisation is observed into the 3-position of the indole, which would not lead to any cleavage of the C_2-N bond.

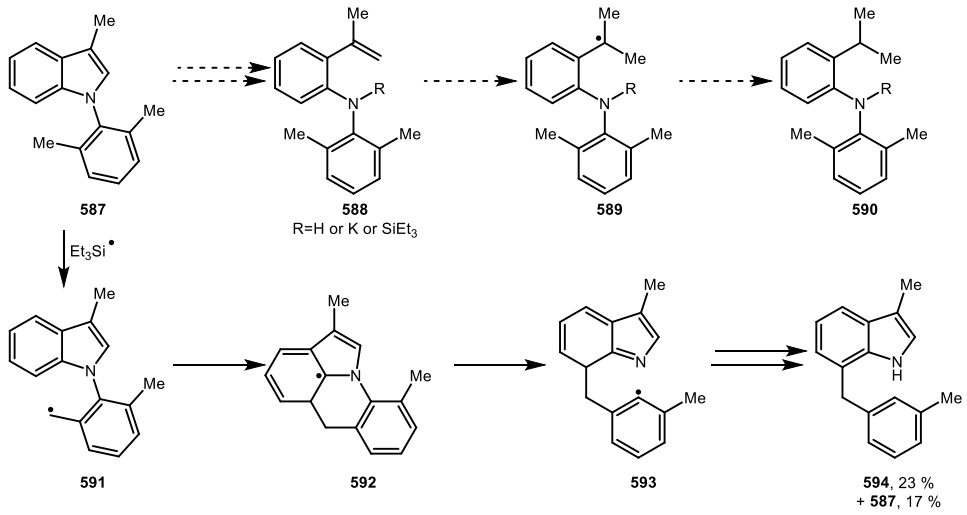


*Scheme 130 - Substrate **581** used to Determine if HAT Causes Ring-Opening*



*Scheme 131 - Treatment of **581** with TTMSS/AIBN and Bu_3SnH/AIBN*

To attempt to trap a reaction intermediate, substrate **587**, which cannot easily undergo cyclisation, was prepared and treated under the Et_3SiH/KO^tBu conditions (Scheme 132). It was thought that this may proceed via styrene **588** as was proposed for the other substrates. HAT could then occur to form **589**, which cannot easily cyclise in this case. Hydrogen atom abstraction may then form a product such as **590**. However, compound **594** was isolated in 23 % yield instead, along with 17 % of recovered **587**. Compound **594** may form by abstraction of a benzylic hydrogen atom by triethylsilyl radicals to afford **591**. This could then undergo rearrangement to intermediate **593** (possibly via intermediate **592**). Proton transfer and hydrogen atom abstraction from Et_3SiH could then generate the product.

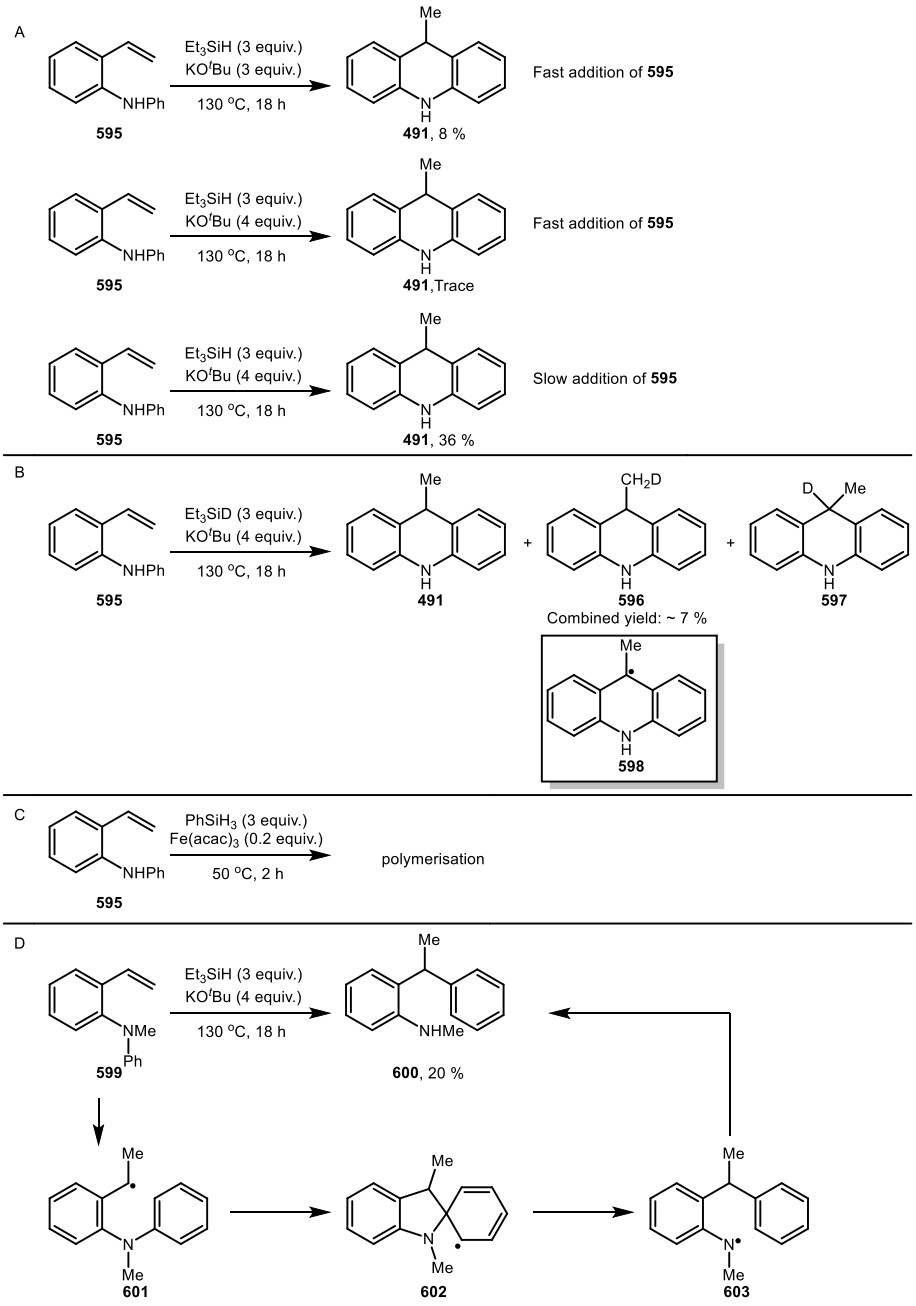


Scheme 132 - Attemped Isolation of a Reaction Intermediate

As the above mechanistic proposals have featured a styrene intermediate, substrate **595** was prepared and used to probe the mechanism of the reaction (Scheme 133A). Upon treatment of **595** with Et_3SiH/KO^tBu, dihydroacridine **491** was isolated in 8 % yield. It appeared as if the rest of the material had polymerised, as diagnosed by the broad nature of the crude ^1H NMR spectrum. Increasing the number of equivalents of KO^tBu from three to four (due to the relative acidity of the NH in **595**) led to a decrease in the yield of **491**. It is likely that due the presence of all of **595** at the start of the reaction, if HAT to the styrene occurs then polymerisation is likely. However, if the styrene concentration is kept low due to slow addition of the substrate, then the yields of polymerisation products may be decreased and the yield of dihydroacridine **491** may increase. This is indeed the case, as when **595** was added slowly to the reaction mixture over a period of one hour, **491** was isolated in 36 % yield.

A study of styrene **595** with Et_3SiD/KO^tBu was also carried out (Scheme 133B). Here, under HAT conditions, deuterium incorporation would only be expected to occur on the methyl group of the resulting dihydroacridine. However, in the mixture of products obtained (**491** and **596**-**597**), a small proportion of deuterium incorporation can be observed in the benzylic position (*i.e.* compound **597**). However, it is not clear if this deuterium incorporation occurs in this position due to a pathway other than HAT being responsible for the conversion of styrene **595** to

dihydroacridines, or if a radical species (such as triethylsilyl radicals) can abstract a benzylic hydrogen atom from a species such as **591** to afford stabilised radical **598**. This stabilised radical can then abstract a hydrogen or a deuterium from Et_3SiH or Et_3SiD, which would lead to some deuterium incorporation in the products.

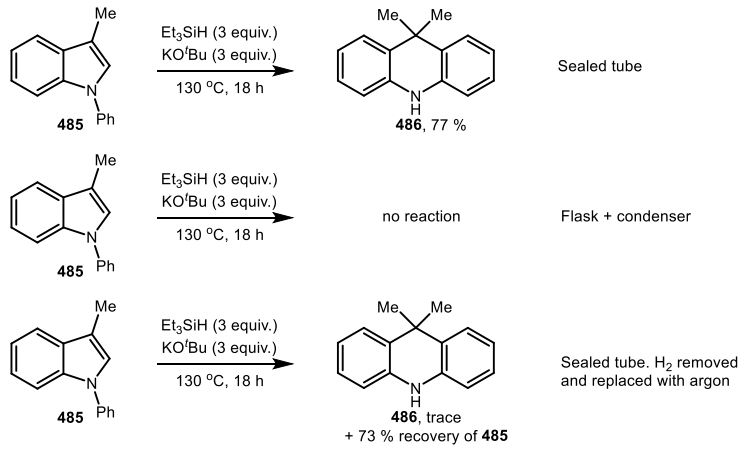


Scheme 133 - Styrene Intermediates used as Mechanistic Probes

Styrene **595** was also treated under the iron-catalysed HAT conditions previously discussed, however no dihydroacridines were produced, and only polymerisation products were observed, as diagnosed by the broad nature of the ^1H NMR spectrum (Scheme 133C).[173] This is consistent with the work of Jeon, where the potassium counterion is necessary for hydrogen atom addition to styrenes.[114]

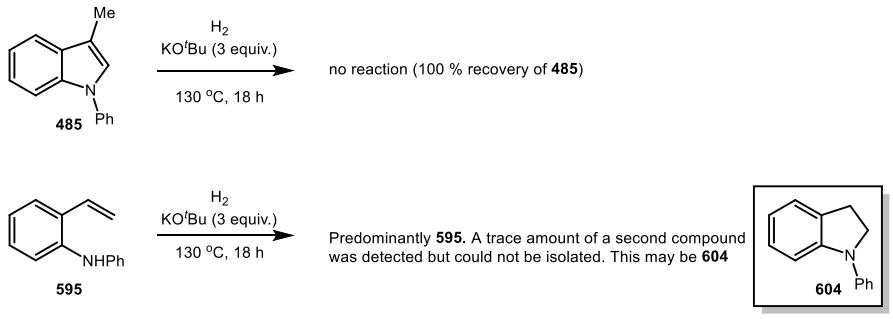
Interestingly, styrene **599** did not form a dihydroacridine as may be expected, but instead formed **600** (Scheme 133D). Upon the formation of radical **601** by HAT, a 5-*exo*-trig cyclisation may occur instead with a neutral trivalent nitrogen atom present to afford spiro-intermediate **602**. This intermediate can then rearomatise with cleavage of the C-N bond, forming radical **603**. This radical can then abstract a hydrogen atom to afford **600**.

Previous work by Grubbs *et al.* has shown that hydrogen gas which is produced *in situ* from the combination of Et_3SiH/KO^tBu is necessary for the stability of the active species formed in the reactions.[1] When the conversion of **485** to **486** was attempted in a flask with a condenser rather than in a sealed pressure tube, no reaction was found to take place (Scheme 134). Similarly, Et_3SiH and KO^tBu were stirred together for an hour, and then the hydrogen gas generated was removed and replaced with argon. Substrate **485** was then added, and the reaction allowed to stir for 18 h. Only a trace amount of **486** was detected by GC-MS, with predominantly starting material **485** recovered. These results show that, similar to Grubbs, hydrogen gas is necessary for the reactions to occur.



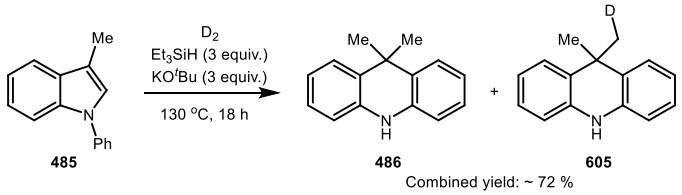
Scheme 134 - Effect of Hydrogen Gas

It has previously been reported that the combination of KO^tBu with hydrogen gas could carry out the reduction of non-enolisable ketones, *e.g.* benzophenone.[174] Although this reduction of non-enolisable ketones takes place under high temperatures and high pressures of hydrogen, it was thought that the hydrogen generated from Et_3SiH/KO^tBu in the conversion of *N*-phenylindoles to dihydroacridines could be interacting with KO^tBu to play a role in the transformation. Therefore, substrates **485** and **595** were treated with KO^tBu in a hydrogen atmosphere (Scheme 135). No dihydroacridine was formed from either substrate, suggesting that the reactivity seen in the $Et_3SiH/KOtBu$ system is not due to the hydrogen interacting with KO^tBu. From **485**, starting material was recovered in 100 % yield. From **595**, a small amount of a second compound was present that could not be isolated. NMR and GC-MS analysis of the crude material suggests that this compound may be **604**, which would form by a 5-*endo*-trig cyclisation. As this is a disfavoured cyclisation, the yield of **604** would be expected to be low.



Scheme 135 - Reactions of Substrates with H_2 and KO^{t}Bu

Interestingly, when the generated hydrogen gas was removed and replaced with deuterium gas, deuterium incorporation was observed in the conversion of **485** to **486** and **605** (Scheme 136). Therefore, it is likely that there is H/D exchange between the gas and the silyl species present in the reaction mixture. Interestingly, deuterium was observed on only one methyl group again, which could be consistent with an SET or an HAT mechanism. The presence of two deuterium atoms on the methyl groups was not observed by ^{13}C NMR in this case, but the presence of this compound cannot be ruled out or confirmed by GC-MS due to the presence of some deuteration on the previously unlabelled aromatic rings in **486** and **605**.



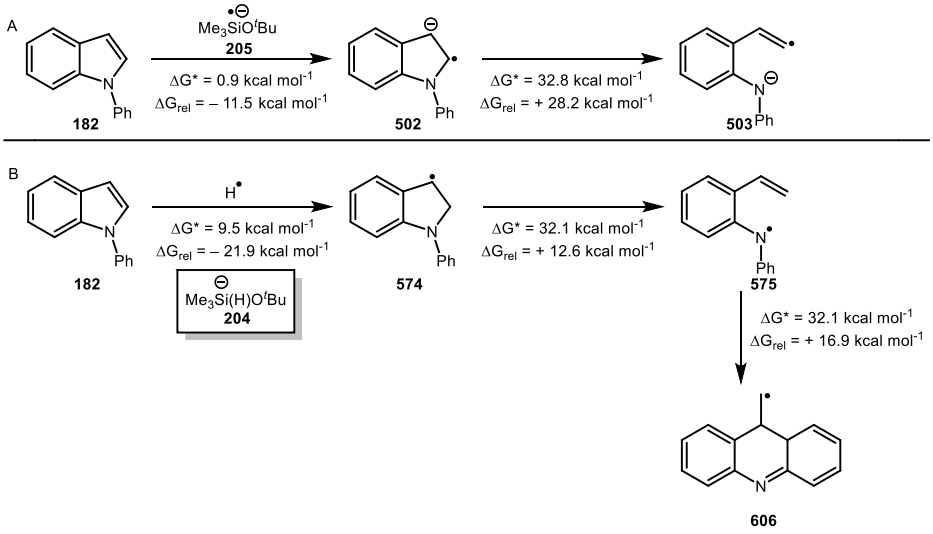
Scheme 136 - Deuterium Incorporation from Deuterium Gas

In Chapter 3, collaboration with computational chemists proved helpful in determining the mechanism of the debenzylation reactions. To probe the mechanism of the conversion of *N*-phenylindoles to dihydroacridines, computational modelling of the various mechanistic possibilities was carried out.[175,i] However in this work, computational chemistry could not help to determine the mechanism of the reaction. The electron transfer mechanism was first studied, with electron transfer from **205** to **182** being facile, with an energy barrier of 0.9 kcal, mol^{-1} and a relative energy of –11.5 kcal, mol^{-1} (Scheme 137A). However, the cleavage of the C_2-N bond in **502** to afford **503** proved to possess a high energy barrier of 32.8 kcal, mol^{-1}, with a relative energy of + 28.2 kcal, mol^{-1}. Therefore, the calculations suggest that it is unlikely that this mechanism is in operation in the conversion of *N*-phenylindoles to dihydroacridines.

Similarly, the hydrogen atom transfer pathway was modelled computationally (Scheme 137B).[i] Hydride transfer from **204** could not be modelled computationally due to the formation of two

[i] These calculations were carried out by Allan Young, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modeled using the CPCM solvation model.

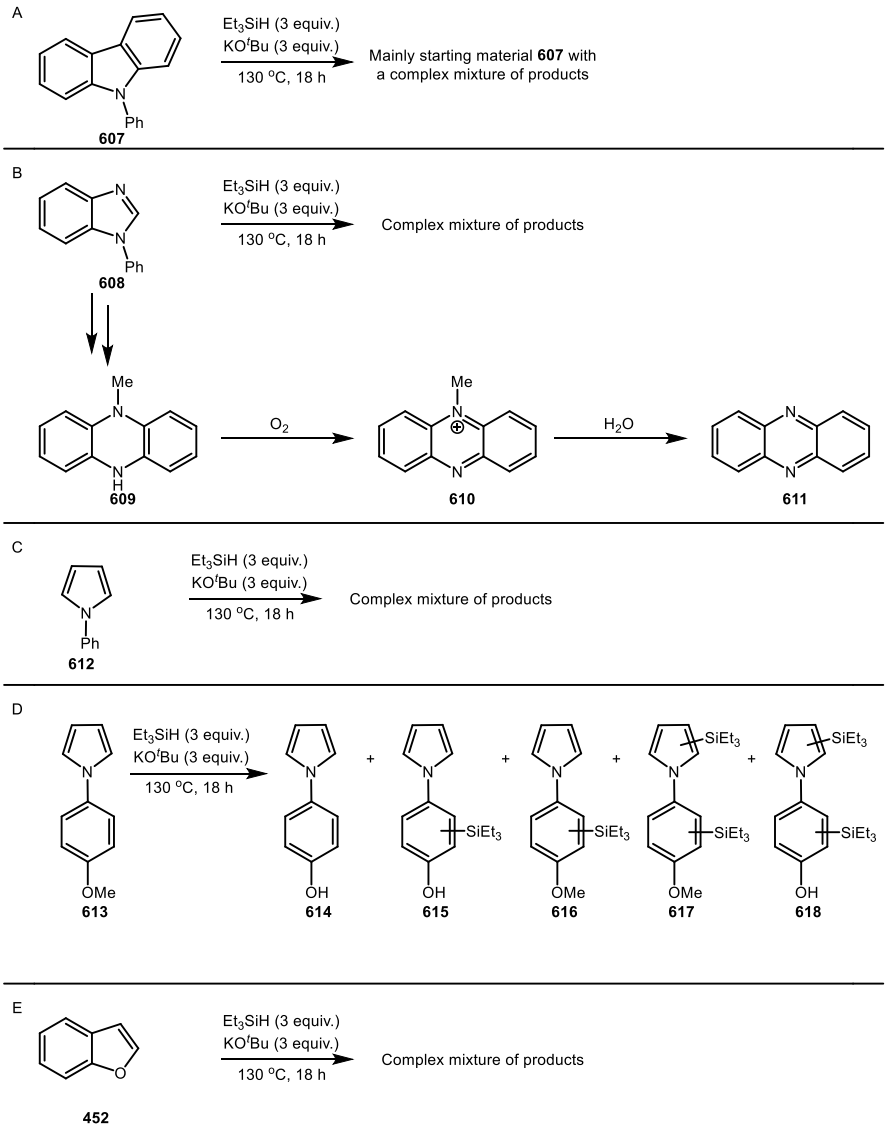
radicals, and therefore a simple hydrogen atom was used to model the hydrogen atom transfer step. This was found to have a barrier of 9.5 kcal, mol^{-1}, with a relative energy of – 21.9 kcal, mol^{-1}, meaning that hydrogen atom transfer could occur to form **574**. However, both the fragmentation of the C_2-N bond to form **575** and the cyclisation onto the styrene to form **606** were found to have a high barrier (32.1 kcal, mol^{-1}) with both steps being endergonic. Therefore, the calculations also suggest that it is unlikely that this mechanism is occurring. However, the calculations do not take into account the stabilisation effect of potassium cations and how this may affect the energies associated with each step. This is something which could be studied in the future. The calculations also do not take into account the stabilisation from potassium species afforded to intermediates in the electron transfer pathway. This could have an effect on the energies calculated. Unfortunately, the calculations do not point clearly to one mechanism or the other.



Scheme 137 - Computational Modelling of the Possible Mechanisms.[i]. ΔG^* represents the energy barrier, whereas ΔG_{rel} represents the change in relative energy.

Finally, a range of similar substrates were treated under the Et_3SiH/KO^tBu conditions to determine if similar transformations could occur. Firstly, compound **607** was tested (Scheme 138A). ^1H NMR and GC-MS analysis of the crude reaction mixture showed that the mixture contained a lot of starting material, with some other products which could not be identified. Quantification of the starting material remaining was difficult due to the overlapping signals in the NMR spectrum.

N-phenylbenzimidazole **608** was found to produce a complex mixture of products (Scheme 138B). GC-MS indicated that there may be a very small amount of **611** present, but this could not be confirmed by isolation. If this compound has formed, it is likely that **608** has followed the same mechanism as the *N*-phenylindoles to afford **609**. This compound would be rapidly oxidised upon exposure to air to **610**, which could undergo demethylation upon aqueous work-up to afford **611**.



Scheme 138 - Further Substrates Treated with Et_3SiH/KO^tBu

Compound **612** was also found to produce a complex mixture of products (Scheme 138C). It was thought that, due to the presence of two monocyclic ring systems in this substrate, electron transfer (if this is the mechanism for ring-opening) may occur to the less electron-rich phenyl group rather than the pyrrole. Therefore, substrate **613** was used in an attempt to make the aryl group more electron rich (Scheme 138D). Cleavage of the methyl ether was observed and compounds **614**-**618** were detected in the crude reaction mixture but could not be purified.

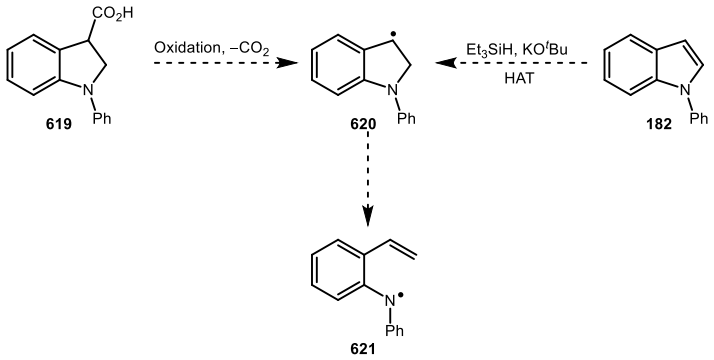
Finally, benzofuran **452** was treated under the Et_3SiH/KO^tBu system (Scheme 138E). This was found to produce a complex mixture of products under our conditions.

4.3: Conclusions and Future Work

In conclusion, the Et_3SiH/KO^tBu system has been shown to facilitate the conversion of *N*-arylindoles to their corresponding 9,10-dihydroacridines. Strong evidence for electron transfer

conditions has been reported, as the reaction was also mediated by K/KO^{t}Bu which cannot proceed via hydrogen atom transfer. However, the formation of cyclopropylacridine **545** from substrate **543** shows strong evidence of hydrogen atom addition to an intermediate styrene. It is therefore likely that HAT to the styrene intermediates is faster than the SET pathway, and this is the reason why complete ring-opening of the cyclopropane does not occur in this case.

Future work that might help to determine the mechanism of the initial ring-opening of the *N*-arylindoles could be to prepare substrate **619** (Scheme 139). This substrate could undergo oxidative decarboxylation to afford radical **620** – which would be the same species formed if HAT occurred to *N*-phenylindole **182**. If the cleavage of the C_2-N bond was observed, then perhaps this would provide evidence for ring-opening by an HAT pathway.

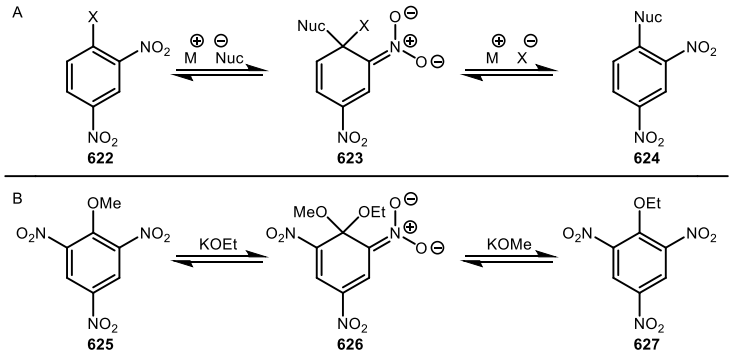


Scheme 139 - Future Work

5: Concerted Nucleophilic Aromatic Substitution (cS$_N$Ar) Reactions Mediated by Et$_3$SiH/KO^{t}Bu

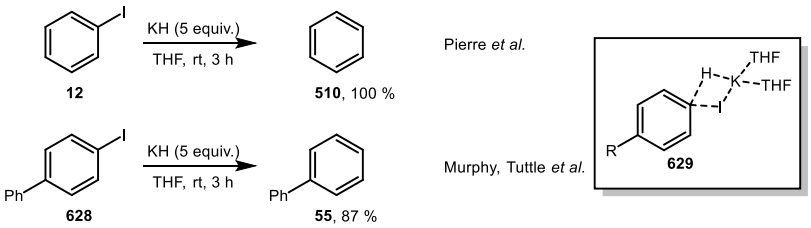
5.1: Introduction

Substitution reactions on aromatic rings are central to organic chemistry, with multiple uses in the synthesis of pharmaceuticals. One class of substitution on aromatic rings is the nucleophilic aromatic substitution reaction (S$_N$Ar). The long-accepted mechanism of S$_N$Ar reactions involves a two-stage process (Scheme 140A).[176] Firstly, a nucleophile adds to a strongly electron-deficient arene *e.g*. **622** to afford a Meisenheimer intermediate **623**. This intermediate can then rearomatise with loss of the leaving group to afford the product **624**. The presence of such an intermediate was confirmed by Meisenheimer, who treated **625** with KOEt and was able to isolate **626** as a red solid.[177] Treatment of this intermediate with acid afforded a mixture of ethers **625** and **627**. Concerted nucleophilic aromatic substitution (cS$_N$Ar) reactions were recently comprehensively reviewed by our group,[109] but some key references are mentioned below to introduce this chapter.



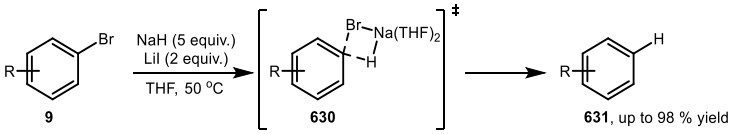
Scheme 140 - Classical Nucleophilic Aromatic Substitution Mechanism

A number of S$_N$Ar reactions have been reported which do not agree with the classical mechanism. Pierre *et al.* (and later Tuttle and Murphy *et al.*) showed that aryl halides without strong electron-withdrawing groups could undergo hydrodehalogenation with KH in THF (Scheme 141).[178,179] This reaction was shown not to proceed via a benzyne intermediate since there was no hydrogen generated during the course of the reaction. The order of reactivity was also shown to be ArI > ArBr > ArCl > ArF, which is the reverse of the reactivity order generally observed in classical S$_N$Ar mechanisms. The group concluded that a concerted S$_N$Ar reaction was occurring via four-centred transition state **629**. This was later confirmed through further computational and experimental studies by Tuttle and Murphy *et al*.[179]



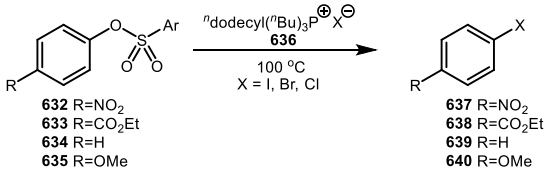
Scheme 141 - Hydrodehalogenation of Haloarenes by cS$_N$Ar

Hydrodehalogenation of bromoarenes was also reported by Hirao and Chiba *et al*. by their NaH/LiI composite.[146] Aryl bromides **9** were reduced to the parent arenes **631** via transition state **630**. Computational studies found that the reaction proceeded without the formation of a Meisenheimer intermediate, and a Hammett plot showed a linear correlation of the dehalogenation of aryl bromides with various electronic properties with ρ = +0.47. These data are consistent with a cS_NAr process.



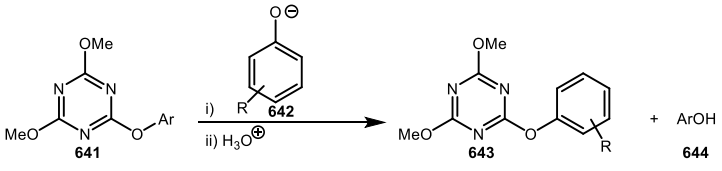
Scheme 142 - Hydrodehalogenation of Bromoarenes

Another early study pointing to cS_NAr reactivity was conducted by Fry and Pienta, who carried out mechanistic studies to determine that the halogenation of arylsulfonates **632**-**635** by dodecyltributylphosphonium salts **636** to form haloarenes **637**-**640** was occurring by a concerted mechanism (Scheme 143).[180] Hammett plots were found to produce straight lines with ρ values of +1.5 and +1.1 for σ and σ* respectively. This means that the effect of the R-group on **632**-**635** is significantly lower than for many literature S_NAr reactions (+3<ρ<+5). Interestingly, substrate **635** bearing a methoxy group was successful, with the methoxy group being unable to stabilise negative charge generated in a conventional S_NAr mechanism. Although these results point towards cS_NAr reactivity, the authors did not speculate on the exact nature of the mechanism.



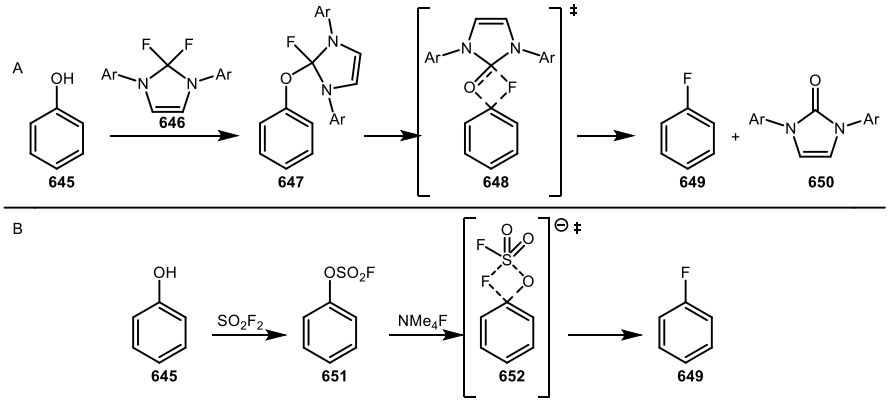
Scheme 143 - Halogenation of Arylsulfonates by Fry and Pienta

Williams *et al*. also reported a number of cS_NAr reactions on substituted 1,3,5-triazines (Scheme 144).[181–183] They found that the reactions of various phenolates **642** with **641** followed a linear Brønsted plot over a range of pK_{ArOH} values above and below that of the conjugate acid of the leaving group (*i.e.* **644**). The lack of curvature in the free energy relationship suggested that there was no change in mechanism when moving from strongly electron-withdrawing groups to weakly electron-donating groups, which is consistent with a concerted mechanism. Similar work in the same 1,3,5-triazine core with aryloxy and pyridine leaving groups was studied with morpholine (ρ = +1.65) and DMAP (ρ = +0.82) as nucleophiles led to the conclusion that a cS_NAr was in operation for these reactions.



Scheme 144 - Early Work by Williams which Proceeds via a cS_NAr Mechanism

Ritter *et al.* have shown that the deoxyfluorination of phenols **645** with PhenoFluor **646** proceeds via concerted transition state **648** (Scheme 145A).[184–188] DFT studies showed a single transition state without the formation of any Meisenheimer intermediate. A large primary kinetic isotope effect (KIE) was observed for $^{16}O/^{18}O$ (1.08 ± 0.02), showing that the cleavage of the C-O bond is involved in the rate-determining step. Furthermore, a Hammett plot revealed no change in mechanism when moving from electron-deficient phenols to electron-rich phenols. The low value of ρ (+1.8) shows that there is not a full build-up of negative charge on the aryl ring in the transition state – again, this is consistent with a concerted mechanism. A similar transformation was reported by Sanford *et al.* who showed the deoxyfluorination of phenols **645** to afford **649** via aryl fluorosulfonate intermediates **651** (Scheme 145B).[189] Again, DFT calculations showed a concerted transformation via transition state **652**, without the formation of a Meisenheimer intermediate.

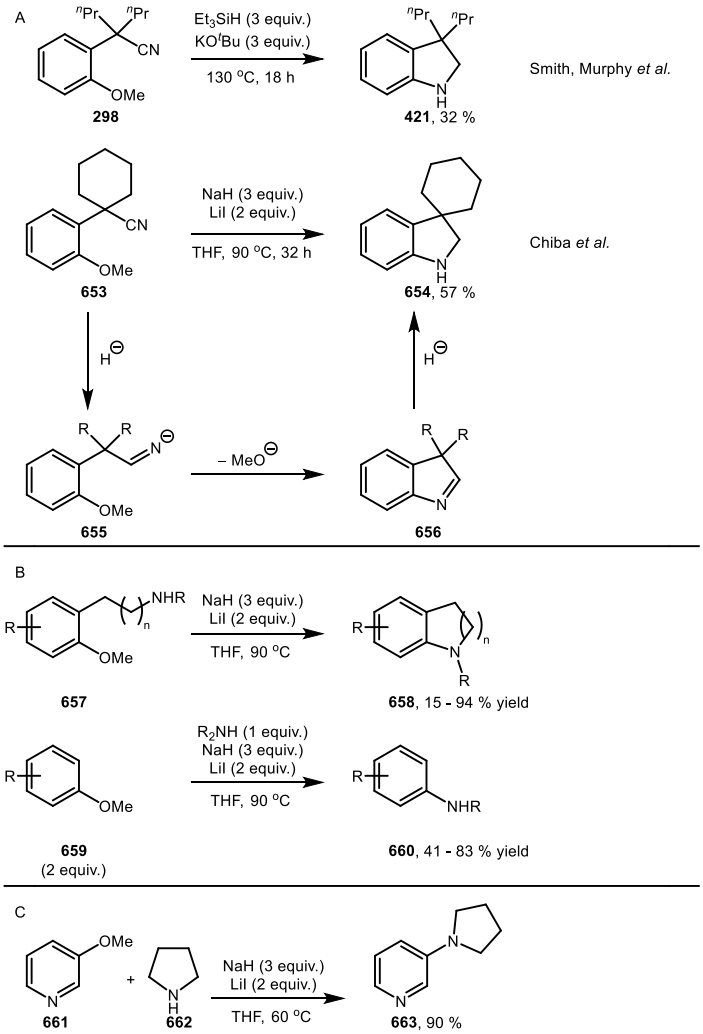


Scheme 145 - Fluorodeoxygenation of Phenols by A) Ritter et al. and B) Sanford et al.

During our previous studies on the reductive decyanation of benzylic nitriles (see Chapter 3), it was discovered that substrate **298** bearing an *ortho*-methoxy group did not undergo reductive decyanation, and instead formed indoline **421** (Scheme 146A). This type of transformation was also reported by Takiti and Chiba *et al.* who used an NaH/LiI composite to undergo hydride transfer to the nitrile of **653**, forming intermediate **655**.[148] The next step involves a concerted nucleophilic aromatic substitution, where the nucleophile displaces the methoxide in a concerted process, without the formation of a Meisenheimer intermediate. This leads to the formation of indolenine **656**. A further hydride transfer from the NaH/LiI composite affords indoline **654**.

Building on this, Takiti and Chiba formed a variety of nitrogen-containing heterocycles starting by the nucleophilic amination of methoxyarenes, via both intra- and intermolecular reactions (Scheme 146B).[148] This procedure was found to be compatible with both electron-deficient and electron-rich methoxyarenes. A Hammett plot showed ρ = +1.99, again indicating that there is no full build-up of negative charge in the transition state. Computational analysis also indicated a single transition state with no formation of a Meisenheimer intermediate, again consistent with a concerted process. A similar concerted process was also proposed by Kusumoto and Nozaki in

a hydroxycyclopentadienyl iridium hydride demethoxylation, but no mechanistic evidence was presented to support this proposal.[190]

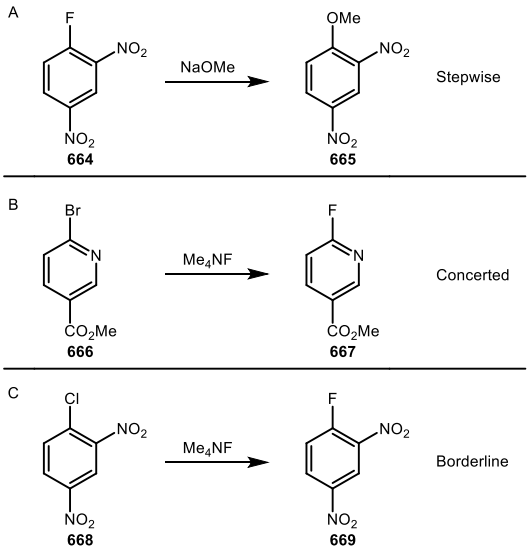


Scheme 146 - Concerted Nucleophilic Aromatic Substitution for the Formation of Indolines

The chemistry of Chiba was further extended to include the amination of methoxypyridines **661** by their NaH/LiI composite (Scheme 146C).[191] Although no Hammett studies or computational analysis was carried out, the amination of the unactivated 3-position of the methoxypyridine **661** makes it likely that this reaction does not proceed via a classical S_NAr pathway with the formation of a Meisenheimer intermediate, and instead proceeds via a cS_NAr pathway.

Jacobsen *et al.* recently surveyed S_NAr reactions by a combination of computational and experimental methods.[192] They based their expectations on the fact that isolated Meisenheimer intermediates can arise when i) substituents on the arene undergoing substitution provide good stabilisation of an intermediate anion and ii) where the leaving group is relatively poor so that the intermediate has some kinetic stability. In their three specific reactions, case A satisfies both of the above criteria, case B features substituents which do not provide such good stabilisation of the negative charge, and case C features substituents that provide excellent stabilisation of the negative charge but also features an excellent leaving group (Scheme 147). In these cases, case

A (**664→665**) would likely proceed via a classical S_NAr mechanism, case B (**666→667**) would likely be a cS_NAr process, and case C (**668→669**) would likely be borderline between the two mechanistic extremes. They then extended their studies to 120 S_NAr reactions with a variety of arenes, nucleophiles and leaving groups. They found that of these 120 reactions, 99 of these (83 %) proceed via a cS_NAr process.



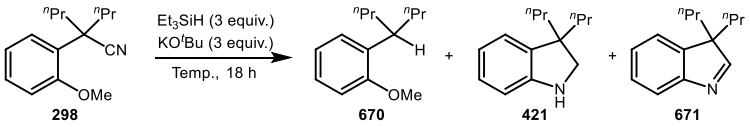
Scheme 147 - Studies on Classical or Concerted S_NAr Mechanisms by Jacobsen

5.2: Results and Discussion

Based on our discovery that the cyclisation of **298** to form indoline **421** is mediated by the Et_3SiH/KO^tBu system, the next steps were to optimise the yield of this cyclisation, carry out some mechanistic studies, and expand the scope of the cyclisation.

Firstly, the temperature of the reaction was varied to attempt to improve the yield of **421** (Table 2). It was found that lowering the reaction temperature to 90 °C (entry 2) allowed for the formation of some decyanated product **670** in 20 % yield, with the yield of cyclised product **421** increasing to 59 %. Further lowering the temperature to room temperature (entry 3) was not successful, and the yield of **421** decreased to 5 %. The yield of **421** began to increase again as the temperature was increased (entries 4-6) up until 70 °C (72 % yield of cyclised product **421**). A further increase to 80 °C (entry 7) was found to cause a decrease in yield again to 66 %. Therefore 70 °C was chosen as the optimum temperature of the cyclisation reaction for future studies. Interestingly, carrying out the reaction at lower temperatures (entries 3-5) led to the isolation of small amount of **671**, which suggests that the cyclisation is likely proceeding in a similar manner to Chiba's substrate.[148]

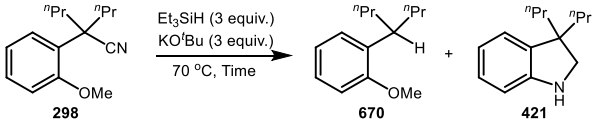
*Table 2 - Effect of Temperature on the Cyclisation of **298** into **421**.*



Entry	T/ °C	**670**	**421**	**671**	**298**
1	130	-	32 %	-	-
2	90	20 %	59 %	-	-
3	rt	-	5 %	2 %	57 %
4	40	15 %	36 %	Trace	18 %
5	60	-	60 %	1 %	Trace
6	70	11 %	72 %	-	Trace
7	80	12 %	66 %	-	Trace

Next, the reaction time was altered to determine if a shorter time than 18 h could be used (Table 3). It was found that upon decreasing the reaction time to 6 h (entry 2), a decrease in the yield of **421** occurred with some recovery of starting material **298**. Therefore, the rest of the optimisation was carried out with a reaction time of 18 h.

*Table 3 - Effect of Reaction Time on the Cyclisation of **298** into **421***



Entry	Time/ h	**670**	**421**	**298**
1	18	11 %	72 %	Trace
2	6	8 %	38 %	10 %

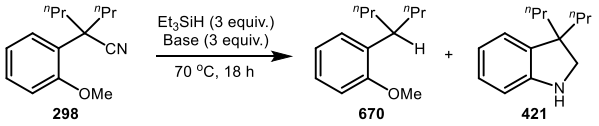
Next, the identity of the base was probed (Table 4). Similar to the results of Grubbs, NaO*t*Bu or LiO*t*Bu (entries 2 and 3) were not suitable replacements for KO*t*Bu (entry 1).[1–3] Similarly, other potassium bases were not effective to allow for the formation of cyclised product **421** (entries 4-6), with the exception of KH (entry 7) where 12 % of **421** was isolated. However, NaH (entry 8) was not effective in the cyclisation, with starting material being recovered. An amine base, namely Et_3N (entry 9) was also not successful in the cyclisation of **298** to **421**. In the cases where a significant portion of the starting material was not recovered (*e.g.* entries 6 and 9), no other products were detected by crude NMR, and so it is therefore not clear what has happened to the remainder of the starting material **298** here.

The effect of the silane identity was studied within the group (Table 5).[j] For Me_2PhSiH, $MePh_2SiH$ and PH_3SiH (entries 2-4), the yield of **421** was lower than for Et_3SiH (entry 1). It was found that tri-*iso*-propylsilane was unsuccessful (entry 5), with starting material being recovered in 98 % yield. This is likely due to the steric bulk around the silicon centre, which would make it difficult for

[j] These reactions were carried out by Jude Arokianathar, University of Strathclyde

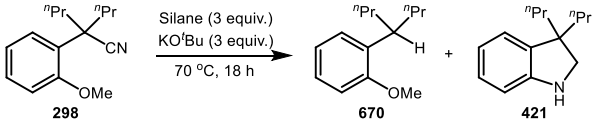
the complexation of KO^{t}Bu to occur. The yield of decyanated product **670** was not determined in the case of entries 2-4 due to the difficulty in separating this material from the non-volatile silanes.

*Table 4 - Effect of the Base on the Cyclisation of **298** into **421***



Entry	Base	**670**	**421**	**298**
1	KO^{t}Bu	11 %	72 %	Trace
2	NaO^{t}Bu	-	-	93 %
3	LiO^{t}Bu	-	-	95 %
4	KHMDS	-	-	81 %
5	KOH	-	-	85 %
6	KOEt	-	-	68 %
7	KH	-	12 %	63 %
8	NaH	-	-	97 %
9	Et_3N	-	-	66 %

*Table 5 - Effect of the Silane on the Cyclisation of **298** into **421**.*[j]

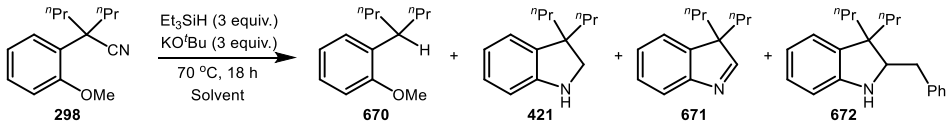


Entry	Silane	**670**	**421**	**298**
1	Et_3SiH	11 %	72 %	Trace
2	Me_2PhSiH	ND	55 %	-
3	$MePh_2SiH$	ND	57 %	-
4	Ph_3SiH	ND	55 %	-
5	$^i Pr_3SiH$	-	-	98 %

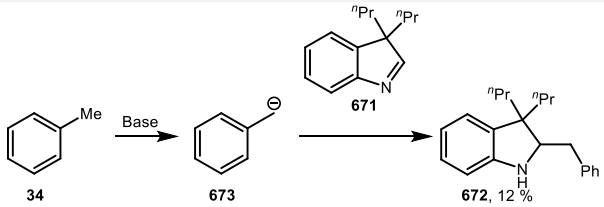
Next, the effect of solvent in the reaction was investigated (Table 6), as the previous reactions has been carried out with no solvent (entry 1). The addition of solvents led to a decrease in the yield of **421** in all cases (entries 2-5), with the least significant solvent effect coming from the use of 1,4-dioxane as a solvent (entry 4). No by-products relating to any decomposition of 1,4-dioxane were detected. When toluene was used as a solvent (entry 3), compound **672** was isolated in 12 % yield. This likely occurs from the deprotonation of toluene under the reaction conditions, and the nucleophilic attack of this toluene anion **673** into a species such as **671** (Scheme 148). Interestingly, the decyanation to **670** is more effective in THF and toluene (entries 2 and 3) than under neat conditions (entry 1) or with 1,4-dioxane or hexane (entries 4-5).

[j] These reactions were carried out by Jude Arokianathar, University of Strathclyde

*Table 6 - Effect of Solvent on the Cyclisation of **298** into **421***



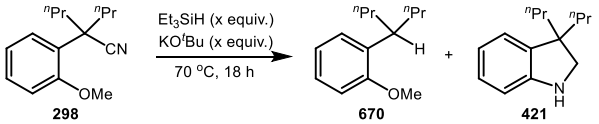
Entry	Solvent	**670**	**421**	**671**	**298**	**672**
1	None	11 %	72 %	-	Trace	-
2	THF	34 %	42 %	1 %	-	-
3	Toluene	25 %	53 %	-	Trace	12 %
4	1,4-Dioxane	6 %	63 %	6 %	Trace	-
5	Hexane	Trace	44 %	-	13 %	-



*Scheme 148 - Formation of Product **672***

The number of equivalents of silane and base was then examined to attempt to increase the yield of the cyclised product **421** (Table 7). Upon lowering the number of equivalents of Et_3SiH/KO^tBu from three (entry 1) to two (entry 2), a decrease in yield of **421** from 72 % to 56 % was observed. When the number of equivalents of Et_3SiH/KO^tBu was increased to four (entry 3), the yield of **421** was comparable to when three equivalents was used (entry 1). Therefore, three equivalents were used for future reactions.

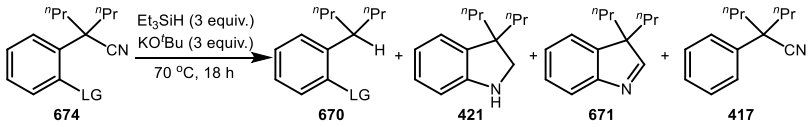
*Table 7 - Effect of Et_3SiH/KO^tBu Equivalents on the Cyclisation of **298***



Entry	x	**670**	**421**	**298**
1	3	11 %	72 %	Trace
2	2	20 %	56 %	21 %
3	4	16 %	69 %	Trace

The next variation involved the leaving group (Table 8). Upon variation of methoxide (entry 1) to fluoride (entry 2), the yield of cyclised product **421** was found to decrease from 72 % to 44 %. With chloride (entry 3), the yield of **421** was found to further decrease to 19 %. With bromide and iodide (entries 4 and 5), no cyclised product was observed, and instead dehalogenation to **417** was found to occur. Again, these halogenated substrates contained diastereotopic protons for the CH_2 groups in the ^1H NMR spectrum due to the restricted rotation in the molecules.

*Table 8 - Effect of the Leaving Group on the Cyclisation of **674***



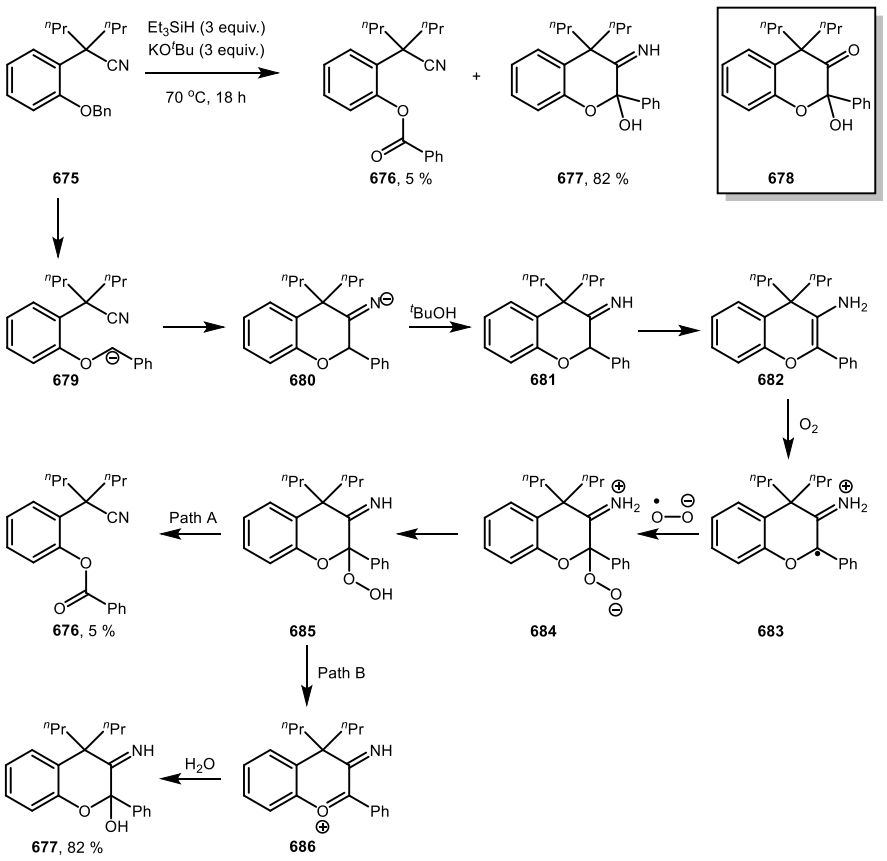
Entry	LG	**670**	**421**	**671**	**674**	**417**
1	OMe	11 %	72 %	-	Trace	-
2	F	-	44 %	Trace	-	-
3	Cl	-	19 %	-	-	-
4*	Br	-	-	-	-	57 %
5	I	-	-	-	-	78 %

* The yield of **417** in entry 4 was determined by addition of 1,3,5-trimethoxybenzene as an internal NMR standard.

The methoxy leaving group was then replaced with a benzyloxy leaving group, and this was also tested under the Et_3SiH/KO^tBu conditions (Scheme 149). Again, diastereotopic CH_2 groups were observed in the ^1H NMR spectrum of **675** to due the restricted rotation in the molecule. Substrate **675** was found to produce a mixture of compounds **676** and **677**. The structure of **677** was confirmed by x-ray crystallography (Figure 4) as the product began to crystallise over time (the x-ray revealed the structure to be **678**, which would form from the hydrolysis of **677**). It is likely that these compounds formed by the deprotonation in the benzylic position to form anion **679**. This anion can then cyclise onto the nitrile to afford **680**, which can protonate from *tert*-butanol generated *in situ* to form **681**. Tautomerisation can then occur to enamine **682** which has an electron-rich alkene structure similar to the super electron donors studied by the Murphy group in the past.[8] Compound **682** would readily donate an electron to oxygen upon opening the sealed tube at the end of the reaction to afford radical cation **683**, which could combine with superoxide to produce **684**. Proton transfer would afford intermediate **685**, which could then follow one of two pathways to lead to the products **676** and **677**. Deprotonation on nitrogen followed by loss of the hydroxyl group would afford minor product **676** via pathway A, or loss of the peroxide anion followed by nucleophilic attack of water via pathway B could afford the major product **677**.

The Et_3SiH/KO^tBu system has been shown to afford at least four different types of reactivity – silyl radical addition, hydrogen atom transfer, hydride transfer, and single electron transfer.[4,5,7,114,155] It seems unlikely that silyl radical addition to the nitrile of **298** would occur to allow for the conversion to **421**, especially as C-2 silylation of the products is not observed. It also seems unlikely that HAT is occurring in the case. The optimal reaction conditions [Et_3SiH (3 equiv.), KO^tBu (3 equiv.), neat, 70 °C, 18 h, LG = OMe], were then taken forward and a mechanistic study was carried out for both hydride transfer and single electron transfer reactivity. For the hydride transfer study, substrate **298** was treated with $LiAlH_4$ at 70 °C, with the aim being to see if a known hydride donor would also afford **421**. Reduction to **687** was found to occur, with this compound being isolated in 72 % yield. Upon repeating the reaction at 130 °C, cyclisation to **421** was found

to occur in 25 % isolated yield (*cf.* 72 % yield with Et_3SiH/KO^tBu), along with **688** in 20 % yield. It is not clear what happened to the rest of the material in this case, as no other products were detected. The rate of cyclisation may be affected by the counterion, with the potassium counterion being more efficient than the lithium counterion at mediating the cyclisation. The isolation of the cyclised product **421**, albeit at higher temperature and with a lower yield than the Et_3SiH/KO^tBu system affords, makes it likely that hydride transfer from a pentavalent silicate is involved in the conversion of **298** to **421**.



Scheme 149 - Use of a Benzyloxy Substituent

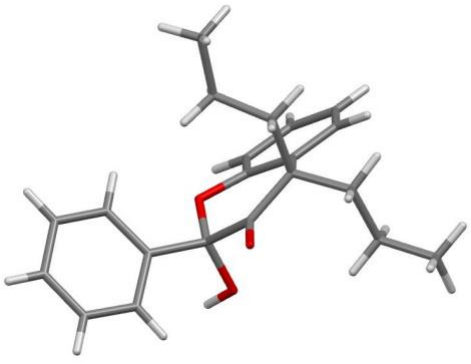
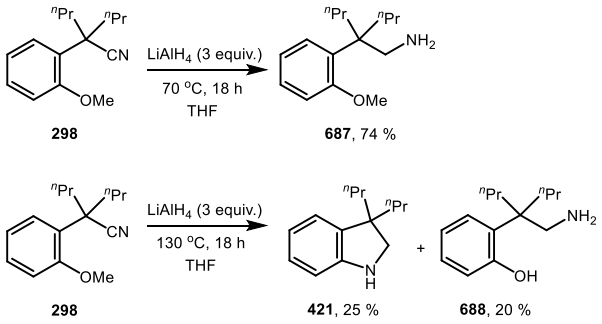
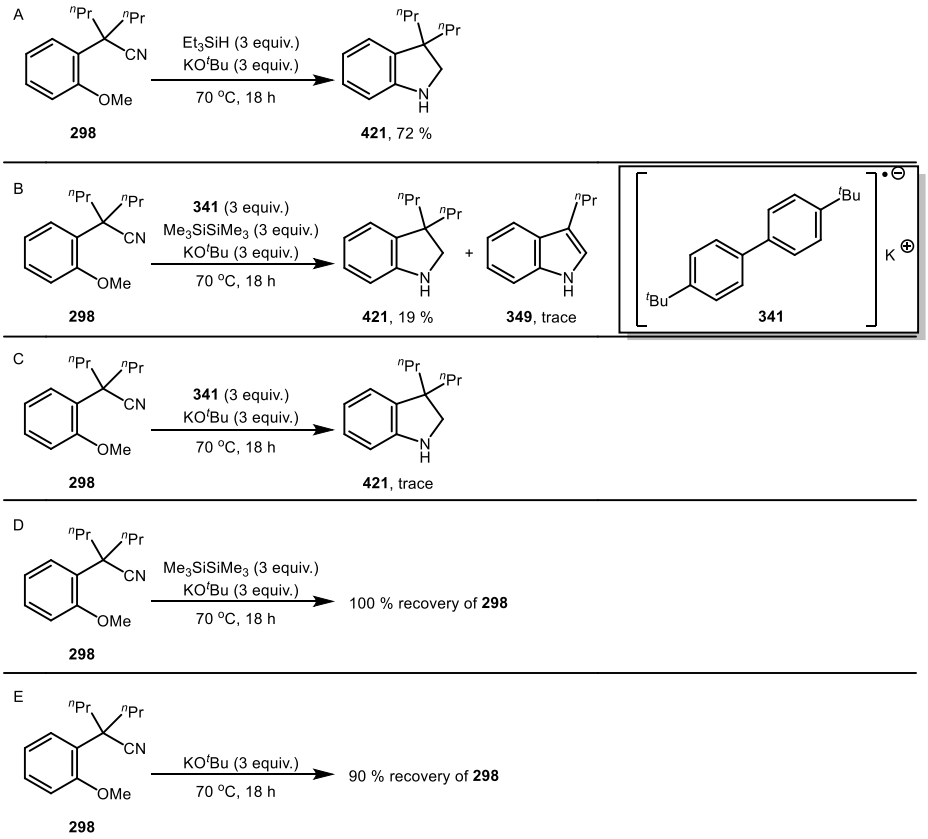


*Figure 4 - X-ray Structure of **678***



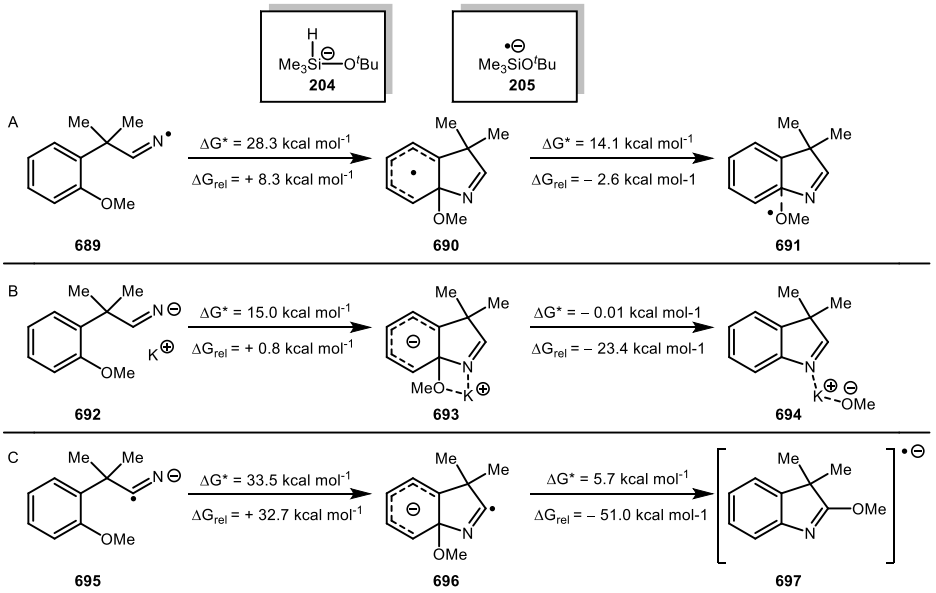
Scheme 150 - Mechanistic Study for Hydride Transfer

A mechanistic study for single electron transfer was also carried out. Similar to the previous electron transfer mechanistic studies, the Et_3SiH/KO^tBu experiment (Scheme 151A) was compared to the reaction with radical anion **341**, hexamethyldisilane, and KO^tBu (Scheme 151B). It was found that in the presence of the radical anion, silyl source and KO^tBu, the reaction still proceeded to form cyclised product **421** in 19 % yield along with a trace amount of indole **349** with cleavage of an alkyl group. This type of transformation will be discussed in more detail later in this chapter. A trace amount (< 1 mg) of **421** was also detected when **298** was treated with radical anion **341** and KO^tBu (Scheme 151C). These results suggest that single electron transfer cannot be completely excluded in the conversion of **298** to **421**. In the absence of the radical anion (Scheme 151D) or with KO^tBu alone (Scheme 151E), no reaction occurs and starting material was recovered in both cases.



Scheme 151 - Mechanistic Study for Single Electron Transfer

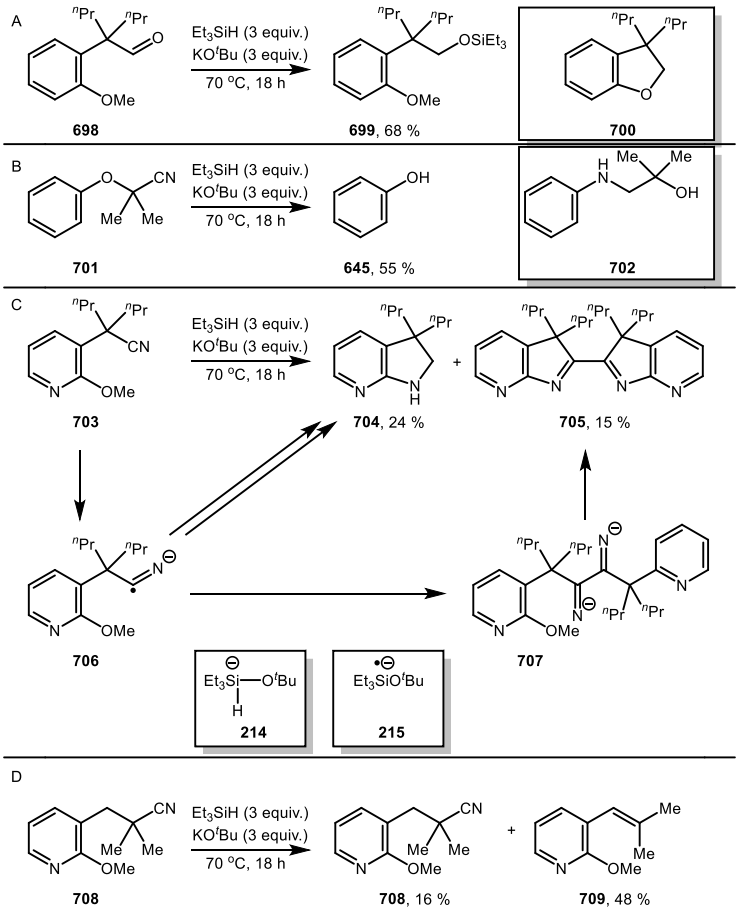
To attempt to determine the mechanism, computational analysis was carried out.[k] Three different mechanisms were modelled computationally in Scheme 152 – A) hydrogen atom transfer from pentavalent silicate **204**, B) hydride transfer from pentavalent silicate **204**, and C) single electron transfer from radical anion **205**. It was concluded that hydrogen atom transfer or single electron transfer are unlikely to be occurring at the reaction temperature of 70 °C, and only the hydride transfer pathway (Scheme 152B) is likely to occur at this temperature. The HAT pathway may become accessible at elevated temperatures >100 °C, and the SET pathway would not become accessible below approximately 200 °C. Therefore, it is likely that the cyclisation reaction is proceeding via hydride transfer from pentavalent silicate **204**. The fact that the barrier for the conversion of **693** to **694** is of lower energy than the intermediate **693** means that this is essentially a concerted S_NAr reaction. It is not clear how cyclised product **421** forms in Scheme 151B under what should be electron transfer conditions if the barrier is inaccessible. It may be that the inclusion of a potassium counterion in the calculation would allow for an accessible barrier. This should be studied as future work.



Scheme 152 - Computational Studies on the Cyclisation Reactions. Methyl groups replace ethyl groups in the calculations for computational simplicity.[k]

Attempts were then made to expand the substrate scope for this chemistry. Firstly, cyclisation was attempted to see if dihydrobenzofuran **700** could be formed using the Et_3SiH/KO^tBu conditions. Instead, reduction of the aldehyde in **698** and silylation was observed, with **699** being isolated in 68 % yield (Scheme 153A). Presumably, hydride transfer from pentavalent silicate **214** occurs to form an intermediate alkoxide, which then undergoes silylation.

[k] These calculations were carried out by Simon Rohrbach, University of Strathclyde. Geometry optimization and energy calculations were performed with the M06-2X method using the 6-31++G(d,p) basis set for all atoms. Solvent effects (solvent = Et_3N) were modelled using the CPCM solvation model.



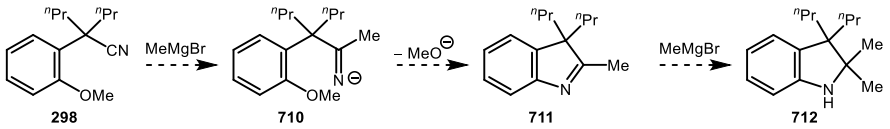
Scheme 153 - Attempts to Expand the Scope of the Cyclisation Reactions

Substrate **701** was also tested under the Et_3SiH/KO^tBu conditions to see if *ipso*-substitution could occur in a Smiles-like rearrangement, forming **702** (Scheme 153B).[193] Instead, elimination occurred under the strong basic reaction conditions, with phenol **645** being isolated in 55 % yield.

Substrate **703** was also treated under the Et_3SiH/KO^tBu conditions (Scheme 153C). Cyclisation was observed to afford **704** in 24 % yield, with dimer **705** also being isolated in 15 % yield. It is likely that the dimer **705** formed from electron transfer to substrate **703**, which would be more favourable for the electron-deficient pyridine system than for the arenes previously studied. The resulting radical anion **706**, formed after electron transfer from **215**, could undergo dimerisation to afford **707**, which could then undergo two cS_NAr reactions to afford **705**. It is possible that cyclised product **704** could result either from radical anion **706** which had been formed via an SET mechanism, or could follow the hydride transfer mechanism previously discussed above.

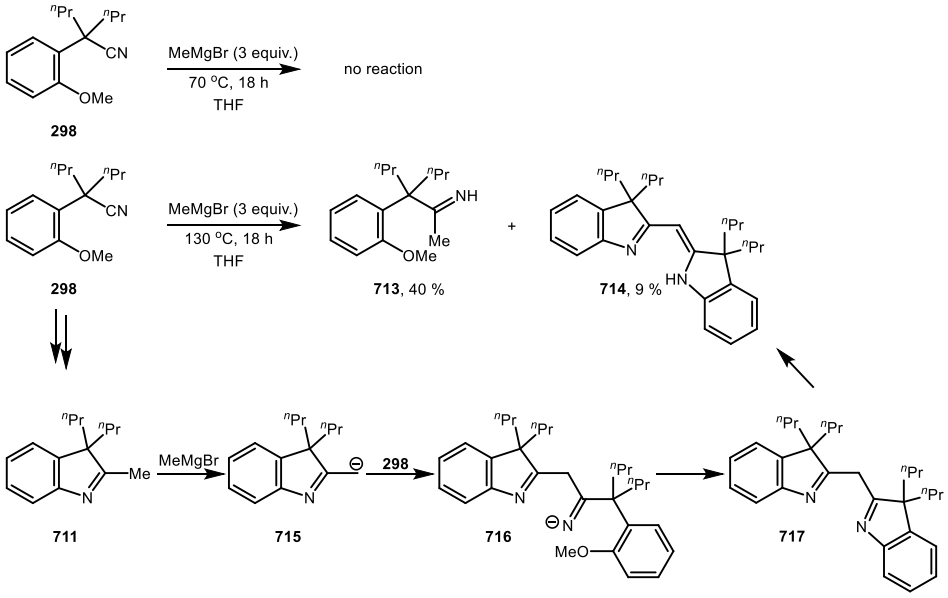
Compound **708** was also prepared to see if this methodology could be extended to the formation of a six-membered ring (Scheme 153D). However, elimination to **709** was found to occur in 48 % yield, along with 16 % recovery of **708**.

To confirm that the cyclisation reactions of **298** were occurring via the cyclisation of an anionic imine intermediate, these were prepared *in situ* by treatment of **298** with a Grignard reagent (Scheme 154). Addition of methylmagnesium bromide to **298** should result in the formation of intermediate **710**, which could then displace the methoxide in a cS_NAr process to form **711**. This may be able to undergo addition of a second equivalent of Grignard reagent to afford **712**, or may be too sterically hindered for the addition of a second equivalent of Grignard reagent and imine **711** would remain.



*Scheme 154 – Planned Conversion of **298** into **711** or **712***

When **298** was treated with three equivalents of methylmagnesium bromide at 70 °C in THF, no reaction occurred (Scheme 155). This may be due to the steric hindrance of the geminal *n*propyl groups which hinder the approach of the Grignard reagent. When the reaction was repeated at 130 °C, **713** and **714** were isolated in the yields indicated in Scheme 155. The isolation of **713** is consistent with the proposed mechanism shown in Scheme 154. However, under the reaction conditions, if this compound cyclised to afford **711**, then this bears an acidic proton α to the imine. This could be deprotonated with excess Grignard reagent to form **715**, which could then nucleophilically attack another molecule of **298** to form **716**. Subsequent cS_NAr to **717** followed by proton transfer would form **714**.

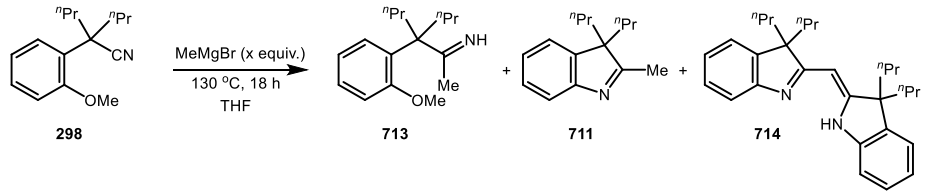


*Scheme 155 – Result of Treatment of **298** with Methylmagnesium Bromide*

It may be that the cyclisation of **710** to form **711** is slower for the reaction with MeMgBr than it is for Et_3SiH/KO^tBu due to a steric clash of an *n*propyl group with a methyl group in the transition state. To try to decrease the yield of dimer **714** and increase the yield of cyclised product **711**, the number of equivalents of Grignard reagent was varied. A decrease in the number of equivalents of MeMgBr from three to two equivalents (Table 9, entries 1 and 2) was first attempted, with the

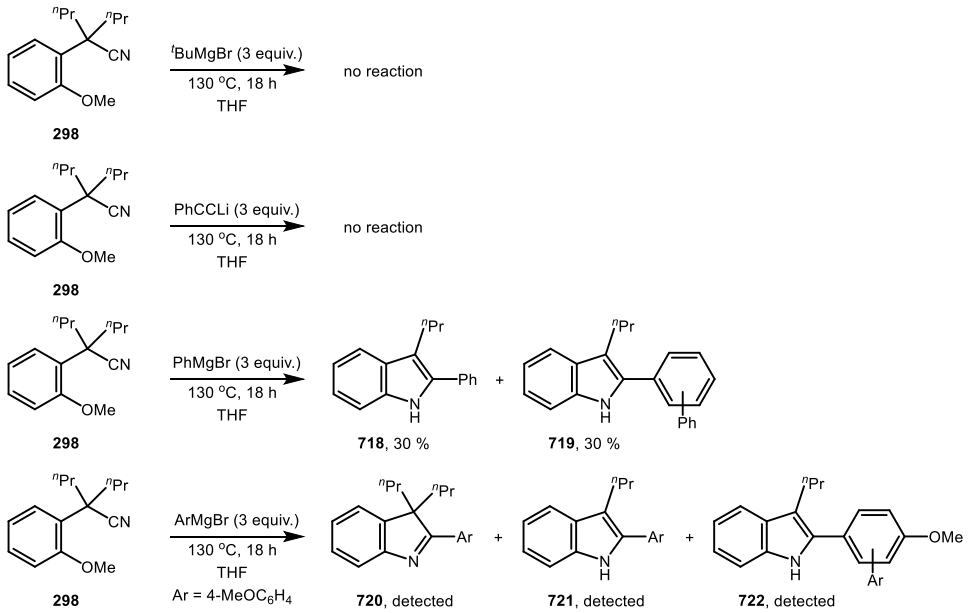
reasoning that less Grignard reagent being present may allow for a lesser degree of deprotonation of **711** to form **714**. However this was not the case, with a decreased yield of **713** being observed and no **711** present. Therefore, it was thought that it may be that increasing the number of equivalents of MeMgBr would be best for increasing the yield of **711**, as there would be more Grignard reagent present which could act as a nucleophile towards **298**, and prevent the dimerisation to **717** occurring. Upon increasing the number of equivalents of MeMgBr to four (entry 3), the yield of **713** again increased to 37 %, and this time cyclised product **711** was isolated in 28 % yield. Upon increasing the number of equivalents of MeMgBr to ten, it was ensured that MeMgBr was capable of outcompeting anion **715** as a nucleophile to react with a neutral molecule of **298**, and dimer **714** was only formed in trace amount in this case (entry 4). The yield of **711** was also found to have increased to 40 %.

Table 9 - Variation of the Equivalents of MeMgBr



Entry	x	**713**	**711**	**714**
1	3	40 %	-	9 %
2	2	24 %	-	4 %
3	4	37 %	28 %	14 %
4	10	15 %	40 %	Trace

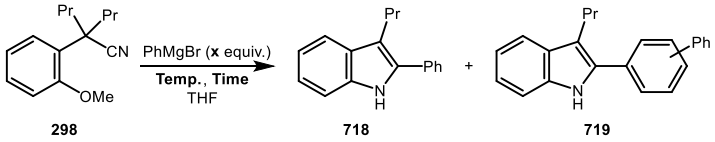
It was thought that using a Grignard reagent that would form an imine with no α-protons would allow for the yield of the imine to increase as dimerisation would not be possible. Firstly, ^{t}BuMgBr was used, however this did not lead to the formation of any products, likely due to the steric hindrance for the approach of the Grignard reagent towards the nitrile of **298**, and only starting material was recovered (Scheme 156). Lithium phenylacetylide also did not lead to the formation of any cyclised products, with starting material **298** being recovered. However, upon treatment of **298** with PhMgBr, cyclisation was indeed observed, with indoles **718** and **719** being produced. These compounds could not be separated from each other by column chromatography, and so the yields were determined by the addition of 1,3,5-trimethoxybenzene as an internal ^{1}H NMR standard (preparative HPLC allowed for separation and characterisation of each component). However, despite **719** being a single isomer, the exact regiochemistry of this isomer could not be determined. Interestingly, the aromatisation to indoles has proceeded with the loss of one of the alkyl groups from the starting material. Indoles were also produced when *p*-methoxyphenylmagnesium bromide was used, with compounds **720-722** being detected by ^{1}H NMR and GC-MS. However, due to the complex nature of the reaction mixture, these compounds could not be purified and could not be quantified by internal standard due to the presence of overlapping peaks in the ^{1}H NMR spectrum. Indoles **718** and **719** were also detected in the crude reaction mixture when PhLi was used instead of PhMgBr, but again, due to the formation of a more complex mixture of products, the yields could not be quantified in this case.



*Scheme 156 - Treatment of **298** with other Grignard Reagents*

To try to increase the yield of indole **718**, and decrease the yield of indole **719**, some attempts to vary the conditions were made (Table 10). Upon lowering the number of equivalents of PhMgBr from three to two, the yields of indoles **718** and **719** were found to be relatively unaffected (entries 1 and 2). However, upon further decreasing the number of equivalents to one (entry 3), the yields of indoles **719** and **719** were found to decrease to 7 % and 5 % respectively. It was thought that decreasing the reaction time might allow for the formation of **718** whilst allowing for less **719** to form. However, upon shortening the reaction time to 6 h (entry 4), a decrease in yield to 6 % and 3 % was observed for indoles **718** and **719** respectively, with 78 % starting material remaining. Lowering the temperature to 100 °C (entry 5) also saw a decrease in yield to 3 % of each of indole **718** and **719**, with 87 % recovery of starting material. Therefore, no further optimisation was carried out.

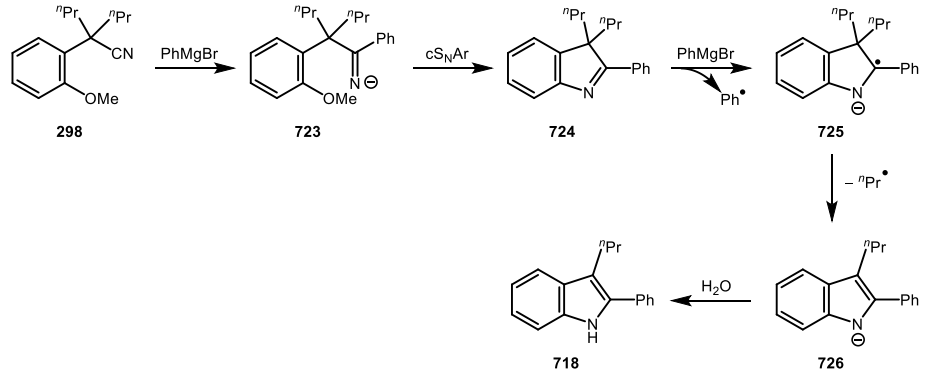
*Table 10 - Attempts to Increase the Yield of **718***



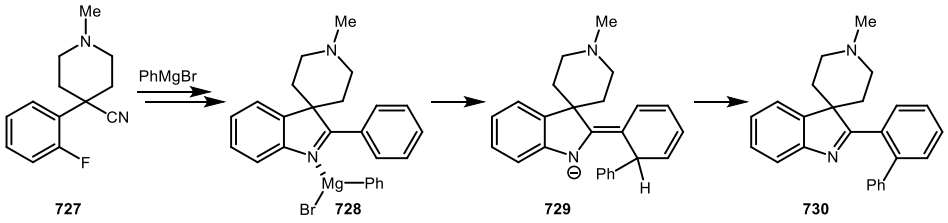
Entry	x	Temp.	Time	**718**	**719**	**298**
1	3	130 °C	18 h	30 %	30 %	2 %
2	2	130 °C	18 h	28 %	22 %	5 %
3	1	130 °C	18 h	7 %	5 %	52 %
4	2	130 °C	6 h	6 %	3 %	78 %
5	2	100 °C	18 h	3 %	3 %	87 %

A mechanistic proposal for the loss of an alkyl group from **298** is shown in Scheme 157. Firstly, PhMgBr acts as a nucleophile to the nitrile of **298** to afford imine anion **723**. Cyclisation to **724** then occurs via a cS_NAr process. It is likely that electron transfer then occurs from the Grignard reagent to form radical anion **725**, which rearomatises via expulsion of a propyl radical firstly to

form **726**, and then protonate on work-up to form **718**. Grignard reagents have previously been reported to act as single electron donors,[194] and if they did so, then a phenyl radical would remain. If this phenyl radical added onto an aryl group on any structure **298**, **718** or **723**-**726**, then this would lead to the formation of **719**. Alternatively, as proposed by Ong, the phenyl group may add by complexation of the Grignard to the indolenine to form **728**, followed by cyclisation to **729** and expulsion of a hydride to form **730** (Scheme 158).[195] However, no mechanistic evidence was provided for this transformation, and the authors do not rule out that another mechanism may be occurring.



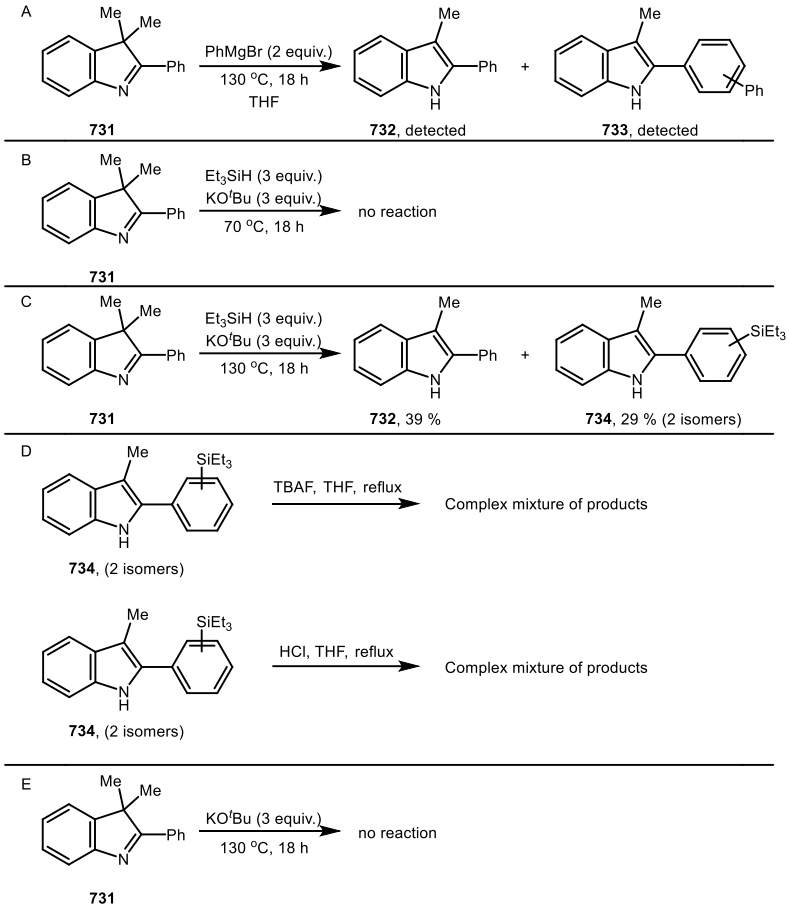
Scheme 157 - Mechanism for the Expulsion of an Alkyl Group



Scheme 158 - Ong's Cyclisation Reactions

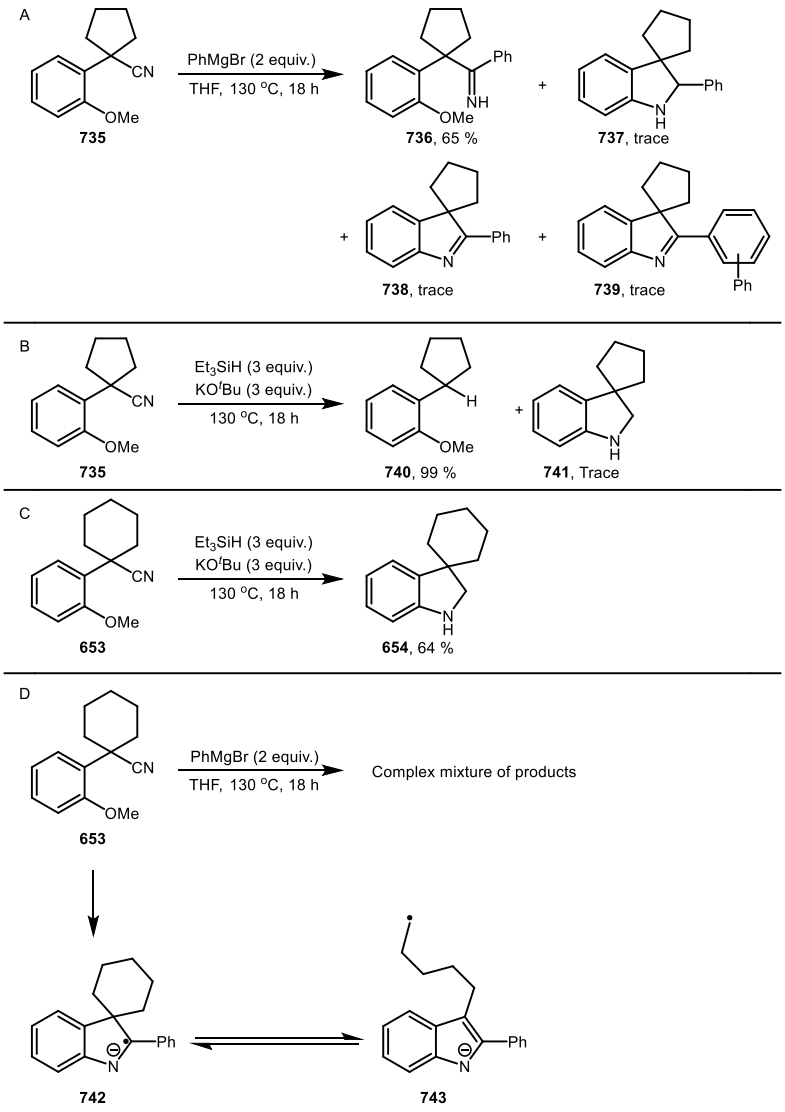
To confirm the presence of **724** as an intermediate in the expulsion of alkyl groups, **731** was prepared independently and treated with PhMgBr. This led to a complex mixture of products, from which indoles **732** and **733** could be detected but not quantified (Scheme 159A). To try to provide evidence that the loss of the alkyl group occurs via single electron transfer, **731** was treated with Et_3SiH/KO^tBu, which form electron donor **215** *in situ*. At 70 °C, no reaction occurred and starting material **731** was recovered in quantitative yield (Scheme 159B). However, upon heating to 130 °C, conversion to indoles **732** and **734** (2 isomers) occurred, and these compounds were isolated in 39 % and 29 % yield respectively (Scheme 159C). Attempts to desilylate the two isomers of **734** to achieve an increased yield of **732** with TBAF and with HCl have so far been unsuccessful, and let to complete degradation of **734** (Scheme 159D). No reaction of **731** occurs in the absence of Et_3SiH (*i.e.* heating with KO^tBu alone), showing that the conversion of **731** to **732** not a base-induced process (Scheme 159E). Therefore, it is likely that indolenines such as **731** (or **724**) are intermediates in the formation of indoles described above. The presence of the phenyl group in the 2-position likely plays two roles in this transformation – i) it slows down the hydride transfer by providing steric bulk, and therefore prevents the formation of indolines in this

case, and ii) it allows for a more facile electron transfer to the conjugated imine which ultimately leads to the formation of the indole products.



*Scheme 159 - Studies with Indolenine **731***

Substrate **735** was also treated with PhMgBr to determine what happens to the alkyl group that is lost upon the conversion of these types of substrates to indoles (Scheme 160A). This alkyl group is tethered to the remainder of the molecule, and so would not be lost as gas as previously. However, only a trace amount of cyclised products **737**-**739** were detected in this case, with imine **736** being isolated as the major compound in 65 % yield, indicating that cyclisation is disfavoured or slow in this case. This was also the case when **735** was treated under the Et_3SiH/KO^tBu conditions, with cyclised product **741** being detected in a trace amount (<1 mg), and reductive decyanation product **740** being isolated in 99 % yield (Scheme 160B). However, upon changing the 5-membered ring for a 6-membered ring in substrate **653**, cyclisation under the Et_3SiH/KO^tBu system occurred to afford **654** in 64 % yield (Scheme 160C). However, upon treatment of **653** with PhMgBr, a complex mixture of products was formed from which nothing could be isolated (Scheme 160D). It is likely that if expulsion of the alkyl group occurs to form radical anion **743**, then this radical can then go on to either recyclise or form other products due to being tethered to the molecule and not being lost.

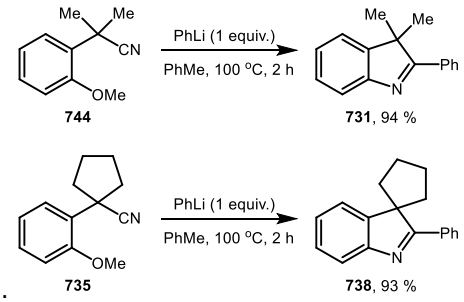


Scheme 160 - Effect of Alkyl Groups on Cyclisation

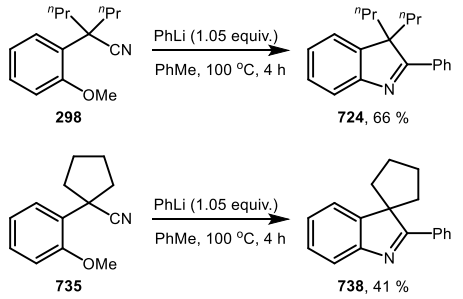
During this study, Gademann *et al*. published a paper which showed the cyclisation of various nitriles to form indolenines mediated by phenyllithium (Scheme 161).[196] However, in contrast to this work, no expulsion of alkyl groups was reported by Gademann. Similarly, the authors do not report on the formation of any product when **744** was treated with PhMgBr (a 0 % yield of **731** is stated, but it is not clear if starting material remained or if another product formed). The authors propose that the reaction proceeds via a concerted nucleophilic aromatic substitution reaction. Also contrary to this work, Gademann shows that substrate **735** cyclises for form indolenine **738**, which was only possible in trace amounts in our work with PhMgBr or Et_3SiH/KO^tBu above. However, this substrate was successful upon repeating the reaction with Gademann's conditions, although the yield was considerably lower in our hands (Scheme 162) than the yield achieved by Gademann (41 % vs. 93 % of **738**).

Gademann had also reported that the presence of a lithium counterion was necessary for the cyclisation reactions to occur. To demonstrate this, his group prepared **745** and treated this with

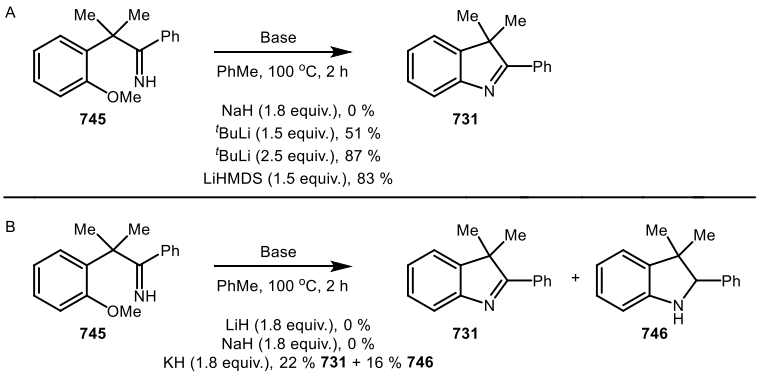
bases to determine if cyclisation could occur. However, it is not clear how comparable the various bases tested by Gademann are to each other, with cyclisation to **731** seen for ^{t}BuLi and LHMDS, but not for NaH. Also, no potassium bases were reported by Gademann, and our work shows that potassium (and indeed magnesium) base-mediated cyclisations are possible. Therefore, compound **745** was prepared in our lab and treated with LiH, NaH and KH. Cyclisation was observed only with KH to form **731** and **746** in 22 % and 16 % respectively. The cyclisation of **745** provides further evidence that this compound is an intermediate in the cyclisation reactions. It is therefore likely that an increase in basicity is what drives the cyclisation of **745** to **731** and/or **746** to completion, and not the identity of the counterion in this case.



Scheme 161 - Gademann's cS$_N$Ar Reactions



Scheme 162 - Repetition of Gademann's Work by our Group



*Scheme 163 - Cyclisation of **745** by A) Gademann and B) Smith and Murphy*

5.3: Conclusions and Future Work

In conclusion, methodology has been developed which allows for the formation of indoles from benzylic nitriles via a cS$_N$Ar displacement of a methoxy group. It is likely that this transformation

proceeds via hydride transfer from a pentavalent silicate species, formed *in situ* from Et_3SiH and KO^tBu, although electron transfer cannot be completely ruled out, based on experimental observations. Benzylic nitriles can also be converted to indoles with expulsion of an alkyl group from the benzylic position upon treatment with PhMgBr. It is likely that this reaction proceeds via electron transfer. Indolenines can also be converted to indoles by expulsion of an alkyl group by treatment with Et_3SiH/KO^tBu, and again it is likely that this reaction proceeds via electron transfer. Further work is ongoing within the group to expand the scope of this reaction, with a variety of leaving groups and organometallic reagents being explored.

6: Overall Conclusions and Future Work

In conclusion, the combination of Et_3SiH and KO^tBu produces a highly reducing system which is capable of carrying out a number of synthetically useful transformations via a variety of mechanisms. This now includes electron transfer, hydride transfer, and hydrogen atom transfer pathways. The reductive cleavage of *N*-benzylindoles by single electron transfer from radical anion **215** (Figure 5) was carried out in good yields of up to 80 %. A combination of experimental and computational chemistry proved useful in deducing the identity of the active electron donor, and a range of other reductions were carried out using this powerful electron donor, including the reductive cleavage of a benzylic ether, deallylation of *N*-allylindoles, and reductive decyanation of a benzylic nitrile.

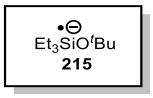


*Figure 5 - Structure of Electron Donor **215***

Ring-opening and cyclisation of *N*-arylindoles to afford 9,10-dihydroacridines has also been demonstrated to occur under the Et_3SiH/KO^tBu system. Strong evidence for electron transfer conditions has been reported, as the reaction was also mediated by K/KO^tBu which cannot proceed via hydrogen atom transfer. However, the formation of cyclopropylacridine **545** from substrate **543** shows strong evidence of hydrogen atom addition to an intermediate styrene. It is therefore likely that HAT to the styrene intermediates is faster than the SET pathway, and this is the reason why complete ring-opening of the cyclopropane does not occur in this case.

Cyclisation of nitriles with displacement of a methoxy group via concerted nucleophilic aromatic substitution has also been demonstrated to be mediated by the Et_3SiH/KO^tBu system. It is likely that this transformation proceeds via hydride transfer from a pentavalent silicate species, formed *in situ* from Et_3SiH and KO^tBu, although electron transfer cannot be completely ruled out based on experimental observations. Benzylic nitriles can also be converted to indoles with expulsion of an alkyl group from the benzylic position upon treatment with PhMgBr. It is likely that this reaction proceeds via electron transfer. Indolenines can also be converted to indoles by expulsion of an alkyl group by treatment with Et_3SiH/KO^tBu, and again it is likely that this reaction proceeds via electron transfer.

Future work in this area would involve further challenging reductions which may be brought about either by Et_3SiH/KO^tBu alone, or by the addition of triethylamine. Computational data suggest that the addition of triethylamine to the reaction mixture may allow for a stronger reducing agent to form. Alternatively, heating the combination of Et_3SiH/KO^tBu produces a blue-black reaction mixture which may be able to be photoexcited to generate an even more powerful reducing system. Initial attempts within our group to measure the uv-visible spectrum of the blue-black

material obtained from heating Et_3SiH/KO^tBu were unsuccessful, so it was not able to be determined which wavelength this mixture absorbs at. If a uv-visible spectrum could be obtained, then the Et_3SiH/KO^tBu system under photoactivation may be able to carry out difficult reductions such as the reduction of dinitrogen. Other reductions which have proven difficult in previous work within the group include the reduction of alkyl-alkyl thioethers. The Et_3SiH/KO^tBu system could be looked at to carry out this type of reduction, with or without the addition of triethylamine or photoactivation.

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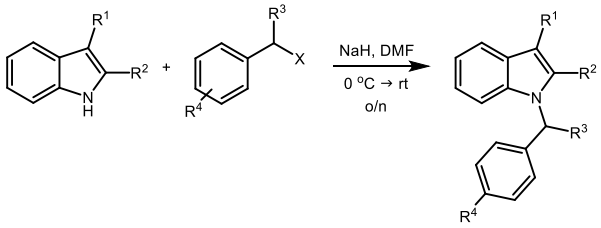
8. Experimental Details

8.1 - General Experimental

All reagents and solvents were obtained from commercial suppliers and were used without further purification. The glovebox was supplied by Innovative Technology Inc., USA, and the atmosphere used is nitrogen. DMF, DMSO and Et_3N were dried over 3 Å molecular sieves (10 % w/v) [which were activated by microwave heating (3 x 5 min)] and degassed by bubbling argon through solvent for 30 min. The solvents were then left to dry for 24 h before use. Anhydrous diethyl ether, THF, DCM, hexane and toluene were dried using a Pure-Solv 400 solvent purification system (Innovative Technology Inc., USA). Sodium hydride was supplied as a 60 % dispersion in mineral oil and was washed with hexane to remove this oil before use, unless otherwise specified. Potassium hydride was supplied as a 30 % dispersion in mineral oil, and was also washed with hexane before use. Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light. Flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel. Fourier Transform Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer at 400 and 101 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz, with $CDCl_3$ referenced at 7.27 (^{1}H) and 77.00 ppm (^{13}C). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sxt, sextet; spt, septet; m, multiplet; br, broad. High resolution mass spectrometry (HRMS) was performed at the University of Swansea in the EPSRC National Mass Spectrometry Centre. Accurate mass was obtained using LTQ Orbitrap XL using Atmospheric Pressure Chemical Ionisation (APCI) or High Resolution Nano-Electrospray (HNESP) using Electrospray Ionisation (ESI). GC-MS spectra were obtained on a Thermo Finnigan Polaris Q, mass range 50-650 Da. The column temperature was 320 °C, and the carrier gas was helium with a flow rate of 1 mL/min. The adsorbent was Crossbond® (0.25 µm) with column dimensions of 30 m x 0.25 mm. Results are reported as *m/z*. All samples were prepared in $CHCl_3$ and electron ionisation (EI) was used as the ionisation method.

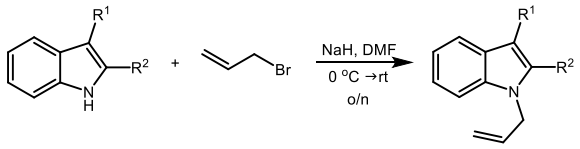
8.2 – General Procedures

General Procedure A - Benzylation of Indoles



N-benzylindoles were prepared according to a literature procedure.[197] To a stirred solution of sodium hydride (144 mg, 6.00 mmol, 1.2 equiv., unless otherwise specified) in DMF (5 mL, unless otherwise specified) was added the appropriate indole (5.00 mmol, 1.0 equiv., unless otherwise specified) in DMF (5 mL unless otherwise specified) at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 30 min before addition of the appropriate benzyl halide (7.50 mmol, 1.5 equiv. unless otherwise specified) at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction mixture was then quenched with water and extracted into ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography as specified below afforded the *N*-benzylindole derivatives.

General Procedure B - Allylation of Indoles



N-allylindoles were prepared by modification of a literature procedure.[197] To a stirred solution of sodium hydride (144 mg, 6.00 mmol, 1.2 equiv., unless otherwise specified) in DMF (5 mL, unless otherwise specified) was added the appropriate indole (5.00 mmol, 1.0 equiv.), unless otherwise specified) in DMF (5 mL, unless otherwise specified) at 0 °C under nitrogen. The resulting mixture was stirred at room temperature for 30 min before addition of allyl bromide (0.65 mL, 7.50 mmol, 1.5 equiv. unless otherwise specified) at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction mixture was then quenched with water and extracted into ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

General Procedure C – Treatment of Substrates under Et_3SiH/KO^tBu Conditions

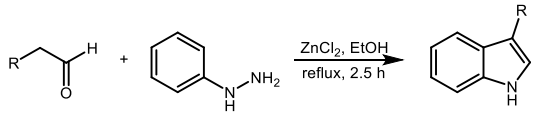
Substrate (0.50 mmol, 1.0 equiv., unless otherwise specified), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv., unless otherwise specified) and potassium *tert*-butoxide (168 mg, 1.50 mmol,

3.0 equiv., unless otherwise specified) were sealed in a pressure tube in a glovebox under nitrogen. The tube was removed and heated at 130 °C for 18 h behind a safety shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

General Procedure D – Treatment of Substrates with KO^{t}Bu Alone

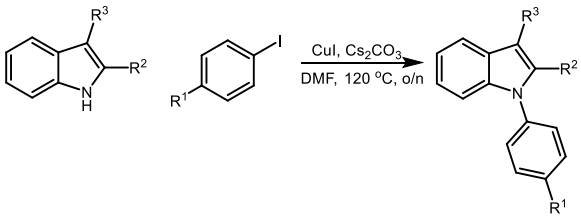
Substrate (0.50 mmol, 1.0 equiv., unless otherwise specified) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv., unless otherwise specified) were sealed in a pressure tube in a glovebox under nitrogen. The tube was removed and heated at 130 °C for 18 h behind a safety shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

General Procedure E – Fischer Indole Synthesis



These reactions were carried out according to a literature procedure.[198] To a three-necked flask under argon and equipped with a stirrer bar and fitted with a condenser was added the appropriate aldehyde (10.0 mmol, 1.0 equiv.) and phenylhydrazine (0.98 mL, 9.95 mmol, 1.0 equiv.). This mixture was stirred for 1 h at room temperature then for 30 min at 100 °C. A solution of zinc chloride (2.45 g, 18.0 mmol, 1.8 equiv.) in ethanol (11 mL) was then added and the mixture was heated under reflux for a further 1 h. After cooling to room temperature, the mixture was filtered, and the solvent was removed under reduced pressure. Hydrochloric acid (2 M) was added to the crude residue and the organic products were extracted into DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography and/or recrystallisation afforded the appropriate indole.

General Procedure F – Ullmann Coupling

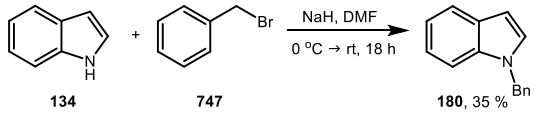


These reactions were carried out according to a literature procedure.[199] To a three-necked flask, under argon, was added the appropriate heterocycle (1.1 or 1.4 equiv.), the appropriate aryl iodide (1.0 equiv.), copper(I) iodide (0.2 equiv.), cesium carbonate (2.0 equiv.) and dry DMF (0.5 M).

The resulting mixture was stirred overnight at 120 °C. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography afforded the relevant *N*-arylindole.

8.3 - Preparation of Substrates for Chapter 3

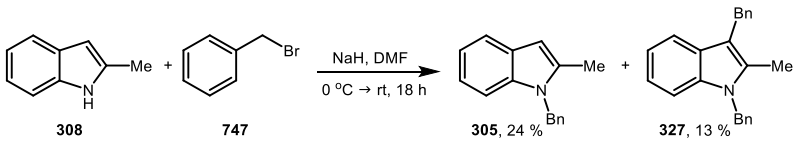
Preparation of 1-Benzyl-1*H*-indole (180)



134 **747** **180**, 35 %

This substrate was prepared according to General Procedure A from 1*H*-indole **134** (586 mg, 5.00 mmol, 1.0 equiv.) and benzyl bromide **747** (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by column chromatography (hexane) followed by distillation (200 °C, 21 mbar) afforded 1-benzyl-1*H*-indole **180** as a yellow oil (364 mg, 35 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 5.35 (s, 2H, CH_2), 6.58 (dd, *J* = 3.3, 0.8 Hz, 1H, ArH), 7.10 - 7.17 (m, 4H, 4 x ArH), 7.20 (app. td, *J* = 7.0, 1.0 Hz, 1H, ArH), 7.24 - 7.36 (m, 4H, 4 x ArH), 7.68 (m, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 50.0, 101.7, 109,7, 119.5, 121.0, 121.7, 126.8, 127.6, 128.2, 128.7 (2 signals overlapping), 136.3, 137.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3025, 1604, 1511, 1454, 1316, 1182, 1013, 740, 715. ***m/z* (EI)** 207.1 ([M$^+$, 87), 116.1 (11), 91.1 (100), 77.1 (3), 65.0 (17). The data for this compound are consistent with those reported in the literature.[146]

Preparation of 1-Benzyl-2-methyl-1*H*-indole (305) and 1,3-Dibenzyl-2-methyl-1*H*-indole (327)

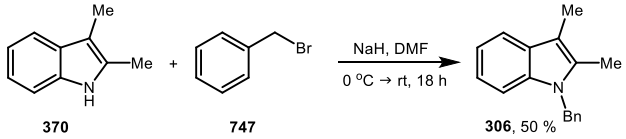


308 **747** **305**, 24 % **327**, 13 %

This substrate was prepared according to General Procedure A from 2-methyl-1*H*-indole **308** (655 mg, 4.99 mmol, 1.0 equiv.) and benzyl bromide **747** (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by column chromatography (hexane:toluene, 4:1) afforded 1-benzyl-2-methyl-1*H*-indole **305** as a white solid (266 mg, 24 %). **Mp** = 42-44 °C (lit. mp = 47-48 °C).[200] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.41 (d, *J* = 0.8 Hz, 3H, CH_3), 5.34 (s, 2H, CH_2), 6.28 - 6.44 (m, 1H, ArH), 7.01 (m, 2H, 2 x ArH), 7.07 - 7.19 (m, 2H, 2 x ArH), 7.20 - 7.34 (m, 4H, 4 x ArH), 7.56 - 7.64 (m, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 12.7, 46.4, 100.4, 109.2, 119.5, 119.7, 120.7, 126.0, 127.2, 128.2, 128.7, 136.7, 137.2, 137.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3022, 2899, 1547, 1452, 1395, 1339, 1311, 1078, 1021, 801, 736, 721, 695. ***m/z* (EI)** 221.1 (M$^+$, 90), 91.1 (100), 77.0 (12), 65.0 (20). The data for this compound are consistent with those reported in the literature.[201] Also isolated was 1,3-dibenzyl-2-methyl-1*H*-indole **327** as a brown oil (205 mg, 13 %). **^{1}H-NMR** (400 MHz,

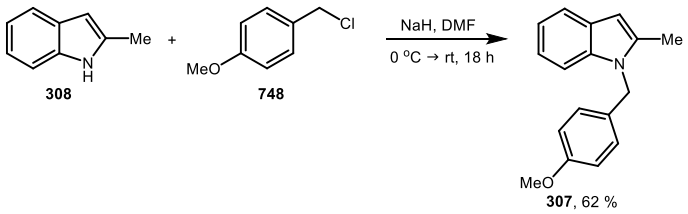
$CDCl_3$) 2.32 (s, 3 H, CH_3), 4.14 (s, 2 H, CH_2), 5.35 (s, 2 H, CH_2), 6.95 - 7.01 (m, 2 H, 2 x ArH), 7.04 (app. td, *J* = 7.8, 1.0 Hz, 1 H, ArH), 7.11 (app. td, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.13 - 7.19 (m, 1 H, ArH), 7.20 - 7.26 (m, 7 H, 7 x ArH), 7.28 - 7.31 (m, 1 H, ArH), 7.46 (d, *J* = 7.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 10.3, 30.4, 46.5, 108.9, 110.5, 118.4, 119.1, 120.9, 125.6, 125.9, 127.2, 128.2, 128.2, 128.2, 128.7, 133.4, 136.6, 138.0, 141.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3024, 2918, 1603, 1584, 1469, 1452, 1339, 1177, 1028, 744, 712. ***m/z* (EI)** 311.2 (M^+, 100), 296.1 (30), 234.1 (35), 220.1 (24), 204.1 (7), 178.1 (15), 152.1 (3), 91.0 (93), 65.0 (13). **HRMS (CI)** calcd. for $C_{23}H_{22}N^+$ ([M+H]$^+$): 312.1747, found: 312.1749.

Preparation of 1-Benzyl-2,3-dimethyl-1*H*-indole (306)



This substrate was prepared according to General Procedure A from 2,3-dimethyl-1*H*-indole **370** (726 mg, 5.00 mmol, 1.0 equiv.) and benzyl bromide **747** (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by column chromatography (hexane:EtOAc, 19:1) afforded 1-benzyl-2,3-dimethyl-1*H*-indole **306** as a waxy pink semi-solid (584 mg, 50 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.34 (s, 3 H, CH_3), 2.35 (d, *J* = 1.0 Hz, 3 H, CH_3), 5.34 (s, 2 H, CH_2), 6.99 - 7.06 (m, 2 H, 2 x ArH), 7.10 - 7.20 (m, 2 H, 2 x ArH), 7.21 - 7.37 (m, 4 H, 4 x ArH), 7.55 - 7.64 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 8.9, 10.1, 46.5, 107.0, 108.8, 118.0, 118.9, 120.8, 126.0, 127.1, 128.7, 132.4, 136.4, 138.3 – one carbon not observed due to overlap.[202] **ATR-IR** ν_{max} (neat)/cm^{-1} 3022, 2912, 2858, 1604, 1581, 1566, 1467, 1452, 1263, 1215, 1180, 1002, 842, 729, 696. ***m/z* (EI)** 235.2 (M^+, 71), 220.1 (3), 158.1 (3), 144.1 (20), 128.1 (5), 115.1 (6), 102.1 (5), 91.1 (100), 77.1 (12), 65.1 (14), 51.0 (4). The data for this compound are consistent with those reported in the literature.[202]

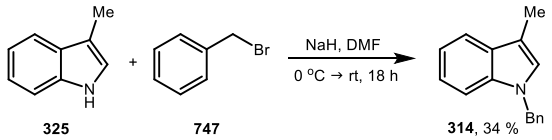
Preparation of 1-(4-Methoxybenzyl)-2-methyl-1*H*-indole (307)



This substrate was prepared according to General Procedure A from 2-methyl-1*H*-indole **308** (655 mg, 4.99 mmol, 1.0 equiv.) and 4-methoxybenzyl chloride **748** (1.02 mL, 7.52 mmol, 1.5 equiv.). Purification by column chromatography (hexane:EtOAc, 19:1 → 9:1) afforded 1-(4-methoxybenzyl)-2-methyl-1*H*-indole **307** as a pink solid (786 mg, 62 %). **Mp** = 80-81 °C (no literature melting point has been reported). **^{1}H-NMR** (400 MHz, $CDCl_3$ 2.39 (d, *J* = 1.0 Hz, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 5.26 (s, 2 H, CH_2), 6.24 - 6.37 (m, 1 H, ArH), 6.81 (m, 2 H, 2 x ArH), 6.88 - 6.97 (m, 2 H, 2 x ArH), 7.05 - 7.15 (m, 2 H, 2 x ArH), 7.20 - 7.25 (m, 1 H, ArH), 7.54 - 7.60

(m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 12.8, 45.9, 55.2, 100.4, 109.2, 114.1, 119.4, 119.7, 120.7, 127.2, 128.1, 129.9, 136.7, 137.1, 158.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3046, 2998, 2936, 2838, 1614, 1547, 1512, 1465, 1437, 1294, 1249, 1177, 1032, 742. ***m/z* (EI)** 251.1 (M^+, 52), 130.0 (6), 121.1 (100), 103.1 (5), 91.0 (7), 77.0 (13), 63.0 (3), 51.0 (2). The data for this compound are consistent with those reported in the literature.[202]

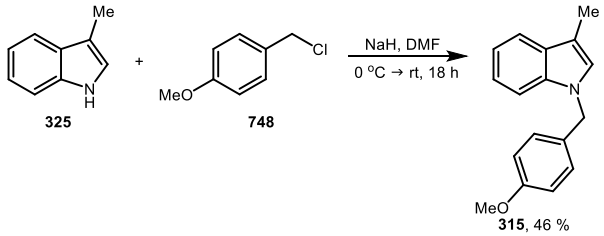
Preparation of 1-Benzyl-3-methyl-1*H*-indole (314)



325 **747** **314**, 34 %

This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and benzyl bromide **747** (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1), followed by recrystallisation from methanol afforded 1-benzyl-3-methyl-1*H*-indole **314** as a green solid (372 mg, 34 %). **Mp** = 72-73 °C (lit. mp = 72-73 °C).[203] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.38 (d, *J* = 1.0 Hz, 3H, CH_3), 5.30 (s, 2H, CH_2), 6.93 (s, 1H, ArH), 7.12 - 7.18 (m, 3H, 3 x ArH), 7.21 (app. td, *J* = 7.8, 1.0 Hz, 1H, ArH), 7.26 - 7.36 (m, 4H, 4 x ArH), 7.63 (d, *J* = 7.8 Hz, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 49.8, 109.4, 110.8, 118.8, 119.0, 121.6, 125.8, 126.8, 127.5, 128.7, 128.9, 136.6, 137.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3042, 3029, 2927, 2912, 1614, 1586, 1462, 1467, 1439, 1359, 1331, 1181, 732, 697. ***m/z* (EI)** 221.1 (87, M^+), 130.1 (14), 91.0 (100), 77.0 (10), 65.0 (15). The data for this compound are consistent with those reported in the literature.[204]

Preparation of 1-(4-Methoxybenzyl)-3-methyl-1*H*-indole (315)

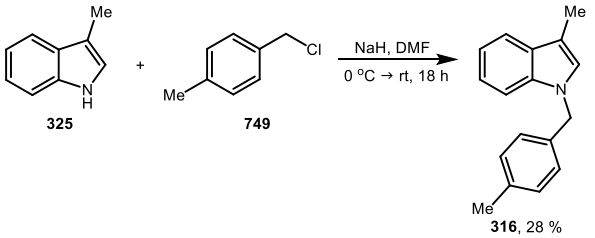


325 **748** **315**, 46 %

This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and 4-methoxybenzyl chloride **748** (1.02 mL, 7.52 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded 1-(4-methoxybenzyl)-3-methyl-1*H*-indole **315** as a yellow solid (584 mg, 46 %). **Mp** = 45-48 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.34 (d, *J* = 1.0 Hz, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 5.21 (s, 2 H, CH_2), 6.84 (m, 2 H, 2 x ArH), 6.88 (m, 1 H, ArH), 7.06 - 7.11 (m, 2 H, 2 x ArH), 7.11 - 7.15 (m, 1 H, ArH), 7.19 (m, 1 H, ArH), 7.25 - 7.32 (m, 1 H, ArH), 7.56 - 7.63 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 49.1, 55.1, 109.4, 110.6, 114.0, 118.7, 118.9, 121.5, 125.6, 128.1, 128.9, 129.8, 136.5, 158.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3042, 2912, 2832, 1612, 1585, 1512, 1465, 1244, 1173,

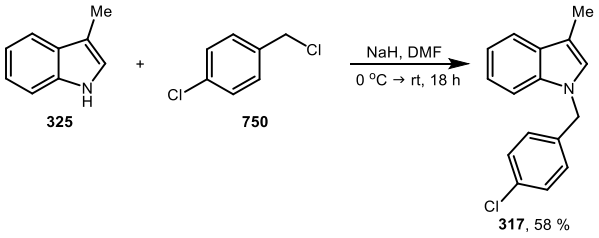
1032, 738. ***m/z* (EI)** 251.1 (M^+, 42), 130.1 (6), 121.1 (100), 103.1 (4), 93.1 (7), 77.1 (17), 63.1 (2), 51.1 (5). **HRMS (CI)** calcd for $C_{17}H_{18}NO^+$ ($[M+H]^+$): 252.1383, found: 252.1384. The data for this compound are consistent with those reported in the literature.[205]

Preparation of 1-(4-Methylbenzyl)-3-methyl-1*H*-indole (316)



This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and 4-methylbenzyl chloride **749** (0.99 mL, 7.48 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-(4-methylbenzyl)-3-methyl-1*H*-indole **316** as a colourless oil (335 mg, 28 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.33 (s, 3H, CH_3), 2.36 (d, *J* = 1.3 Hz, 3H, CH_3), 5.24 (s, 2H, CH_2), 6.90 (m, 1H, ArH), 7.04 (d, *J* = 8.0 Hz, 2H, 2 x ArH), 7.09 - 7.16 (m, 3H, 3 x ArH), 7.19 (m, 1H, ArH), 7.28 (m, 1H, ArH), 7.57 - 7.64 (m, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 21.0, 49.5, 109.4, 110.7, 118.6, 119.0, 121.5, 125.7, 126.8, 128.9, 129.3, 134.8, 136.6, 137.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3022, 2914, 1614, 1515, 1467, 1329, 1183, 1015, 736. ***m/z* (EI)** 235.1 (M^+, 78), 218.1 (2), 204.1 (2), 130.1 (16), 105.1 (100), 89.0 (2), 77.0 (19), 63.0 (2), 51.0 (3). **HRMS (CI)** calcd. for $C_{17}H_{18}N^+$ ($[M+H]^+$): 236.1434, found: 236.1434.

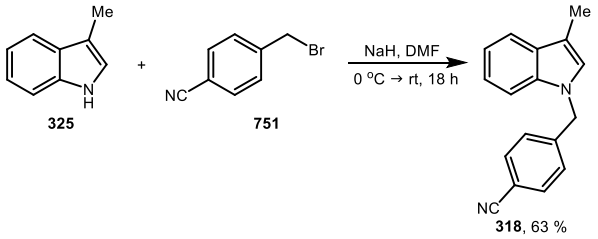
Preparation of 1-(4-Chlorobenzyl)-3-methyl-1*H*-indole (317)



This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and 4-chlorobenzyl chloride **750** (1.21 g, 7.51 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-(4-chlorobenzyl)-3-methyl-1*H*-indole **317** as an off-white solid (740 mg, 58 %). **Mp** = 57-59 °C. (lit. mp = 42-44 °C).[206] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.37 (d, *J* = 1.0 Hz, 3 H, CH_3), 5.24 (s, 2 H, CH_2), 6.87 - 6.91 (m, 1 H, ArH), 7.05 (m, 2 H, 2 x ArH), 7.11 - 7.19 (m, 1 H, ArH), 7.19 - 7.25 (m, 2 H, 2 x ArH), 7.25 - 7.31 (m, 2 H, 2 x ArH), 7.58 - 7.65 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 49.1, 109.3, 111.2, 118.9, 119.1, 121.8, 125.6, 128.1, 128.9, 129.0, 133.3, 136.4, 136.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3055, 2914, 2856, 1612, 1571, 1490, 1463, 1328, 1176, 1093, 1012, 732

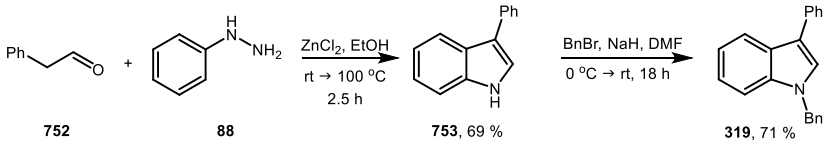
m/z (EI) 257.1 (M^+, 17), 255.1 (M^+, 48), 220.1 (3), 144.1 (2), 130.1 (12), 127.1 (34), 125.1 (100), 102.1 (12), 89.0 (17), 77.0 (12), 63.0 (7), 51.1 (4). **HRMS (CI)** calcd for $C_{16}H_{15}NCl$ ($[M+H]^+$): 256.0888 and 258.0858, found: 256.0890 and 258.0860 (3:1 ratio). The data for this compound are consistent with those reported in the literature.[206]

Preparation of 4-((3-Methyl-1H-indol-1-yl)methyl)benzonitrile (318)



This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and 4-cyanobenzyl bromide **751** (1.47 g, 7.50 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded 4-((3-methyl-1H-indol-1-yl)methyl)benzonitrile **318** as a yellow oil (774 mg, 63 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.37 (d, *J* = 1.0 Hz, 3 H, CH_3), 5.33 (s, 2 H, CH_2), 6.86 - 6.92 (m, 1 H, ArH), 7.09 - 7.23 (m, 5 H, 5 x ArH), 7.57 (app. dt, *J* = 8.3, 1.8 Hz, 2 H, 2 x ArH), 7.60 - 7.65 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 49.3, 109.1, 111.4, 111.7, 118.6, 119.2, 119.3, 122.0, 125.6, 127.1, 129.1, 132.6, 136.4, 143.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3045, 2914, 2229, 1608, 1504, 1465, 1415, 1354, 1330, 1307, 1257, 1184, 1112, 1012, 948, 821, 756, 731. **m/z (EI)** 246.2 (M^+, 100), 229.1 (3), 144.1 (10), 130.1 (96), 116.1 (48), 103.1 (20), 89.0 (23), 77.1 (27), 63.0 (8), 51.0 (7). **HRMS (CI)** calcd. for $C_{17}H_{15}N_2$ ($[M+H]^+$): 247.1230, found: 247.1232.

Preparation of 1-Benzyl-3-phenyl-1*H*-indole (319)

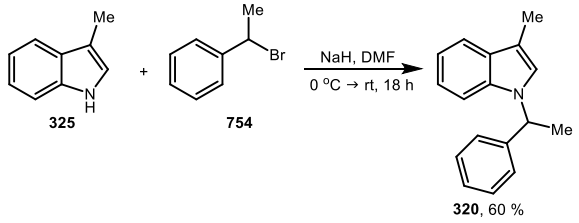


The first step was carried out according to a literature procedure.[198] A mixture of phenylacetaldehyde **752** (1.17 mL, 10.0 mmol, 1.0 equiv.) and phenylhydrazine **88** (0.98 mL, 9.95 mmol, 1.0 equiv.) was stirred at room temperature for 1 h under argon. The mixture was then heated to 100 °C and stirred for 30 min. A solution of zinc chloride (2.45 g, 18.0 mmol, 1.8 equiv.) in ethanol (11 mL) was added to the reaction mixture and this was refluxed at 100 °C for 1 h. After cooling to room temperature, the mixture was filtered, and the solvent was removed under reduced pressure. 2 M HCl was added to the crude residue and the organic products were extracted into DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 3:1) afforded 3-phenyl-1*H*-indole **753** as an orange solid (1.34 g, 69%). **Mp** = 81-83 °C (lit. mp = 83-85 °C).[207] **^{1}H-NMR** (400 MHz, $CDCl_3$) 7.15 - 7.38 (m, 4H, 4 x ArH), 7.41 (d, *J* = 7.9 Hz, 1H, ArH), 7.50 (app.

t, *J* = 7.6 Hz, 2H, 2 x ArH), 7.72 (d, *J* = 7.5 Hz, 2H, 2 x ArH), 8.01 (d, *J* = 7.9 Hz, 1H, ArH), 8.08 (br. s., 1H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 111.4, 118.2, 119.8, 120.3, 121.8, 122.4, 125.7, 126.0, 127.4, 128.7, 135.5, 136.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3400, 1597, 1541, 1456, 1417, 1338, 1259, 1236, 1112, 1101, 1010, 823, 769, 694, 632. ***m/z* (EI)** 193.2 (M^+, 100), 165.1 (37). The data for this compound are consistent with those reported in the literature.[208]

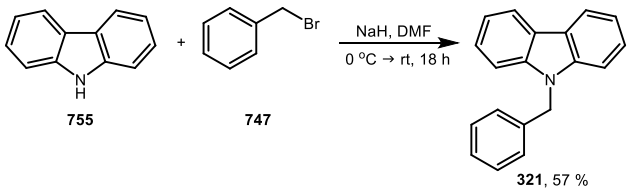
The second step was carried out according to General Procedure A from 3-phenyl-1*H*-indole **753** (750 mg, 3.88 mmol, 1.0 equiv.) and benzyl bromide (0.69 mL, 5.82 mmol, 1.5 equiv.), with NaH (112 mg, 4.66 mmol, 1.2 equiv.) in DMF (8 mL). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-benzyl-3-phenyl-1*H*-indole **319** as a white solid (782 mg, 71%). **Mp** = 58-60 °C (lit. mp = 62-63 °C).[209] **^{1}H-NMR** (400 MHz, $CDCl_3$) 5.38 (s, 2H, CH_2), 7.17 - 7.26 (m, 4H, 4 x ArH), 7.27 - 7.30 (m, 2H, 2 x ArH), 7.30 - 7.38 (m, 4H, 4 x ArH), 7.44 (app. t, *J* = 7.7 Hz, 2 H, 2 x ArH), 7.68 (d, *J* = 7.0 Hz, 2 H, 2 x ArH), 7.98 (d, *J* = 7.7 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 49.9, 110.0, 117.2, 120.0, 120.1, 122.1, 125.8, 125.9, 126.4, 126.8, 127.3, 127.6, 128.7, 128.7, 135.5, 137.1, 137.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3026, 1598, 1539, 1467, 1454, 1435, 1388, 1359, 1322, 1242, 1203, 1188, 1070, 1018, 968, 937, 898, 813, 763, 692. ***m/z* (EI)** 283.2 (M^+, 100), 192.1 (51), 165.1 (24), 91.1 (86), 65.1 (14). The data for this compound are consistent with those reported in the literature.[210]

Preparation of 1-(1-Phenylethyl)-3-methyl-1*H*-indole (320)



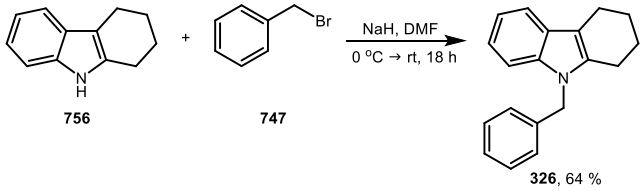
This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and (1-bromoethyl)benzene **754** (1.02 mL, 7.47 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded 1-(1-phenylethyl)-3-methyl-1*H*-indole **320** as a colourless oil (706 mg, 60%). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.91 (d, *J* = 7.0 Hz, 3H, CH_3), 2.37 (d, *J* = 1.0 Hz, 3H, CH_3), 5.65 (q, *J* = 7.1 Hz 1H, CH), 7.05-7.07 (m, 1H, ArH), 7.07 - 7.19 (m, 4H, 4 x ArH), 7.19 - 7.27 (m, 2H, 2 x ArH), 7.27 - 7.34 (m, 2H, 2 x ArH), 7.56-7.63 (m, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.8, 21.6, 54.4, 109.8, 110.5, 118.8, 118.9, 121.4, 122.4, 125.9, 127.3, 128.6, 128.9, 136.4, 142.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3024, 2972, 2912, 1612, 1452, 1355, 1233, 1186, 1015, 736, 699. **m/z (EI)** 235.1 (M^+, 94), 220.1 (7), 204.1 (7), 131.1 (100), 130.1 (86), 105.1 (90), 77.0 (33), 63.0 (3), 51.0 (9). **HRMS (CI)** calcd. for $C_{17}H_{18}N^+$ ($[M+H]^+$): 236.1434, found: 236.1435.

Preparation of 9-Benzyl-9*H*-carbazole (321)



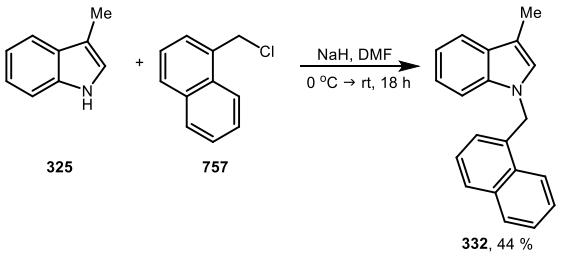
This substrate was prepared according to General Procedure A from 9*H*-carbazole **755** (836 mg, 5.00 mmol, 1.0 equiv.) and benzyl bromide **747** (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by recrystallisation from diethyl ether afforded 9-benzyl-9*H*-carbazole **321** as a white solid (732 mg, 57 %). **Mp** = 115-116 °C (lit. mp = 114-116 °C).[211] **^{1}H-NMR** (400 MHz, $CDCl_3$) 5.54 (s, 2H, CH_2), 7.16 (m, 2H, 2 x ArH), 7.21 - 7.33 (m, 5H, 5 x ArH), 7.39 (d, *J* = 8.1 Hz, 2H, 2 x ArH), 7.45 (ddd, *J* = 8.2, 7, 1.1 Hz, 2H, 2 x ArH), 8.15 (app. dt, *J* = 7.7, 0.9 Hz, 2H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 46.6, 108.9, 119.2, 120.4, 123.0, 125.8, 126.4, 127.4, 128.8, 137.2, 140.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3046, 2925, 1595, 1484, 1450, 1326, 1207, 995, 842, 747, 721, 695. ***m/z* (EI)** 257.1 (M^+, 98), 207.0 (15), 180.1 (17), 166.1 (25), 140.1 (17), 91.0 (100), 65.0 (15). The data for this compound are consistent with those reported in the literature.[211]

Preparation of 9-Benzyl-1,2,3,4-tetrahydrocarbazole (326)



This substrate was prepared according to General Procedure A from 1,2,3,4-tetrahydrocarbazole **756** (856 mg, 5.00 mmol, 1.0 equiv.) and benzyl bromide **747** (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by column chromatography (petroleum ether:diethyl ether, 19:1) afforded 9-benzyl-1,2,3,4-tetrahydro-1*H*-carbazole **326** as a colourless oil (838 mg, 64 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.82 - 2.08 (m, 4 H, 2 x CH_2), 2.65 (t, *J* = 5.9 Hz, 2 H, CH_2), 2.78 (t, *J* = 5.9 Hz, 2 H, CH_2), 5.26 (s, 2 H, CH_2), 7.02 (d, *J* = 7.8 Hz, 2 H, 2 x ArH), 7.06 - 7.15 (m, 2 H, 2 x ArH,), 7.18 - 7.32 (m, 4 H, 4 x ArH), 7.49 - 7.55 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 21.1, 22.1, 23.2, 23.2, 46.1, 108.9, 109.8, 117.7, 118.8, 120.7, 126.1, 127.1, 127.4, 128.6, 135.5, 136.5, 138.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3026, 2921, 2836, 1614, 1495, 1467, 1316, 1179, 1030, 909, 732, 697. **m/*z* (EI)** 261.1 (M^+, 100), 232.1 (46), 218.1 (10), 170.1 (16), 154.1 (4), 142.1 (10), 128.1 (10), 115.1 (12), 91.0 (60), 77.0 (2), 65.0 (10), 51.0 (2). The data for this compound are consistent with those reported in the literature.[212]

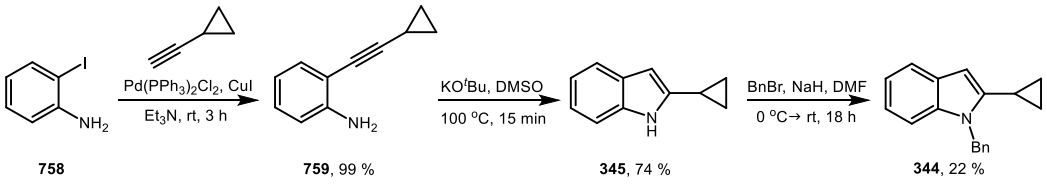
Preparation of 1-(Naphthalen-1-ylmethyl)-3-methyl-1*H*-indole (**332**)



325 **757** **332**, 44 %

This substrate was prepared according to General Procedure A from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.) and 1-(chloromethyl)naphthalene **757** (1.12 mL, 7.48 mmol, 1.5 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-(naphthalen-1-ylmethyl)-3-methyl-1*H*-indole **332** as a viscous colourless oil (603 mg, 44%). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.37 (d, *J* = 1.0 Hz, 3 H, CH_3), 5.73 (s, 2 H, CH_2), 6.82 - 6.87 (m, 1 H, ArH), 6.95 (dd, *J* = 7.2, 0.9 Hz, 1 H, ArH), 7.19 (app. td, *J* = 7.3, 1.4 Hz, 1 H, ArH), 7.24 (app. td, *J* = 7.5, 1.4 Hz, 1 H, ArH), 7.31 - 7.36 (m, 1 H, ArH), 7.36 - 7.40 (m, 1 H, ArH), 7.53 - 7.60 (m, 2 H, 2 x ArH), 7.65 - 7.70 (m, 1 H, ArH), 7.83 (d, *J* = 8.3 Hz, 1 H, ArH), 7.91 - 7.97 (m, 1 H, ArH), 7.99 - 8.04 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.7, 47.2, 109.3, 110.8, 118.9, 119.1, 121.6, 122.6, 124.8, 125.5, 125.7, 125.8, 126.4, 128.1, 128.8, 128.9, 130.8, 132.8, 133.6, 136.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3044, 2912, 1599, 1467, 1324, 1188, 1013, 792, 732. **m/z (EI)** 271.1 (M^+, 59), 254.1 (2), 141.1 (100), 128.0 (4), 115.1 (30), 102.1 (4), 89.0 (2), 77.0 (5), 63.0 (2), 51.0 (1). **HRMS (CI)** calcd. for $C_{20}H_{19}N^+$ ([M+H]$^+$): 272.1434, found: 272.1436.

Preparation of 1-Benzyl-2-cyclopropyl-1*H*-indole (**344**)



758 **759**, 99 % **345**, 74 % **344**, 22 %

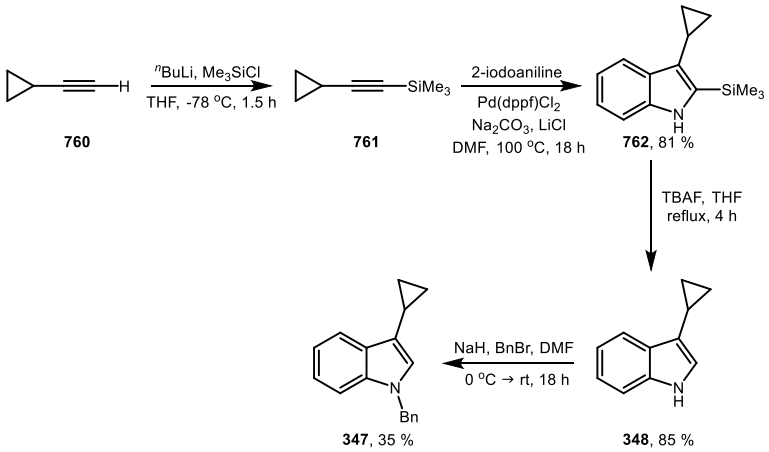
The first step was carried out according to a literature procedure.[213] Cyclopropylacetylene (1.86 mL, 22.0 mmol, 1.1 equiv.) was added to a stirred suspension of $Pd(PPh_3)_2Cl_2$ (350 mg, 0.50 mmol, 2.5 mol %) CuI (46.0 mg, 0.24 mmol, 1.2 mol %) and 2-iodoaniline **758** (4.38 g, 20.0 mmol, 1.0 equiv.) in triethylamine (100 mL). The mixture was stirred at room temperature for 3 h. After this time, the triethylamine was removed under reduced pressure and the crude mixture was diluted with water and DCM. The organic layer was separated, and the aqueous layer was further extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 0:100 → 4:1) afforded 2-(cyclopropylethynyl)aniline **759** as an orange oil (3.11 g, 99 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.78 - 0.96 (m, 4 H, 2 x CH_2), 1.46 - 1.57 (m, 1 H, CH), 6.72 (app. td, *J* = 7.5, 1.0 Hz, 1 H, ArH), 6.79 (d, *J* = 8.0 Hz, 1 H, ArH), 7.10 (app. td, *J* = 7.7, 1.5 Hz, 1 H, ArH), 7.25 (dd, *J* = 7.7, 1.5 Hz, 1 H, ArH) – NH_2 not observed. **^{13}C-NMR** (101 MHz, $CDCl_3$) 0.3, 8.9, 72.1, 98.8, 108.8, 114.1, 117.8, 128.8, 132.2, 147.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3396, 3311, 3082,

3053, 3005, 2360, 2341, 1685, 1614, 1487, 1321, 1309, 1151, 1095, 1051, 1020, 972, 883, 775, 675. **m/z (EI)** 157.0 (M^+, 87), 140.0 (4), 130.0 (100), 115.0 (15), 102.0 (26), 89.0 (17), 77.0 (28), 63.0 (29), 52.0 (22). **HRMS (CI)** calcd. for $C_{11}H_{12}N^+$ ([M+H]$^+$): 158.0964, found: 158.0963. The ^{1}H NMR for this compound is consistent with that reported in the literature.[214]

The second step was carried out according to a literature procedure.[215] Potassium *tert*-butoxide (5.55 g, 49.5 mmol, 2.5 equiv.) was added to a solution of 2-(cyclopropylethynyl)aniline **759** (3.10 g, 19.7 mmol, 1.0 equiv.) in DMSO (20 mL). The mixture was stirred at 100 °C under argon for 15 min. After cooling to room temperature, brine was added to the reaction mixture and the product was extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 4:1) afforded 2-cyclopropyl-1*H*-indole **345** as a white solid (2.29 g, 74 %). **Mp** = 64-67 °C (lit. mp = 57 °C).[215] **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.72 - 0.85 (m, 2 H, 2 x CH), 0.91 - 1.04 (m, 2 H, 2 x CH), 1.91 - 2.04 (m, 1 H, CH), 6.16 (s, 1 H, ArH), 7.07 (app. t, *J* = 7.2 Hz, 1 H, ArH), 7.11 (app. t, *J* = 6.8 Hz, 1 H, ArH), 7.29 (d, *J* = 8.0 Hz, 1 H, ArH), 7.51 (d, *J* = 7.6 Hz, 1 H, ArH), 7.94 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 7.3, 8.8, 97.7, 110.2, 119.6, 119.7, 121.0, 128.7, 135.7, 141.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3340, 1681, 1612, 1458, 1321, 1238, 1195, 1145, 1101, 1060, 1018, 970, 925, 823, 771, 702, 677 **m/z (EI)** 157.0 (M^+, 77), 140.1 (2), 130.0 (100), 117.0 (9), 102.0 (12), 89.0 (14), 77.0 (20), 63.0 (19), 51.0 (15). The data for this compound are consistent with those reported in the literature.[215]

The third step was carried out according to General Procedure A from 2-cyclopropyl-1*H*-indole **345** (600 mg, 3.82 mmol, 1.0 equiv.) and benzyl bromide (0.68 mL, 5.73 mmol, 1.5 equiv.), with NaH (110 mg, 4.58 mmol, 1.2 equiv.) in DMF (8 mL). Purification by column chromatography (hexane) afforded 1-benzyl-2-cyclopropyl-1*H*-indole **344** as a yellow solid (274 mg, 22 %). **Mp** = 37-39 °C **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.69 - 0.76 (m, 2 H, 2 x CH), 0.85 - 0.96 (m, 2 H, 2 x CH), 1.78 (tt, *J* = 8.3, 5.2 Hz, 1 H, CH), 5.49 (s, 2 H, CH_2), 6.21 (app. br. s., 1 H, ArH), 7.00 - 7.06 (m, 2 H, 2 x ArH), 7.06 - 7.13 (m, 2 H, 2 x ArH), 7.14 - 7.26 (m, 3 H, 3 x ArH), 7.53 - 7.60 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 6.5, 7.4, 46.7, 98.0, 109.1, 119.5, 120.0, 121.0, 126.1, 127.1, 127.8, 128.7, 137.3, 138.2, 143.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3080, 3028, 2995, 1602, 1552, 1494, 1463, 1452, 1355, 1303, 1178, 1018, 727, 696. **m/z (EI)** 247.1 (M^+, 77), 232.1 (13), 218.1 (25), 204.1 (2), 170.1 (3), 156.1 (23), 128.1 (17), 115.1 (6), 102.1 (3), 91.0 (100), 77.0 (6), 65.0 (20), 51.0 (5). **HRMS (CI)** calcd. for $C_{18}H_{18}N^+$ ([M+H]$^+$): 248.1439, found: 248.1441.

Preparation of 1-Benzyl-3-cyclopropyl-1*H*-indole (**347**)



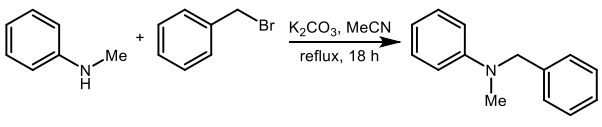
The first three steps were carried out according to a literature procedure.[4] To a stirring solution of cyclopropylacetylene **760** (1.27 mL, 15.0 mmol, 1.00 equiv.) in dry THF (5 mL) at –78 °C was added ^{n}BuLi (2.05 M in hexane, 7.50 mL, 15.45 mmol, 1.03 equiv.). The solution was stirred at this temperature for 30 min before trimethylsilyl chloride (1.98 mL, 15.6 mmol, 1.04 equiv.) was added. The solution was stirred at –78 °C for 1 h. The reaction mixture was then warmed to room temperature, diluted with diethyl ether and filtered through a pad of Na_2SO_4 layered on silica gel, eluting with pentane:diethyl ether (4:1). The filtrate was carefully concentrated under reduced pressure and used in the next step with no further purification.

The crude mixture from step one (~15.0 mmol, ~1.50 equiv.) was added to a suspension of $Pd(dppf)Cl_2$ (817 mg, 1.00 mmol, 0.10 equiv.), lithium chloride (445 mg, 10.5 mmol, 1.05 equiv.), sodium carbonate (3.18 g, 30.0 mmol, 3.00 equiv.) and 2-iodoaniline (2.19 g, 10.0 mmol, 1.00 equiv.) in DMF (200 mL) under argon. The mixture was stirred at 100 °C overnight. After cooling to room temperature, the mixture was diluted with diethyl ether and washed with aqueous NH_4Cl solution followed by water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 4:1) afforded 3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole **762** as an orange waxy solid (1.86 g, 81 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.42 (s, 9 H, $SiMe_3$), 0.76 - 0.86 (m, 2 H, 2 x CH), 0.91 - 0.99 (m, 2 H, 2 x CH), 1.90 - 2.01 (m, 1 H, CH), 7.07 (app. td, *J* = 7.5, 0.9 Hz, 1 H, ArH), 7.16 (app. td, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.34 (d, *J* = 8.0 Hz, 1 H, ArH), 7.73 (d, *J* = 8.0 Hz, 1 H, ArH), 7.88 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 1.0, 5.9, 6.1, 111.0, 119.2, 119.2, 120.4, 122.1, 128.1, 136.4 – one carbon not observed due to overlapping signals. **ATR-IR** ν_{max} (neat)/cm^{-1} 3369, 3045, 2966, 2914, 2229, 1608, 1465, 1415, 1386, 1332, 1184, 1111, 1022, 948, 821, 731. ***m/z* (EI)** 157.0 ([M–$SiMe_3$+H]$^{+}$]. **HRMS (CI)** calcd. for $C_{14}H_{20}NSi^{+}$ ([M+H]$^{+}$): 230.1365, found: 230.1367.

3-Cyclopropyl-2-(trimethylsilyl)-1*H*-indole **762** (1.85 g, 8.09 mmol, 1.0 equiv.) was dissolved in THF (16 mL) and TBAF (1 M in THF, 10.5 mL, 10.5 mmol, 1.3 equiv.) was added. The resulting solution was refluxed overnight and then cooled to room temperature. The mixture was quenched by the addition of water and extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 19:1) afforded 3-cyclopropyl-1*H*-indole **348** as an orange solid (1.09 g, 85 %). **Mp** = 55-57 °C (lit. mp = 59-60 °C).[216] **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.53 - 0.71 (m, 2 H, 2 x CH), 0.83 - 0.95 (m, 2 H, 2 x CH), 1.87 - 2.04 (m, 1 H, CH), 6.87 – 6.93 (m, 1 H, ArH), 7.13 (app. td, *J* = 7.4, 1.0 Hz, 1 H, ArH), 7.20 (app. td, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.35 (d, *J* = 8.0, 1 H, ArH), 7.75 (d, *J* = 8.0 Hz, 1 H, ArH), 7.84 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 5.9, 6.1, 111.0, 119.1, 119.2 (two signals), 120.4, 122.1, 128.1, 136.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3398, 3053, 2906, 1598, 1490, 1454, 1336, 1222, 1087, 1074, 1008, 798, 707. ***m/z* (EI)** 157.2 (M^+, 93), 130.1 (100), 115.1 (14), 102.1 (21), 89.1 (15), 77.2 (33), 63.1 (22), 51.1 (21). The data for this compound are consistent with those reported in the literature.[216]

Step four was carried out according to General Procedure A from 3-cyclopropyl-1*H*-indole **348** (786 mg, 5.00 mmol, 1.0 equiv.) and benzyl bromide (0.89 mL, 7.49 mmol, 1.5 equiv.). Purification by column chromatography afforded 1-benzyl-3-cyclopropyl-1*H*-indole **347** as an off-white solid (430 mg, 22 %). **Mp** = 37-39 °C. **^{1}H-NMR** (500 MHz, $CDCl_3$) 0.57 - 0.69 (m, 2 H, 2 x CH), 0.84 - 0.93 (m, 2 H, 2 x CH), 1.91 - 2.02 (m, 1 H, CH), 5.25 (s, 2 H, CH_2), 6.82 (s, 1 H, ArH), 7.08 - 7.14 (m, 3 H, 3 x ArH), 7.18 (app. td, *J* = 7.6, 1.1 Hz, 1 H, ArH), 7.24 (d, *J* = 9.2 Hz, 2 H, 2 x ArH), 7.28 - 7.32 (m, 2 H, 2 x ArH), 7.75 (d, *J* = 7.8 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 6.1, 6.1, 49.8, 109.6, 118.3, 118.8, 119.3, 121.8, 124.5, 126.8, 127.5, 128.7, 128.7, 136.7, 137.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3078, 3026, 2993, 1602, 1583, 1465, 1354, 1301, 1178, 1008, 960, 729, 696. ***m/z* (EI)** 247.1 (M^+, 88), 232.1 (6), 220.1 (6), 204.1 (2), 170.1 (2), 156.1 (29), 140.1 (1), 128.1 (19), 115.1 (3), 102.1 (4), 91.1 (100), 77.0 (5), 65.1 (18), 51.0 (4). **HRMS (CI)** calcd. for $C_{18}H_{18}N^+$ ($[M+H]^+$): 248.1439, found: 248.1440.

Preparation of *N*-Benzyl-*N*-methylaniline (367)

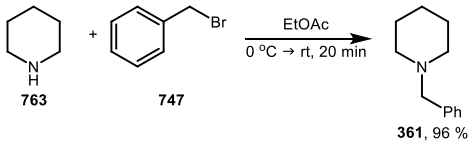


87 **747** **359**, 61 %

This substrate was prepared according to a modified literature procedure.[217] *N*-methylaniline **87** (0.54 mL, 4.98 mmol, 1.0 equiv.), potassium carbonate (1.38 g, 9.98 mmol, 2.0 equiv.) and benzyl bromide **747** (0.71 mL, 5.98 mmol, 1.2 equiv.) were dissolved in acetonitrile (5 mL) and heated at reflux for 18 h. The reaction mixture was then cooled to room temperature and dissolved in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum

ether:diethyl ether, 9:1) afforded *N*-benzyl-*N*-methylaniline **359** as a brown oil (606 mg, 61 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 3.04 (s, 3 H, NCH_3), 4.56 (s, 2 H, CH_2), 6.74 (app. tt, *J* = 7.2, 1.0 Hz, 1 H, ArH), 6.76 - 6.81 (m, 2 H, 2 x ArH), 7.22 - 7.30 (m, 5 H, 5 x ArH), 7.31 - 7.37 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 38.5, 56.6, 112.4, 116.5, 126.7, 126.8, 128.5, 129.2, 139.0, 149.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3059, 3024, 2877, 2812, 1597, 1502, 1450, 1352, 1247, 1211, 1190, 1114, 1026, 985, 943, 860, 746, 725. ***m/z* (EI)** 197.2 (M^+, 94), 120.1 (78), 104.1 (12), 91.1 (100), 77.1 (30), 65.1 (20). The data for this compound are consistent with those reported in the literature.[218]

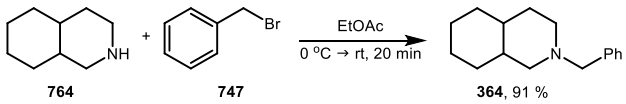
Preparation of N-Benzylpiperidine (361)



763 **747** **361**, 96 %

This substrate was prepared according to a literature procedure.[219] A solution of benzyl bromide **747** (0.59 mL, 4.97 mmol, 1.0 equiv.) in ethyl acetate (8 mL) was cooled to 0 °C and piperidine **763** (2.47 mL, 25.0 mmol, 5.0 equiv.) was added dropwise. The reaction was stirred at room temperature for 20 min and then diluted with ethyl acetate and washed with water. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether:diethyl ether, 9:1) afforded *N*-benzylpiperidine **361** as an orange oil (842 mg, 96 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.33 - 1.52 (m, 2 H, CH_2), 1.52 - 1.76 (m, 4 H, 2 x CH_2), 2.24 - 2.53 (m, 4 H, 2 x CH_2), 3.51 (s, 2 H, CH_2), 7.18 - 7.46 (m, 5 H, 5 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 24.4, 26.0, 54.4, 63.8, 126.7, 128.0, 129.1, 138.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3026, 2931, 2850, 2791, 2752, 1492, 1452, 1367, 1346, 1298, 1271, 1247, 1197, 1153, 1112, 1037, 995, 906, 860, 788, 732. ***m/z* (EI)** 175.1 (M^+, 41), 174.1 (52), 146.1 (5), 132.1 (4), 118.1 (4), 104.1 (3), 98.1 (33), 91.1 (100), 84.1 (26), 77.1 (4), 65.1 (22), 55.1 (10). The data for this compound are consistent with those reported in the literature.[220]

Preparation of 2-Benzyldecahydroisoquinoline (364)

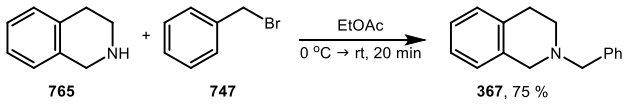


764 **747** **364**, 91 %

This substrate was prepared according to a modified literature procedure.[219] A solution of benzyl bromide **747** (0.59 mL, 4.97 mmol, 1 equiv.) in ethyl acetate (8 mL) was cooled to 0 °C and perhydroisoquinoline **764** (mixture of *cis*- and *trans*- isomers, 3.7 mL, 24.9 mmol, 5.0 equiv.) was added dropwise. The reaction was stirred at room temperature for 20 min and then diluted with ethyl acetate and washed with water. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether:diethyl ether, 4:1) afforded 2-benzyldecahydroisoquinoline **364** as an orange oil (1.04 g,

91 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.80 - 1.06 (m, 3 H, 3 x CH), 1.16 - 1.30 (m, 3 H, 3 x CH), 1.34 (td, *J* = 12.0, 4.0 Hz, 1 H, CH), 1.46 - 1.56 (m, 2 H, 2 x CH), 1.57 - 1.67 (m, 2 H, 2 x CH), 1.67 - 1.78 (m, 2 H, 2 x CH), 1.96 (ddd, *J* = 12.2, 11.2, 2.8 Hz, 1 H, CH), 2.75 (ddd, *J* = 10.8, 3.5, 1.8 Hz, 1 H, CH), 2.90 (app. dquin, *J* = 11.0, 2.3 Hz, 1 H, CH), 3.48 (s, 2 H, CH_2), 7.22 - 7.28 (m, 1 H, ArH), 7.28 - 7.35 (m, 4 H, 4 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 26.1, 26.5, 30.7, 33.0, 33.0, 41.9 (two signals), 55.4, 60.5, 63.5, 126.8, 128.0, 129.1, 138.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 2916, 2846, 1494, 1446, 732, 696. ***m/z* (EI)** 229.1 (M^+, 59), 228.2 (77), 214.1 (3), 152.1 (34), 138.1 (40), 134.0 (11), 120.1 (10), 109.1 (5), 91.1 (100), 79.1 (4), 65.1 (15), 55.1 (5). **HRMS (CI)** calcd. for $C_{16}H_{24}N^+$ ($[M+H]^+$): 230.1903, found: 230.1905.

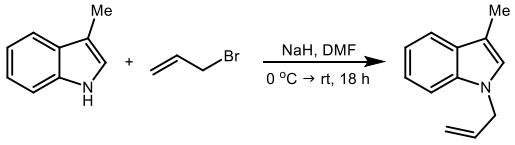
Preparation of 2-Benzyl-1,2,3,4-tetrahydroisoquinoline (367)



765 **747** **367**, 75 %

This substrate was prepared according to a modified literature procedure.[219] A solution of benzyl bromide **747** (0.59 mL, 4.97 mmol, 1.0 equiv.) in ethyl acetate (8 mL) was cooled to 0 °C and 1,2,3,4-tetrahydroisoquinoline **765** (3.13 mL, 25.0 mmol, 5.0 equiv.) was added dropwise. The reaction was stirred at room temperature for 20 min and then diluted with ethyl acetate and washed with water. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether:diethyl ether, 9:1) afforded 2-benzyl-1,2,3,4-tetrahydroisoquinoline **367** as an orange oil (836 mg, 75 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.77 (t, *J* = 5.9 Hz, 2 H, CH_2), 2.93 (t, *J* = 5.9 Hz, 2 H, CH_2), 3.66 (s, 2 H, CH_2), 3.71 (s, 2 H, CH_2), 7.00 (dd, *J* = 8.3, 1.3 Hz, 1 H, ArH), 7.08 - 7.18 (m, 3 H, 3 x ArH), 7.27 - 7.32 (m, 1 H, ArH), 7.33 - 7.39 (m, 2 H, 2 x ArH), 7.40 - 7.45 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 29.2, 50.6, 56.1, 62.8, 125.5, 126.1, 126.6, 127.1, 128.3, 128.7, 129.1, 134.4, 135.0, 138.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3022, 2912, 2796, 2854, 1653, 1494, 1452, 1365, 1130, 1091, 933, 736, 696. ***m/z* (EI)** 223.2 (M^+, 59), 222.2 (100), 146.1 (17), 132.1 (44), 117.1 (9), 104.1 (40), 91.1 (80), 78.1 (14), 65.1 (17), 51.0 (6). The data for this compound are consistent with those reported in the literature.[221]

Preparation of 1-Allyl-3-methyl-1*H*-indole (294)

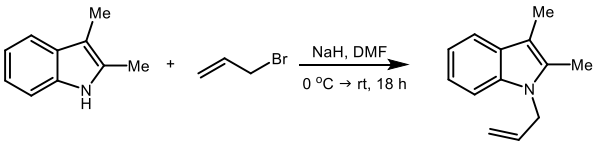


325 **766** **294**, 64 %

This substrate was prepared according to General Procedure B from 3-methyl-1*H*-indole **325** (655 mg, 4.99 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-allyl-3-methyl-1*H*-indole **294** as a pink oil (546 mg, 64%). **^{1}H-NMR** (400 MHz,

$CDCl_3$) 2.38 (d, *J* = 1.0 Hz, 3H, CH_3), 4.70 (app. dt, *J* = 5.5, 1.5 Hz, 2H, CH_2), 5.13 (app. dq, *J* = 17.1, 1.6 Hz, 1H, CH), 5.22 (app. dq, *J* = 10.3, 1.4 Hz, 1H, CH), 6.02 (app. ddt, *J* = 17.1, 10.4, 5.3 Hz, 1H, CH), 6.87 - 6.92 (m, 1 H, ArH), 7.10 - 7.20 (m, 1H, ArH), 7.24 (app. td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.32 (d, *J* = 8.3 Hz, 1H, ArH), 7.62 (app. dt, *J* = 7.8, 1.0 Hz, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 48.5, 109.3, 110.5, 117.0, 118.6, 119.0, 121.4, 125.4, 128.8, 133.8, 136.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3053, 2914, 1463, 1436, 1417, 1384, 1361, 1328, 1186, 1126, 1012, 987, 918, 786, 688. ***m/z* (EI)** 171.2 (M^+, 100), 156.1 (49), 144.1 (35), 130.1 (57), 115.1 (11), 103.1 (23), 89.1 (4), 77.1 (30), 63.1 (6). The data for this compound are consistent with those reported in the literature.[222]

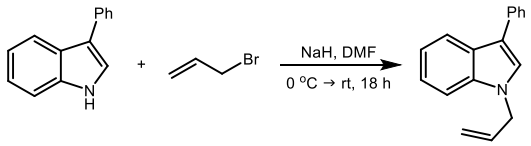
Preparation of 1-Allyl-2,3-dimethyl-1*H*-indole (369)



370 **766** **369**, 35 %

This substrate was prepared according to General Procedure B from 2,3-dimethylindole **370** (726 mg, 5.00 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-allyl-2,3-dimethyl-1*H*-indole **369** as a red oil (342 mg, 35 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.27 (d, *J* = 0.5 Hz, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 4.68 (app. dt, *J* = 4.6, 2.0 Hz, 2 H, CH_2), 4.84 (app. dq, *J* = 17.2, 1.6 Hz, 1 H, CH), 5.10 (app. dq, *J* = 10.3, 1.6 Hz, 1 H, CH), 5.93 (ddt, *J* = 17.1, 10.3, 4.7 Hz, 1 H, CH), 7.08 (ddd, *J* = 7.8, 7.5, 1.3 Hz, 1 H, ArH), 7.14 (app. td, *J* = 7.5, 1.4 Hz, 1 H, ArH), 7.19 - 7.24 (m, 1 H, ArH), 7.47 - 7.53 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 8.8, 9.9, 45.2, 106.6, 108.6, 115.9, 117.9, 118.6, 120.5, 128.6, 132.2, 133.7, 136.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3053, 2980, 2912, 2856, 1643, 1614, 1570, 1487, 1413, 1363, 1328, 1261, 1215, 1182, 1147, 1126, 1016, 985, 916, 792, 663. ***m/z* (EI)** 185.2 (M^+, 100), 170.2 (33), 158.1 (21), 144.1 (58), 128.1 (14), 115.1 (14), 102.1 (9), 91.1 (3), 77.0 (19), 63.1 (4), 51.1 (6). **HRMS (CI)** calcd. for $C_{13}H_{16}N^+$ ($[M+H]^+$): 186.1277, found: 186.1276. The data for this compound are consistent with those reported in the literature.[223]

Preparation of 1-Allyl-3-phenyl-1*H*-indole (371)

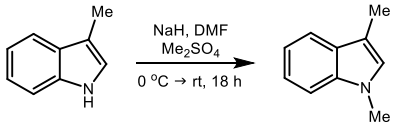


753 **766** **371**, 45 %

This substrate was prepared according to General Procedure B from 3-phenyl-1*H*-indole **753** (750 mg, 3.88 mmol, 1.0 equiv.) and allyl bromide **766** (0.50 mL, 5.82 mmol, 1.5 equiv.), with NaH (112 mg, 4.62 mmol, 1.2 equiv.) in DMF (8 mL). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1-allyl-3-phenyl-1*H*-indole **371** as a yellow oil (403 mg,

45 %). **^{1}H-NMR** (500 MHz, $CDCl_3$) 4.80 (d, *J* = 5.3 Hz, 2 H, CH_2), 5.20 (dd, *J* = 17.0, 1.1 Hz, 1 H, CH), 5.27 (dd, *J* = 10.5, 1.2 Hz, 1 H, CH), 5.94 - 6.16 (m, 1 H, CH), 7.23 (app. t, *J* = 7.6 Hz, 1 H, ArH), 7.27 - 7.34 (m, 3 H, 3 x ArH), 7.40 (d, *J* = 8.2 Hz, 1 H, ArH), 7.47 (app. t, *J* = 7.7 Hz, 2 H, ArH), 7.70 (d, *J* = 7.2 Hz, 2 H, 2 x ArH), 7.99 (d, *J* = 7.9 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 48.9, 109.9, 117.1, 117.6, 120.0, 122.0, 125.5, 125.7, 126.4, 127.3, 128.7, 133.2, 135.6, 136.9 – one carbon not observed due to overlap of signals. **ATR-IR** ν_{max} (neat)/cm^{-1} 3047, 2916, 1600, 1544, 1463, 1373, 1330, 1234, 1188, 1070, 1016, 989, 921, 765, 734, 696 ***m/z* (EI)** 233.1 (M^+, 100), 217.1 (2), 206.1 (12), 192.1 (75), 177.1 (3), 165.1 (36), 154.1 (4), 139.1 (6), 128.1 (2), 115.1 (4), 102.1 (2), 89.0 (2), 77.0 (2), 63.0 (2), 51.0 (1). **HRMS (CI)** calcd. for $C_{17}H_{16}N^+$ ($[M+H]^+$): 234.1277, found: 234.1279.

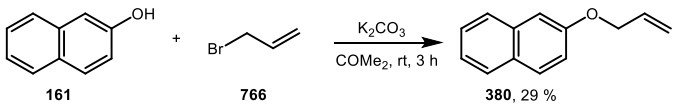
Preparation of 1,3-Dimethyl-1*H*-indole (**378**)



325 **378**, 83 %

This substrate was prepared by modification of a literature procedure.[197] To a stirred solution of sodium hydride (86 mg, 3.6 mmol, 1.2 equiv.) in DMF (3 mL) was added 3-methyl-1*H*-indole **325** (394 mg, 3.00 mmol, 1.0 equiv.) at 0 °C under argon. After stirring at room temperature for 30 min, a solution of dimethylsulfate (0.43 mL, 4.54 mmol, 1.5 equiv.) in DMF (3 mL) was added at 0 °C. The resulting mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted into EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 1,3-dimethyl-1*H*-indole **378** as a colourless oil (360 mg, 83 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.39 (d, *J* = 1.0 Hz, 3 H, CH_3), 3.78 (s, 3 H, NCH_3), 6.83 - 6.90 (m, 1 H, ArH), 7.17 (ddd, *J* = 7.9, 6.9, 1.3 Hz, 1 H, ArH), 7.25 - 7.30 (m, 1 H, ArH), 7.34 (app. dt, *J* = 8.0, 1.0 Hz, 1 H, ArH), 7.63 (app. dt, *J* = 8.0, 0.9 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.5, 32.4, 108.9, 110.1, 118.5, 118.9, 121.4, 126.5, 128.6, 137.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3051, 2914, 2881, 1616, 1558, 1469, 1423, 1384, 1365, 1323, 1246, 1201, 1157, 1124, 1062, 1010, 920, 839, 792, 732. ***m/z* (EI)** 145.1 (M^+, 71), 144.1 (100), 128.1 (9), 115.1 (9), 102.1 (9), 77.0 (10), 63.0 (4), 51.1 (5). The data for this compound are consistent with those reported in the literature.[224]

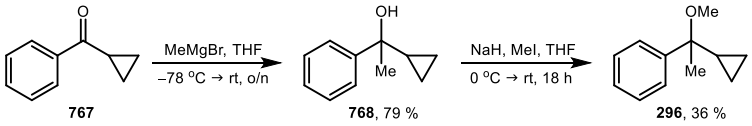
Preparation of 2-(Allyloxy)naphthalene (**380**)



161 **766** **380**, 29 %

This substrate was prepared according to a literature procedure.[225] To a solution of 2-naphthol **161** (721 mg, 5.00 mmol, 1.0 equiv.) in acetone (4 mL) was added K_2CO_3 (2.76 g, 20.0 mmol, 4.0 equiv.) followed by allyl bromide **766** (0.65 mL, 7.50 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 3 h and then filtered. The solid was washed with acetone, and then the filtrate was concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 19:1) afforded 2-(allyloxy)naphthalene **380** as a colourless oil (268 mg, 29 %). **^{1}H-NMR** (600 MHz, $CDCl_3$) 4.67 (d, *J* = 5.3 Hz, 2 H, CH_2), 5.34 (app. dd, *J* = 10.8, 0.9 Hz, 1 H, CH), 5.49 (app. dd, *J* = 17.2, 1.3 Hz, 1 H, CH), 6.03 - 6.18 (m, 1 H, CH), 7.13 - 7.17 (m, 1 H, ArH), 7.19 (dd, *J* = 8.8, 2.4 Hz, 1 H, ArH), 7.34 (app. t, *J* = 7.0 Hz, 1 H, ArH), 7.44 (app. t, *J* = 7.2 Hz, 1 H, ArH), 7.71 - 7.80 (m, 3 H, 3 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 68.8, 107.0, 117.8, 119.0, 123.6, 126.3, 126.8, 127.6, 129.0, 129.4, 133.2, 134.5, 156.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3055, 2910, 1627, 1598, 1508, 1467, 1388, 1255, 1213, 1174, 1118, 1014, 997, 921, 833, 806, 742. ***m/z* (EI)** 184.1 (M^+, 100), 169.1 (71), 165.1 (39), 152.1 (20), 141.1 (26), 128.1 (39), 115.1 (22), 102.1 (6), 91.1 (6), 77.1 (10), 63.1 (10), 51.1 (9). The data for this compound are consistent with those reported in the literature.[226]

Preparation of (1-Cyclopropyl-1-methoxyethyl)benzene (296)

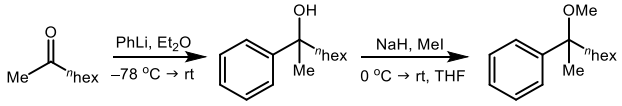


767 **768**, 79 % **296**, 36 %

The first step was carried out according to a modified literature procedure.[227] Cyclopropyl phenyl ketone **767** (1.38 mL, 9.99 mmol, 1.0 equiv.) was dissolved in THF (11 mL) and cooled to –78 °C. Methylmagnesium bromide (3 M in Et_2O, 3.33 mL, 9.99 mmol, 1.0 equiv.) was added and the reaction mixture was allowed to warm to room temperature with stirring for 18 h. The reaction was found to be incomplete, so a further portion of methylmagnesium bromide (3 M in Et_2O, 1.67 mL, 5.01 mmol, 0.5 equiv.) was added and the mixture stirred for 3 h at room temperature. The reaction mixture was quenched by the slow addition of 2 M HCl. Ethyl acetate was then added, and the layers were separated. The aqueous layer was twice more extracted into ethyl acetate, and the combined organic layers were washed with 2 M HCl and brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether: diethyl ether, 9:1) afforded 1-cyclopropyl-1-phenylethan-1-ol **768** as a colourless oil (1.28 g, 79 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.31 - 0.59 (m, 4 H, 2 x CH_2), 1.20 - 1.38 (m, 1 H, CH), 1.52 (s, 3 H, CH_3), 7.27 (app. tt, *J* = 7.3, 2.3 Hz, 1 H, ArH), 7.32 - 7.43 (m, 2 H, 2 x ArH), 7.48 - 7.63 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 1.1, 1.9, 22.8, 28.5, 73.1, 125.1, 126.7, 128.0, 148.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3379, 2972, 1492, 1444, 1369, 1020, 948, 856, 817, 758, 698. ***m/z* (EI)** 147.1 ($[M\text{-}Me]^+$, 18), 134.1 (100), 128.1 (7), 121.1 (20), 115.1 (10), 105.1 (45), 91.0 (40), 77.1 (26), 69.0 (6), 51.1 (12). The data for this compound are consistent with those reported in the literature.[227–229]

The second step was carried out according to a literature procedure.[137] A solution of 1-cyclopropyl-1-phenylethan-1-ol **768** (1.27 g, 7.83 mmol, 1.0 equiv.) in dry THF (5 mL) was added to a suspension of sodium hydride (60 % dispersion in oil, 312 mg, 7.80 mmol, 1.0 equiv.) in dry THF (5 mL) at 0 °C under argon. The resulting solution was stirred for 45 min at room temperature then a solution of iodomethane (0.73 mL, 11.7 mmol, 1.5 equiv.) in dry THF (4 mL) was added slowly. The reaction was then stirred at room temperature for 24 h. The reaction mixture was then quenched with water and extracted into diethyl ether. The combined organic layers were washed with water and brine, and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether:diethyl ether, 49:1) afforded (1-cyclopropyl-1-methoxyethyl)benzene **296** as a colourless oil (486 mg, 36 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.30 - 0.60 (m, 4 H, 2 x CH_2), 1.13 - 1.28 (m, 1 H, CH), 1.41 (s, 3 H, CH_3), 3.16 (s, 3 H, OCH_3), 7.27 (app. tt, *J* = 7.3, 2.0 Hz, 1 H, ArH), 7.32 - 7.41 (m, 2 H, 2 x ArH), 7.41 - 7.52 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 0.9, 2.3, 21.3, 22.6, 50.4, 78.5, 126.5, 126.8, 127.9, 145.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 2931, 1444, 1367, 1228, 1087, 1068, 1020, 921, 754, 698. ***m/z* (EI)** 176.1 (M^+, 14), 131.1 (100), 115.1 (26), 103.1 (7), 91.1 (44), 77.1 (11), 65.1 (5), 51.1 (8). The data for this compound are consistent with those reported in the literature.[137]

Preparation of (2-Methoxyoctan-2-yl)benzene (390)



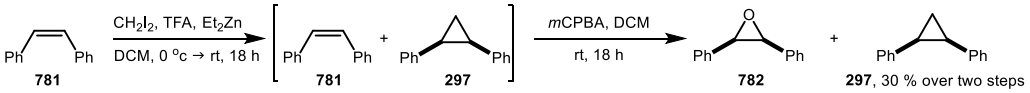
769 **780**, 59 % **390**, 42 %

The first step was carried out according to a modified literature procedure.[227] To a solution of 2-octanone **769** (0.78 mL, 4.99 mmol, 1.0 equiv.) in dry diethyl ether (5 mL) under argon was added phenyllithium (1.8 M solution in Bu_2O, 3.3 mL, 5.94 mmol, 1.2 equiv.) dropwise at – 78 °C. The solution was then warmed to room temperature and stirred for 1 h. The reaction was then quenched by careful addition of isopropanol and then hydrochloric acid (1 M). The organic materials were then extracted into diethyl ether, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 2-phenyloctan-2-ol **780** as a colourless oil (610 mg, 59 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.79 - 0.91 (m, 3H, CH_3), 1.12 - 1.35 (m, 8H, 4 x CH_2), 1.56 (s, 3H, CH_3), 1.73 - 1.87 (m, 2H, CH_2), 7.25 (app. tt, *J* = 7.3, 1.5 Hz, 1H, ArH), 7.35 (app. tt, *J* = 7.5, 2.3 Hz, 2H, 2 x ArH), 7.39 - 7.50 (m, 2H, 2 x ArH) – OH not observed. **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 22.6, 23.9, 29.6, 30.1, 31.7, 44.2, 74.7, 124.8, 126.4, 128.1, 148.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3414, 2929, 1492, 1444, 1373, 1151, 1067, 1028, 931, 900, 862, 763. ***m/z* (EI)** 206.2 (M^+, 1), 191.2 (13), 121.1 (100), 105.1 (34), 91.1 (21), 77.1 (35). The data for this compound are consistent with those reported in the literature.[230]

The second step was carried out according to a modified literature procedure.[137] 2-Phenyloctan-2-ol **780** (610 mg, 2.96 mmol, 1.0 equiv.) was added at 0 °C to a suspension of sodium hydride

(71 mg, 2.96 mmol, 1 equiv.) in dry THF (5 mL) under nitrogen. The resulting solution was then stirred for 45 min at room temperature before again cooling to 0 °C. Methyl iodide (0.28 mL, 4.50 mmol, 1.5 equiv.) was added dropwise before being warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with water and extracted into diethyl ether. The organic phase was washed with water and brine, then dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (hexane:diethyl ether, 49:1) afforded (2-methoxyoctan-2-yl)benzene **390** as a colourless oil (271 mg, 42%). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.85 (t, *J* = 6.9 Hz, 3H, CH_3), 1.08 - 1.18 (m, 1H, CH), 1.18 - 1.31 (m, 7H, CH + 3 x CH_2), 1.53 (s, 3H, CH_3), 1.69 - 1.80 (m, 2H, CH_2), 3.09 (s, 3H, OCH_3), 7.22 - 7.28 (m, 1H, ArH), 7.32 - 7.42 (m, 4H, 4 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 22.6, 23.0, 23.9, 29.7, 31.8, 42.7, 50.3, 79.1, 126.2, 126.6, 128.0, 145.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 2929, 2854, 1492, 1480, 1444, 1165, 1132, 1072, 1023, 912, 840, 763. ***m/z* (EI)** 205.2 ([M-Me]$^+$, 4), 135.1 (100), 105.1, (22), 91.1 (19), 77.1 (18). The data for this compound are consistent with those reported in the literature.[231]

Preparation of *cis*-1,2-Diphenylcyclopropane (297)



This substrate was prepared according to a literature procedure.[138] To an oven-dried three-necked flask under argon was added dry DCM (6 mL), then diethyl zinc (1 M solution in hexane, 5.00 mL, 5.00 mmol, 1.0 equiv.) was added slowly at 0 °C. A solution of trifluoroacetic acid (0.38 mL, 4.96 mmol, 1.0 equiv.) in DCM (2.5 mL) was added slowly and the mixture was stirred for 30 min. A solution of diiodomethane (0.40 mL, 4.97 mmol, 1.0 equiv.) in DCM (2.5 mL) was then added and the mixture was stirred for 30 min. Finally, a solution of *cis*-stilbene **781** (0.89 mL, 4.99 mmol, 1.0 equiv.) in DCM (2 mL) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was carefully quenched by the slow addition of 2 M HCl, and the DCM layer separated. The aqueous layer was further extracted with hexane, and the combined organic layers were washed with $NaHCO_3$ solution and then water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude ^{1}H NMR indicated that a mixture of *cis*-stilbene **781** and *cis*-1,2-diphenylcyclopropane **297** was present in a ratio of 2.47:1. This was determined by integrating the cyclopropane signal of **297** at 1.44-1.48 ppm (2H) to one unit, and comparing this to the integration of the alkenyl peak of *cis*-stilbene **781** at 6.69 ppm (2H). This was found to integrate to 2.47 units.

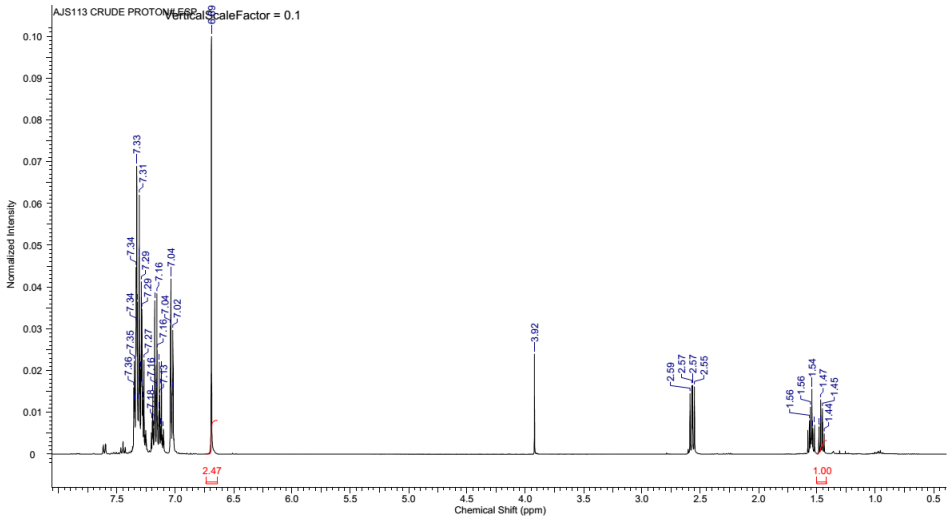
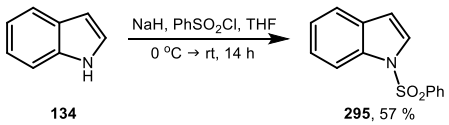


*Figure 6 - ^{1}H NMR Spectrum of the Mixture of cis-Stilbene **781** and cis-1,2-Diphenylcyclopropane **297***

The crude mixture of **781** and **297** (843 mg) was dissolved in DCM (15 mL) and *m*CPBA (518 mg, 3.00 mmol) was added. The mixture was stirred at room temperature overnight, and then quenched with $Na_2S_2O_3$ solution. The layers were separated, and the organic layer was washed with $Na_2S_2O_3$ solution and brine, and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether) afforded *cis*-1,2-diphenylcyclopropane **297** as a colourless oil (289 mg, 30 % over two steps). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.39 (td, *J* = 6.5, 5.5 Hz, 1 H, CH), 1.48 (td, *J* = 8.7, 5.5 Hz, 1 H, ArH), 2.50 (dd, *J* = 8.7, 6.4 Hz, 2 H, 2 x CH), 6.91 - 6.99 (m, 4 H, 4 x ArH), 7.02 - 7.07 (m, 2 H, 2 x ArH), 7.07 - 7.14 (m, 4 H, 4 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 11.3, 24.3, 125.6, 127.6, 128.9, 138.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3059, 3024, 1600, 1496, 1458, 1444, 1197, 1072, 1028, 906, 829, 775, 758. ***m/z* (EI)** 194.3 (M^+, 95), 179.2 (51), 165.1 (19), 152.2 (7), 139.1 (2), 128.1 (4), 115.2 (100), 103.1 (23), 91.2 (39), 78.2 (31), 63.1 (23), 51.1 (29). The data for this compound are consistent with those reported in the literature.[138]

Preparation of 1-(Phenylsulfonyl)-1H-indole (295)

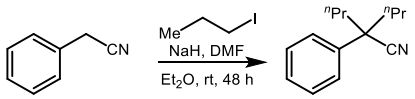


134 **295**, 57 %

This substrate was prepared according to a literature procedure.[232] Sodium hydride (180 mg, 7.50 mmol, 1.5 equiv.) was added to a stirred solution of 1*H*-indole **134** (586 mg, 5.00 mmol, 1.0 equiv.) in THF (9 mL) at 0 °C. Benzenesulfonyl chloride (0.77 mL, 6.03 mmol, 1.2 equiv.) was then added and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was then diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (petroleum ether:ethyl acetate, 19:1) afforded 1-(phenylsulfonyl)-1*H*-indole **295** as a white solid (732 mg, 57 %). **mp** = 71-72 °C (lit. mp = 76-78 °C).[232] **^{1}H-NMR** (400 MHz, $CDCl_3$)

6.68 (dd, *J* = 3.8, 0.8 Hz, 1 H, ArH), 7.24 (app. td, *J* = 7.8, 1.0 Hz, 1 H, ArH), 7.32 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1 H, ArH), 7.40 - 7.48 (m, 2 H, 2 x ArH), 7.51 - 7.57 (m, 2 H, 2 x ArH), 7.58 (d, *J* = 3.8 Hz, 1 H, ArH), 7.84 - 7.93 (m, 2 H, 2 x ArH), 8.01 (dd, *J* = 8.3, 0.8 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 109.2, 113.5, 121.4, 123.4, 124.6, 126.3, 126.7, 129.2, 130.7, 133.8, 134.9, 138.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3140, 3116, 1529, 1446, 1373, 1263, 1168, 1120, 987, 775, 754, 723, 682, 655. ***m/z* (EI)** 257.0 (M^+, 96), 192.1 (4), 165.1 (9), 141.0 (26), 132.1 (7), 116.1 (100), 89.0 (48), 77.0 (58), 63.0 (19), 51.0 (23). The data for this compound are consistent with those reported in the literature.[232]

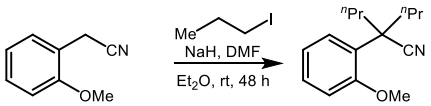
Preparation of 2-Phenyl-2-propylpentanenitrile (**417**)



783 **417**, 79 %

This substrate was prepared according to a modified literature procedure.[233] To a suspension of NaH (227 mg, 9.46 mmol, 3.1 equiv.) in dry DMF (11 mL) was added a solution of benzyl cyanide **783** (0.35 mL, 3.03 mmol, 1.0 equiv.) and 1-iodopropane (1.32 mL, 13.5 mmol, 4.5 equiv.) in dry diethyl ether (5.5 mL) at room temperature. This mixture was stirred for 48 h at room temperature, and was then quenched with methanol and concentrated under reduced pressure. The crude residue was redissolved in dry diethyl ether, and then washed with water, sodium bisulfite solution and sodium carbonate solution. The organic layer was then dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (hexane:diethyl ether, 49:1) afforded 2-phenyl-2-propylpentanenitrile **417** as a colourless oil (476 mg, 79 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.89 (t, *J* = 7.5 Hz, 6 H, 2 x CH_3), 1.05 - 1.24 (m, 2 H, 2 x CH), 1.40 - 1.58 (m, 2 H, 2 x CH), 1.81-1.89 (ddd, *J* = 13.6, 12.3, 4.8 Hz, 2 H, 2 x CH), 1.92-2.00 (ddd, *J* = 13.3, 12.0, 4.5 Hz, 2 H, 2 x CH), 7.25 - 7.34 (m, 1 H, ArH), 7.35 - 7.44 (m, 4 H, 4 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.9, 18.6, 43.2, 48.3, 122.7, 125.9, 127.5, 128.8, 138.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 2958, 2872, 2233, 1600, 1492, 1463, 1448, 1379, 1201, 1112, 1083, 1029, 912, 763, 738, 698. ***m/z* (EI)** 201.2 (M^+, 25), 159.1 (77), 130.1 (78), 116.1 (100), 103.1 (48), 91.1 (14), 77.1 (16). **HRMS (CI):** calcd. for $C_{14}H_{20}N^+$ ([M+H]$^+$): 202.1596, found: 202.1594.

Preparation of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (**298**)

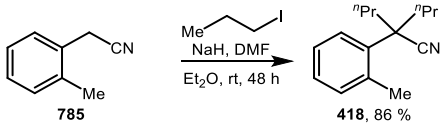


784 **298**, 81 %

This substrate was prepared according to a modified literature procedure.[233] To a suspension of NaH (227 mg, 9.46 mmol, 3.1 equiv.) in dry DMF (11 mL) was added a solution 2-methoxyphenylacetonitrile **784** (442 mg, 3.00 mmol, 1.0 equiv.) and 1-iodopropane (1.32 mL, 13.5 mmol, 4.5 equiv.) in dry diethyl ether (5.5 mL) at room temperature. This mixture was stirred

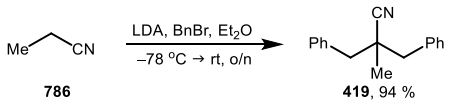
for 48 h at room temperature, and was then quenched with methanol and concentrated under reduced pressure. The crude residue was redissolved in diethyl ether, and then washed with water, sodium bisulfite solution and sodium carbonate solution. The organic layer was then dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (hexane:diethyl ether, 49:1) afforded 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** as a colourless oil (559 mg, 81 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.89 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.02 - 1.22 (m, 2 H, 2 x CH), 1.38 - 1.51 (m, 2 H, 2 x CH), 1.91 (ddd, *J* = 13.5, 12.0, 4.9 Hz, 2 H, 2 x CH), 2.27 (ddd, *J* = 13.5, 12.2, 4.7 Hz, 2 H, 2 x CH), 3.85 (s, 3 H, OCH_3), 6.91 (dd, *J* = 8.3, 1.0 Hz, 1 H, ArH), 6.96 (app. td, *J* = 7.6, 1.5 Hz, 1 H, ArH), 7.25 - 7.33 (m, 1 H, ArH), 7.52 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH). **^{13}C NMR** (101 MHz, $CDCl_3$) 14.0, 19.0, 39.7, 48.4, 55.3, 111.8, 120.7, 123.7, 125.6, 129.0, 129.5, 157.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 2958, 2931, 2872, 2231, 1583, 1492, 1463, 1435, 1242, 1097, 1024, 788. ***m/z* (EI)** 231.2 (34, M^+), 188.1 (100), 161.1 (85), 146.1 (63), 131.1 (9), 116.1 (16), 105.1 (9), 91.1 (22), 77.1 (9), 65.1 (3), 51.0 (3). **HRMS (CI)** calcd. for $C_{15}H_{22}NO$ ($[M+H]^+$): 232.1696, found: 232.1696.

Preparation of 2-(2-Methylphenyl)-2-propylpentanenitrile (418)



This substrate was prepared according to a modified literature procedure.[233] To a suspension of NaH (227 mg, 9.46 mmol, 3.1 equiv.) in dry DMF (11 mL) was added a solution 2-methylphenylacetonitrile **785** (0.39 mL, 3.00 mmol, 1.0 equiv.) and 1-iodopropane (1.32 mL, 13.5 mmol, 4.5 equiv.) in dry diethyl ether (5.5 mL) at room temperature. This mixture was stirred for 48 h at room temperature, and was then quenched with methanol and concentrated under reduced pressure. The crude residue was redissolved in diethyl ether, and then washed with water, sodium bisulfite solution and sodium carbonate solution. The organic layer was then dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (hexane:diethyl ether, 49:1) afforded 2-(2-methylphenyl)-2-propylpentanenitrile **418** as a colourless oil (600 mg, 86 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.93 (t, *J* = 7.4 Hz, 6 H, 2 x CH_3), 1.18 - 1.35 (m, 2 H, 2 x CH), 1.39 - 1.55 (m, 2 H, 2 x CH), 1.96 (ddd, *J* = 13.9, 12.2, 4.8 Hz, 2 H, 2 x CH), 2.09 (ddd, *J* = 13.8, 12.1, 4.8 Hz, 2 H, 2 x CH), 2.53 (s, 3 H, CH_3), 7.07 - 7.25 (m, 3 H, 3 x ArH), 7.35 - 7.49 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 18.7, 21.9, 41.0, 47.9, 123.9, 126.2, 127.6, 128.0, 133.0, 135.5, 135.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 2958, 2933, 2872, 2229, 1685, 1600, 1489, 1454, 1381, 1091, 758, 721. ***m/z* (EI)** 215.2 (M^+, 17), 186.1 (3), 172.1 (23), 144.1 (26), 130.1 (100), 115.1 (20), 103.1 (17), 91.1 (10), 77.1 (7), 65.1 (6), 51.1 (3). **HRMS (CI)** calcd. for $C_{15}H_{25}N_2^+$ ($[M+NH_4]^+$): 233.2012, found: 233.2013, and calcd. for $C_{15}H_{21}NNa$ ($[M+Na]^+$) 238.1566, found: 238.1566

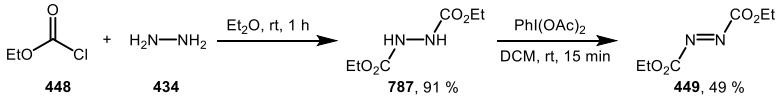
Preparation of 2-Benzyl-2-methyl-3-phenylpropanenitrile (419)



786 **419**, 94 %

This substrate was prepared according to a modified literature procedure. To a solution of LDA (0.78 M in heptane, 7.7 mL, 6.01 mmol, 2.0 equiv.) in diethyl ether (7.5 mL) was added propionitrile **786** (0.21 mL, 2.94 mmol, 1.0 equiv.) dropwise at – 78 °C. The resulting mixture was stirred for 30 min at this temperature, before benzyl bromide (0.71 mL, 5.97 mmol, 2.0 equiv.) was added. The reaction mixture was stirred for 1.5 h at -78 °C, and then overnight at room temperature. The reaction was found not to have gone to completion, so the flask was cooled to -78 °C and more LDA (0.78 M in heptane, 3.85 mL, 3.00 mmol, 1.0 equiv.) and benzyl bromide (0.35 mL, 2.94 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at room temperature for 3 h. The contents of the flask were poured over ice and acidified with 10 % H_2SO_4. The organic phase was separated, and the aqueous phase was further extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 2-benzyl-2-methyl-3-phenylpropanenitrile **419** as a white solid (664 mg, 94 %). **Mp** = 97-99 °C (lit. mp = 101-102 °C).[234] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.24 (s, 3 H, CH_3), 2.79 (d, *J* = 13.3 Hz, 2 H, 2 x CH), 2.99 (d, *J* = 13.6 Hz, 2 H, 2 x CH), 7.28 - 7.40 (m, 10 H, 10 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 23.4, 38.9, 45.5, 123.3, 127.3, 128.3, 130.3, 135.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3059, 3030, 2987, 2962, 2953, 2225, 1600, 1494, 1450, 1379, 1265, 1120, 1029, 916, 894, 850, 819, 754, 734, 695, 648. ***m/z* (EI)** 235.1, (M^+, 36), 115.1 (8), 91.1 (100), 77.0 (3), 65.1 (20), 51.1 (3). The data for this compound are consistent with those reported in the literature.[235,236]

Preparation of Diethyl diazene-1,2-dicarboxylate (449)



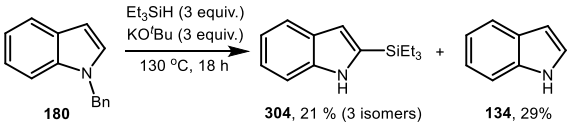
448 **434** **787**, 91 % **449**, 49 %

The first step was carried out according to a literature procedure.[237] Ethyl chloroformate **448** (0.19 mL, 1.99 mmol, 3.2 equiv.) was added dropwise to a suspension of hydrazine monohydrate **434** (0.03 mL, 0.62 mmol, 1.0 equiv.) and NaOH (80 mg, 2.00 mmol, 3.2 equiv.) in diethyl ether (1 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature. The mixture was then poured into ice-water, filtered and the solid was dried under reduced pressure. Recrystallisation of this solid from ethanol afforded diethyl hydrazine-1,2-dicarboxylate **787** as a white solid (160 mg, 91 %). **Mp** = 130-131 °C (lit. mp = 131-133 °C).[238] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.29 (t, *J* = 7.2 Hz, 6 H, 2 x CH_3), 4.23 (q, *J* = 7.0 Hz, 4 H, 2 x CH_2), 6.37 (br. s., 2 H, 2 x NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.4, 62.3, 156.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3238, 2804, 1751, 1467, 1452, 1355, 1328, 1369, 1195, 729, 696. The mass of **787** was not detected after GC-MS or LCMS due to the instability of this compound. The data for this compound are consistent with those reported in the literature.[239]

The second step was carried out according to a literature procedure.[240] Diethyl hydrazine-1,2-dicarboxylate **787** (160 mg, 0.91 mmol, 1.0 equiv.) and diacetoxyiodobenzene (293 mg, 0.91 mmol, 1.0 equiv.) were dissolved in DCM (2 mL) and stirred at room temperature for 15 min. The resulting mixture was washed with $NaHCO_3$ and water, and the organic layer was dried by passing through a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane) afforded diethyl diazene-1,2-dicarboxylate **449** as an orange oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.46 (t, *J* = 7.2 Hz, 6 H, 2 x CH_3), 4.52 (q, *J* = 7.1 Hz, 4 H, 2 x CH_2). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 65.5, 160.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 2985, 1776, 1369, 1230, 1097, 1018, 862, 808. The mass of **449** was not detected after GC-MS or LCMS due to the instability of this compound The data for this compound are consistent with those reported in the literature.[241–244]

8.4 - Treating Substrates with Et_3SiH/KO^tBu System from Chapter 3

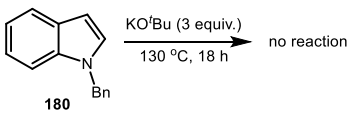
Treatment of 1-Benzyl-1*H*-indole (180) with Et_3SiH/KO^tBu



180 **304**, 21 % (3 isomers) **134**, 29%

This reaction was carried out according to General Procedure C from **180** (104 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded a complex fraction (24 mg) from which **304** was tentatively identified. GC-MS indicates the presence of three isomers (*m/z* = 231.1, retention times 14.207, 14.698, 14.813 min). The major isomer by ^{1}H NMR contains the triethylsilyl group in the 2-position of the indole, as drawn above, with ^{1}H NMR signals consistent with the literature.[245] This is evidenced by the presence of the C3 proton appearing as a singlet at 6.77 ppm in the major component. Also isolated was *1H*-indole, which was further purified by recrystallisation from hexane to afford **134** as a yellow solid (17 mg, 29 %). **Mp** = 50-51 °C (lit. mp = 52-54 °C).[246] **^{1}H-NMR** (400 MHz, $CDCl_3$) 6.47 - 6.65 (m, 1 H, ArH), 7.07 - 7.17 (m, 1 H, ArH), 7.17 - 7.25 (m, 2 H, 2 x ArH), 7.37 - 7.45 (m, 1 H, ArH), 7.62 - 7.71 (m, 1 H, ArH), 8.15 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 102.7, 111.0, 119.8, 120.7, 122.0, 124.1, 127.9, 135.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3393, 3047, 1576, 1455, 1335, 1247, 1059, 743, 721. ***m/z* (EI):** 117.0 (M^+, 100), 90.0 (42), 63.0 (24). The data for this compound are consistent with those reported in the literature.[247]

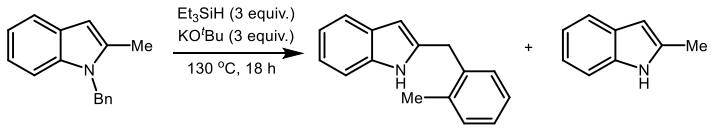
Treatment of 1-Benzyl-1*H*-indole (180) with KO^tBu Alone



180

This reaction was carried out according to General Procedure D from **180** (104 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **180** was recovered, with data consistent with those reported above (88 mg, 85 %).

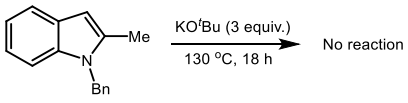
Treatment of 1-Benzyl-2-methyl-1*H*-indole (305) with Et_3SiH/KO^tBu



305 **309**, 15% **308**, 49 %

This reaction was carried out according to General Procedure C from **305** (111 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded 2-(2-methylbenzyl)-1*H*-indole **309** as a brown oil (16 mg, 15 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.31 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 6.22 - 6.33 (m, 1H, ArH), 7.03 - 7.17 (m, 2H, 2 x ArH), 7.18 - 7.24 (m, 4H, 4 x ArH), 7.24 - 7.27 (m, 1 H, ArH), 7.51 - 7.57 (m, 1 H, ArH), 7.73 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 19.4, 32.6, 100.9, 110.4, 119.7, 119.9, 121.2, 126.3, 127.1, 128.8, 129.5, 130.6, 136.0, 136.5, 136.9, 137.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3412, 3050, 2912, 1603, 1495, 1452, 1328, 1181, 1013, 747, 727. ***m/z* (EI):** 221.1 (M^+, 100), 204.1 (20), 130.1 (52), 117.1 (28), 104.1 (30), 89.0 (7), 77.0 (11), 63.0 (5). The data for this compound are consistent with those reported in the literature.[248] Also isolated was 2-methyl-1*H*-indole **308** as an orange solid (32 mg, 49 %). **Mp** = 53-54 °C (lit. mp = 56-57 °C).[249] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.46 (s, 3H, CH_3), 6.17 - 6.30 (m, 1H, ArH), 7.08 (app. td, *J* = 7.3, 1.1 Hz, 1H, ArH), 7.12 (app. td, *J* = 6.9, 1.4 Hz, 1 H, ArH), 7.29 (d, *J* = 7.8 Hz, 1 H, ArH), 7.53 (d, *J* = 7.6 Hz, 1 H, ArH), 7.84 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.7, 100.4, 110.2, 119.6 (two signals), 120.9, 129.1, 135.0, 136.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3379, 3050, 2936, 1549, 1452, 1344, 1285, 1037, 783, 749. ***m/z* (EI):** 131.1 (M^+, 75), 130.1 (100), 103.1 (11), 89.0 (4), 77.0 (12), 63.0 (6). The data for this compound are consistent with those reported in the literature.[249]

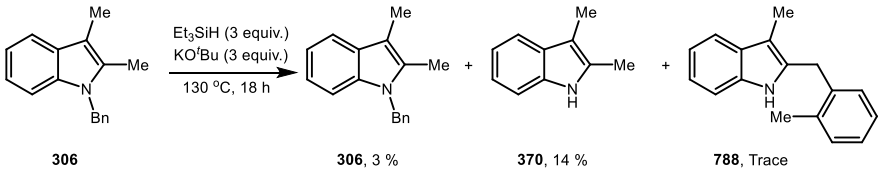
Treatment of 1-Benzyl-2-methyl-1*H*-indole (305) with KO^tBu Alone



305

This reaction was carried out according to General Procedure D from **305** ((111 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **305** was recovered, with data consistent with those reported above (110 mg, 99 %).

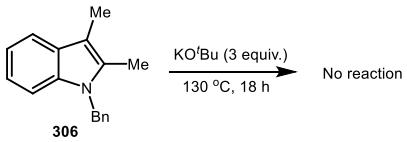
Treatment of 1-Benzyl-2,3-dimethyl-1*H*-indole (306) with Et_3SiH/KO^tBu



306 **306**, 3 % **370**, 14 % **788**, Trace

This reaction was carried out according to General Procedure C from **306** (118 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded recovered starting material **306**, with data consistent with those reported previously (4 mg, 3 %). Also isolated was 2,3-dimethyl-1*H*-indole **370** as a red solid (10 mg, 14 %). **Mp** = 98-101 °C (lit. mp = 104-106 °C).[250] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.24 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 7.08 (app. td, *J* = 7.2, 1.2 Hz, 1 H, ArH), 7.12 (app. td, *J* = 7.0, 1.4 Hz, 1 H, ArH), 7.25 - 7.27 (m, 1 H, ArH), 7.48 (d, *J* = 7.2 Hz, 1 H, ArH), 7.68 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 8.4, 11.5, 107.1, 110.0, 117.9, 119.0, 120.9, 129.5, 130.6, 135.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3404, 2954, 2912, 2870, 2360, 1610, 1462, 1240, 1143, 1105, 1008, 669. ***m/z* (EI):** 145.1 (M^+, 81), 144.1 (100), 130.1 (57), 115.1 (13), 102.1 (9), 89.1 (6), 77.1 (17), 63.0 (11), 51.0 (13). The data for this compound are consistent with those reported in the literature.[224] Also isolated was an impure fraction (3 mg) from which 3-methyl-2-(2-methylbenzyl)-1*H*-indole **788** was tentatively identified by ^{1}H NMR, with key chemical shifts 2.28 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 4.09 (s, 2 H, CH_2). The aromatic region was found to over-integrate due to impurities.

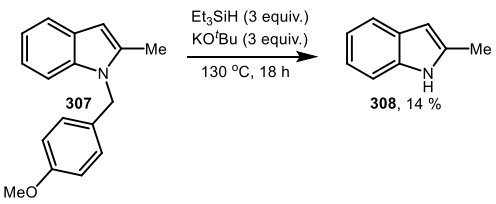
Treatment of 1-Benzyl-2,3-dimethyl-1*H*-indole (306) with KO^tBu Alone



306

This reaction was carried out according to General Procedure D from **306** (118 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **306** was recovered, with data consistent with those reported previously (107 mg, 91 %).

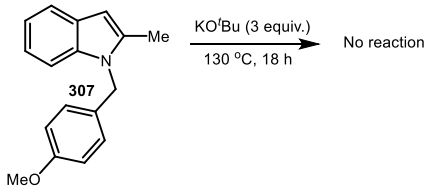
Treatment of 1-(4-Methoxybenzyl)-2-methyl-1*H*-indole (307) with Et_3SiH/KO^tBu



307 **308**, 14 %

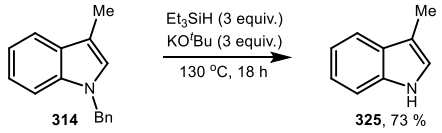
This reaction was carried out according to General Procedure C from **307** (126 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 4:1) afforded 2-methyl-1*H*-indole **308**, with data consistent with those reported above (9 mg, 14 %).

Treatment of 1-(4-Methoxybenzyl)-2-methyl-1*H*-indole (**307**) with KO^{t}Bu Alone



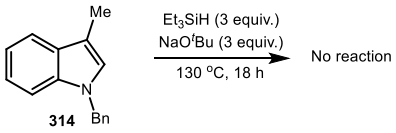
This reaction was carried out according to General Procedure D from **307** (126 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **307** was recovered, with data consistent with those reported previously (124 mg, 98 %).

Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with Et_3SiH/KO^{t}Bu



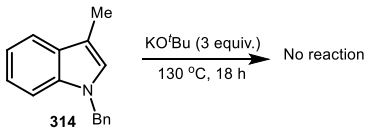
This reaction was carried out according to General Procedure C from **314** (104 mg, 0.50 mmol, 1.0 equiv.) Purification by column chromatography (hexane:diethyl ether, 9:1) afforded 3-methyl-1*H*-indole **325** as a yellow solid (48 mg, 73 %). **Mp** = 91-93 °C (lit. mp = 97 °C).[251] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.36 (d, *J* = 1.0 Hz, 3 H, CH_3), 6.98 (q, *J* = 1.0 Hz, 1 H, ArH), 7.14 (ddd, *J* = 7.8, 7.0, 1.0 Hz, 1 H, ArH), 7.20 (app. td, *J* = 7.0, 1.3 Hz, 1 H, ArH), 7.36 (app. dt, *J* = 8.0, 0.9 Hz, 1 H, ArH), 7.54 - 7.66 (m, 1 H, ArH), 7.87 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 110.9, 111.8, 118.8, 119.1, 121.5, 121.9, 128.3, 136.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3396, 3052, 2916, 1616, 1456, 1333, 1088, 1010, 738. ***m/z* (EI)** 131.1 (M^+, 55), 130.0 (100), 103.0 (8), 77.0 (19), 63.0 (6), 51.0 (9). The data for this compound are consistent with those reported in the literature.[252]

Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with Et_3SiH/NaO^{t}Bu



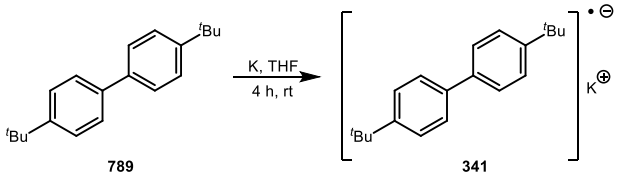
This reaction was carried out according to General Procedure C from **314** (104 mg, 0.50 mmol, 1.0 equiv.), using NaO^{t}Bu (144 mg, 1.50 mmol, 3.0 equiv.) instead of KO^{t}Bu. No reaction was found to occur, and **314** was recovered after column chromatography (hexane:diethyl ether, 19:1), with data consistent with those reported previously (92 mg, 88 %).

Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with KO^{t}Bu Alone



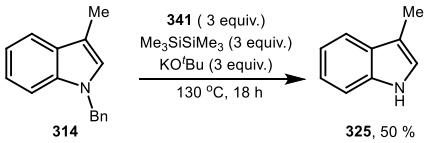
This reaction was carried out according to General Procedure D from **314** (104 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **314** was recovered, with data consistent with those reported previously (102 mg, 98 %).

Preparation of Potassium 4,4'-di-tert-butyl-1,1'-biphenyl (**341**)



This reaction was carried out according to a literature procedure.[253] Potassium metal was washed with hexane under argon atmosphere to remove mineral oil. The hexane was removed by needle and syringe and quenched with isopropanol, and the potassium metal was then transferred to the glovebox where the residual hexane was removed under vacuum. The oxide layer was removed from potassium in the glovebox by scraping with a knife, exposing a fresh metallic surface. Potassium metal (177 mg, 4.53 mmol, 1.01 equiv.) was then added to a solution of 4,4'-di-*tert*-butylbiphenyl **789** (1.20 g, 4.50 mmol, 1.00 equiv.) in THF (180 mL). The resulting solution was stirred under nitrogen until an intense green colour formed (~4 h). THF was then evaporated under vacuum in the glovebox, affording a green/white solid which was used immediately without further purification.

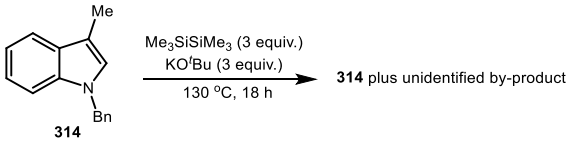
Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with **341**, $Me_3SiSiMe_3$ and KO^{t}Bu



Radical anion **341** (458 mg, 1.50 mmol, 3.0 equiv.), 1-benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.), KO^{t}Bu (168 mg, 1.50 mmol, 3.0 equiv.) and hexamethyldisilane (0.31 mL, 1.51 mmol, 3.0 equiv.) were added to a pressure tube in a glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded 4,4'-di-*tert*-butylbiphenyl **789**, with data matching the commercial material, followed by 1-benzyl-3-methyl-1*H*-indole **314**, with data consistent with those reported above (54 mg,

49 %), followed by 3-methyl-1*H*-indole **325**, with data consistent with those reported above (33 mg, 50 %).

Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with $Me_3SiSiMe_3$ and KO^{t}Bu



1-Benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.), KO^{t}Bu (168 mg, 1.50 mmol, 3.0 equiv.) and hexamethyldisilane (0.31 mL, 1.51 mmol, 3.0 equiv.) were added to a pressure tube in a glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded an inseparable mixture of starting material **314**, and a second unidentified component which could not be detected by GC-MS. The ^{1}H NMR spectrum is shown below. The major peaks correspond to **314**, with the smaller peaks corresponding to the unidentified component.

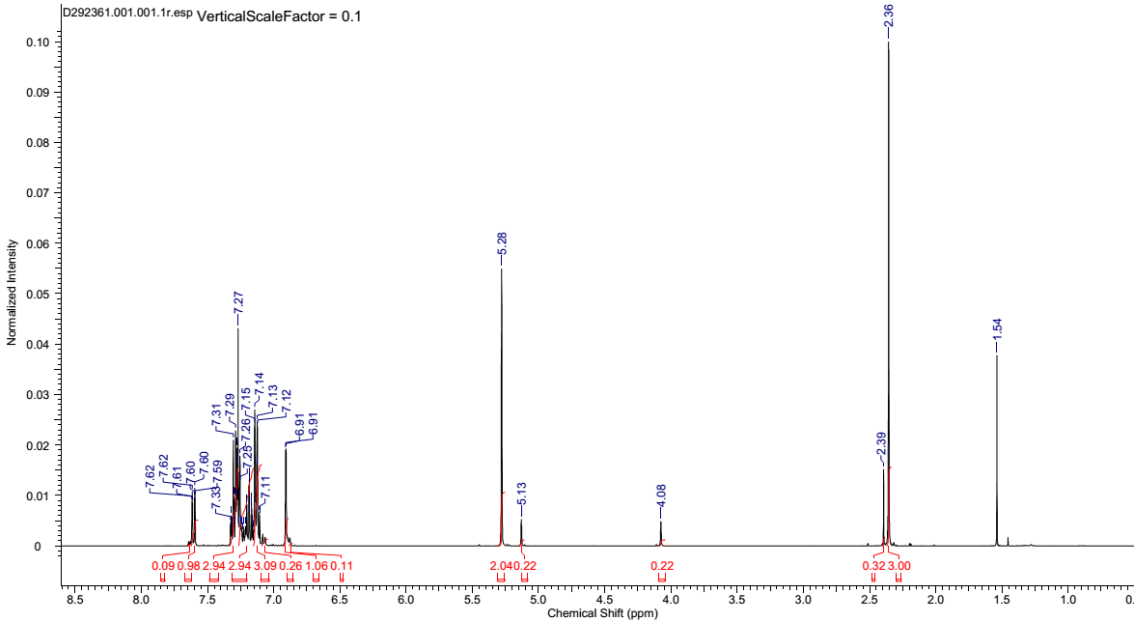
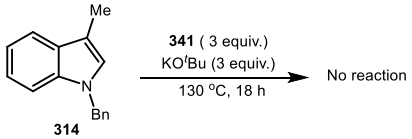


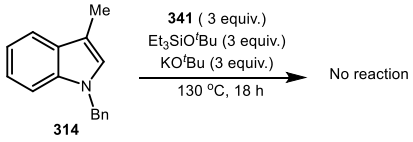
*Figure 7 - ^{1}H NMR of 1-Benzyl-3-methyl-1H-indole **314** and Unknown Component*

Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with **341** and KO^{t}Bu



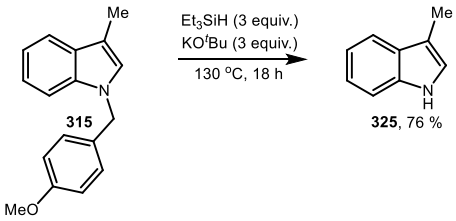
Radical anion **341** (458 mg, 1.50 mmol, 3.0 equiv.), 1-benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.), and KO^{t}Bu (168 mg, 1.50 mmol, 3.0 equiv.) were added to a pressure tube in a glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. No reaction was found to have occurred by ^{1}H NMR or TLC analysis of the crude reaction mixture, with only 4,4'-di-*tert*-butylbiphenyl **789** and starting material **314** detected.

Treatment of 1-Benzyl-3-methyl-1*H*-indole (314) with 341, Et_3SiO^tBu and KO^tBu



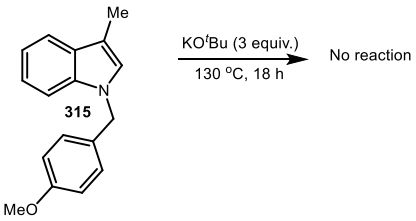
Radical anion **341** (458 mg, 1.50 mmol, 3.0 equiv.), 1-benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.), *tert*-butoxyltriethylsilane (0.35 mL, 1.50 mmol, 3.0 equiv.) and KO^{t}Bu (168 mg, 1.50 mmol, 3.0 equiv.) were added to a pressure tube in a glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. No reaction was found to have occurred by ^{1}H NMR or TLC analysis of the crude reaction mixture, with only 4,4'-di-*tert*-butylbiphenyl **789** and starting material **314** detected.

Treatment of 1-(4-Methoxybenzyl)-3-methyl-1*H*-indole (315) with Et_3SiH/KO^tBu



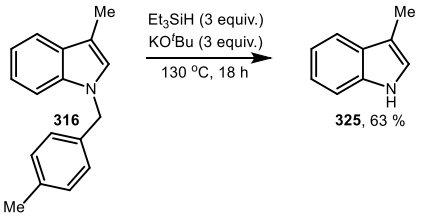
This reaction was carried out according to General Procedure C from **315** (126 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded 3-methyl-1*H*-indole **325** as a white solid, with data consistent with those reported above (50 mg, 76 %).

Treatment of 1-(4-Methoxybenzyl)-3-methyl-1*H*-indole (**315**) with KO^{t}Bu Alone



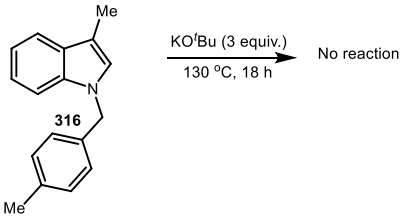
This reaction was carried out according to General Procedure D from **315** (126 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **315** was recovered, with data consistent with those reported previously (124 mg, 98 %).

Treatment of 1-(4-Methylbenzyl)-3-methyl-1*H*-indole (**316**) with Et$_3$SiH/KO^{t}Bu



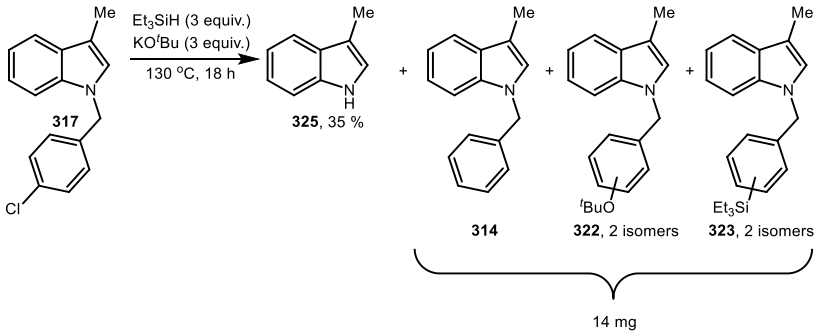
This reaction was carried out according to General Procedure C from **316** (118 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded 3-methyl-1*H*-indole **325**, with data consistent with those reported above (41 mg, 63 %).

Treatment of 1-(4-Methylbenzyl)-3-methyl-1*H*-indole (**316**) with KO^{t}Bu Alone



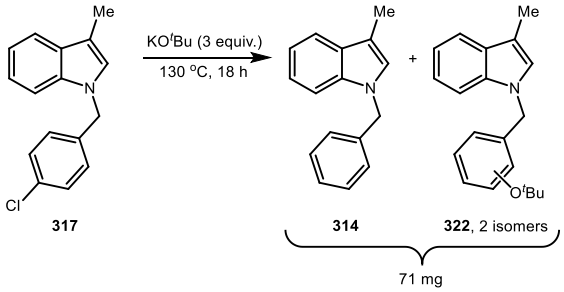
This reaction was carried out according to General Procedure D from **316** (118 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **316** was recovered, with data consistent with those reported previously (101 mg, 86 %).

Treatment of 1-(4-Chlorobenzyl)-3-methyl-1*H*-indole (**317**) with Et_3SiH/KO^tBu



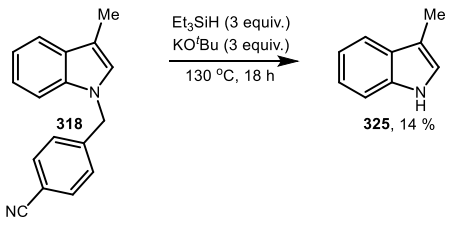
This reaction was carried out according to General Procedure C from **317** (128 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded 3-methyl-1*H*-indole **325**, with data consistent with those reported above (23 mg, 35 %). Also tentatively identified by GC-MS was **314** (*m/z* = 221.1, retention time = 14.659 min), two isomers of **322** (*m/z* = 293.2, retention time = 16.033 and 16.132 min) and two isomers of **323** (*m/z* = 335.2, retention times = 16.940 and 17.476 min).

Treatment of 1-(4-Chlorobenzyl)-3-methyl-1*H*-indole (**317**) with KO^tBu Alone



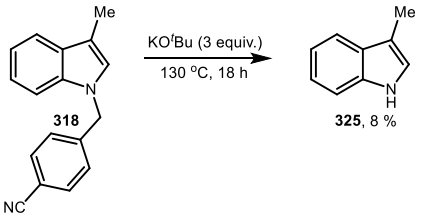
This reaction was carried out according to General Procedure D from **317** (128 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was produced, from which an inseparable mixture of **314**, and **322** was isolated (combined yield = 71 mg). Determination of the yields by addition of an internal ^1H NMR sample was not possible due to overlapping signals, but the major components are the isomers of **322**. These isomers were tentatively identified by GC-MS (*m/z* = 293.2, retention time = 16.110 min and 16.568 min). Compound **314** was also detected by GC-MS (*m/z* = 221.1, retention time = 14.676 min).

Treatment of 4-((3-Methyl-1H-indol-1-yl)methyl)benzonitrile (**318**) with Et_3SiH/KO^tBu



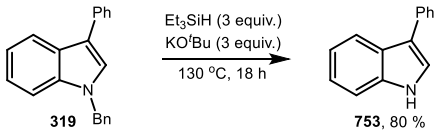
This reaction was carried out according to General Procedure C from **318** (123 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 4:1 → 1:1) afforded 3-methyl-1*H*-indole **325**, with data consistent with those reported above (9 mg, 14 %). Also detected by ^{1}H NMR and GC-MS was a small amount of starting material **318**, with data consistent with those reported above. This could not be purified or quantified.

Treatment of 4-((3-Methyl-1H-indol-1-yl)methyl)benzonitrile (318) with KO^{t}Bu Alone



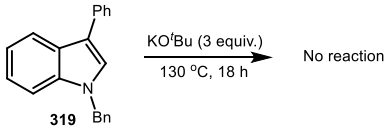
This reaction was carried out according to General Procedure D from **318** (123 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 4:1 → 1:1) afforded 3-methyl-1*H*-indole **325**, with data consistent with those reported above (5 mg, 8 %). Also isolated was starting material **318**, with data consistent with those reported above (11 mg, 9 %).

Treatment of 1-Benzyl-3-phenyl-1*H*-indole (319) with Et$_3$SiH/KO^{t}Bu



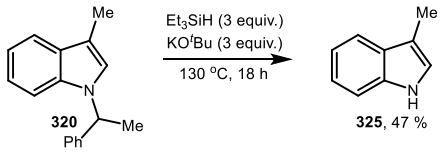
This reaction was carried out according to General Procedure C from **319** (142 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1 → 3:1) afforded 3-phenyl-1*H*-indole **753**, with data consistent with those reported above (77 mg, 80 %).

Treatment of 1-Benzyl-3-phenyl-1*H*-indole (319) with KO^{t}Bu Alone



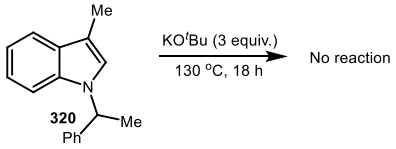
This reaction was carried out according to General Procedure D from **319** (142 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **319** was recovered, with data consistent with those reported previously (142 mg, 100 %).

Treatment of 1-(1-Phenylethyl)-3-methyl-1*H*-indole (**320**) with Et_3SiH/KO^tBu



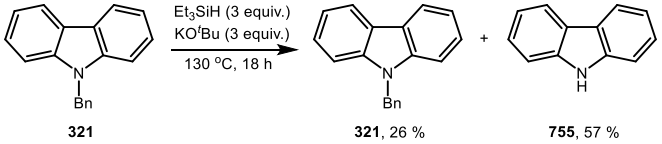
This reaction was carried out according to General Procedure C from **320** (118 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded 3-methyl-1*H*-indole **325**, with data consistent with those reported above (31 mg, 47 %).

Treatment of 1-(1-Phenylethyl)-3-methyl-1*H*-indole (**320**) with KO^tBu Alone



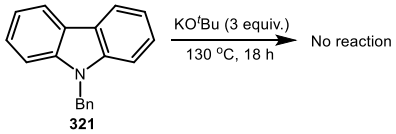
This reaction was carried out according to General Procedure D from **320** (118 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **320** was recovered, with data consistent with those reported above (110 mg, 93 %).

Treatment of 9-Benzyl-9*H*-carbazole (**321**) with Et_3SiH/KO^tBu



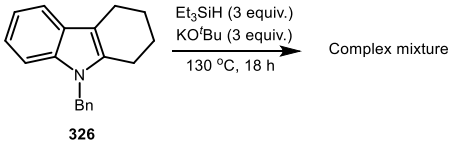
This reaction was carried out according to General Procedure C from **321** (129 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded starting material **321** as a white solid, with data consistent with those reported above (34 mg, 26 %), and 9*H*-carbazole **755** as a white solid (48 mg, 57 %). **Mp** = 238-240 °C (lit. 237-238 °C).[254] **^{1}H-NMR** (400 MHz, $CDCl_3$) 7.22 - 7.27 (m, 2H, 2 x ArH), 7.38 - 7.50 (m, 4H, 4 x ArH), 8.06 (br. s., 1H, NH), 8.07 - 8.13 (m, 2H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 110.6, 119.4, 120.3, 123.4, 125.8, 139.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3412, 3050, 1599, 1450, 1326, 930, 747, 723. ***m/z* (EI)** 167.1 (M^+, 100), 139.0 (15), 113.0 (4), 83.5 (8). The data for this compound are consistent with those reported in the literature.[255]

Treatment of 9-Benzyl-9*H*-Carbazole (**321**) with KO^tBu Alone



This reaction was carried out according to General Procedure D from **321** (129 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **321** was recovered, with data consistent with those reported previously (124 mg, 96 %).

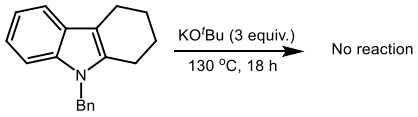
Treatment of 9-Benzyl-1,2,3,4-tetrahydrocarbazole (326) with Et_3SiH/KO^tBu



326

This reaction was carried out according to General Procedure C from **326** (131 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was formed, from which nothing could be isolated. A trace amount (<1 mg) of 1,2,3,4-tetrahydrocarbazole was tentatively identified by ^{1}H NMR (400 MHz, $CDCl_3$) 1.79 - 2.02 (m, 4 H, 2 x CH_2), 2.59 - 2.85 (m, 4 H, 2 x CH_2), 7.04 - 7.15 (m, 2 H, 2 x ArH), 7.27 - 7.31 (m, 1 H, ArH), 7.42 - 7.49 (m, 2 H, 2 x ArH), 7.68 (br. s., 1 H, NH), and by GC-MS (*m/z* = 171.1, retention time = 13.727 min). The data for this compound are consistent with those reported in the literature.[256]

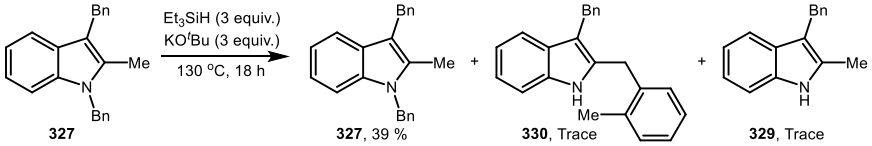
Treatment of 9-Benzyl-1,2,3,4-tetrahydrocarbazole (326) with KO^tBu Alone



326

This reaction was carried out according to General Procedure D from **326** (131 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **326** was recovered, with data consistent with those reported previously (126 mg, 96 %).

Treatment of 1,3-Dibenzyl-2-methyl-1*H*-indole (327) with Et_3SiH/KO^tBu

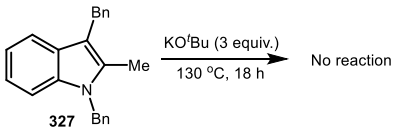


327 **327**, 39 % **330**, Trace **329**, Trace

This reaction was carried out according to General Procedure C from **327** (93 mg, 0.30 mmol, 1.0 equiv.), with Et_3SiH (0.14 mL, 0.88 mmol, 2.9 equiv.) and KO^tBu (101 mg, 0.90 mmol, 3.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded starting material **327** with data consistent with those reported above (36 mg, 39 %). Also tentatively identified was 3-benzyl-2-(2-methylbenzyl)-1*H*-indole **330** (<1 mg) by ^{1}H NMR (400 MHz, $CDCl_3$) 2.20 (s, 3 H, CH_3), 4.08 (s, 2 H, CH_2), 4.18 (s, 2 H, CH_2), 7.50 - 7.56 (br. s, 1 H, NH) – the aromatic signals were found to over-integrate due to impurities in the sample. Also tentatively identified

was 3-benzyl-2-methyl-1*H*-indole **329** (<1 mg) by ^{1}H NMR. The key signals are ^{1}H NMR (400 MHz, $CDCl_3$) 2.43 (s, 3 H, CH_3), 4.12 (s, 2 H, CH_2), 7.79 (br. s., 1 H, NH). The ^{1}H NMR spectrum is consistent with that reported in the literature.[257]

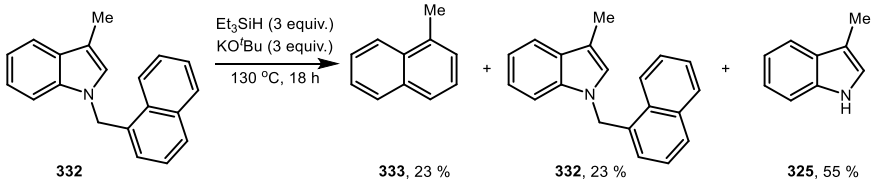
Treatment of 1,3-Dibenzyl-2-methyl-1*H*-indole (327) with KO^{t}Bu Alone



327

This reaction was carried out according to General Procedure D from **327** (93 mg, 0.30 mmol, 1.0 equiv.), with KO^{t}Bu (101 mg, 0.90 mmol, 3.0 equiv.). No reaction was found to occur, and **327** was recovered, with data consistent with those reported previously (80 mg, 86 %).

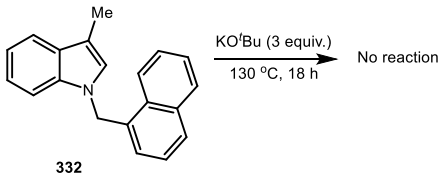
Treatment of 1-(Naphthalen-1-ylmethyl)-3-methyl-1*H*-indole (332) with Et_3SiH/KO^{t}Bu



332 **333**, 23 % **332**, 23 % **325**, 55 %

This reaction was carried out according to General Procedure C from **332** (136 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded **333** as an inseparable mixture with *tert*-butoxytriethylsilane (35 mg), starting material **332** as a colourless oil, with data consistent with those reported above (31 mg, 23 %), and 3-methyl-1*H*-indole **325** as a yellow solid, with data consistent with those reported above (36 mg, 55 %). The inseparable mixture from fraction 1 was dissolved in THF (2 mL) and stirred with concentrated hydrochloric acid (2 mL) for 48 h at room temperature. After this time, the crude reaction was diluted with water and extracted into dichloromethane. The combined organic phases were dried over Na_2SO_4 and carefully concentrated under reduced pressure. Purification by column chromatography (hexane) afforded 1-methylnaphthalene **333** as a colourless oil (16 mg, 23 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.73 (s, 3 H, CH_3), 7.35 (d, *J* = 7.0 Hz, 1 H, ArH), 7.40 (app. t, *J* = 7.0 Hz, 1 H, ArH), 7.51 (app. td, *J* = 6.8, 1.3 Hz, 1 H, ArH), 7.55 (app. td, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.74 (d, *J* = 8.3 Hz, 1 H, ArH), 7.83 - 7.92 (m, 1 H, ArH), 8.03 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 19.5, 124.2, 125.7, 125.7, 125.8, 126.5, 126.7, 128.7, 132.7, 133.7, 134.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3037, 1597, 1508, 1462, 1438, 1396, 1267, 1213, 1165, 107, 1020, 854, 786, 767. ***m/z* (EI)** 142 (M^+, 100), 141 (75), 139 (10), 115 (40) 63 (5).

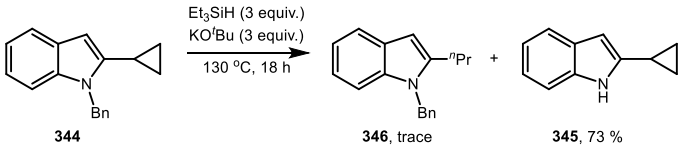
Treatment of 1-(Naphthalen-1-ylmethyl)-3-methyl-1*H*-indole (**332**) with KO^{t}Bu Alone



332

This reaction was carried out according to General Procedure D from **332** (136 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **332** was recovered, with data consistent with those reported previously (119 mg, 88 %).

Treatment of 1-Benzyl-2-cyclopropyl-1*H*-indole (**344**) with Et_3SiH/KO^{t}Bu



344 **346**, trace **345**, 73 %

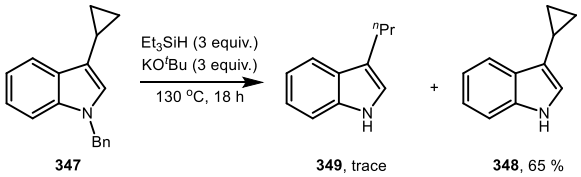
This reaction was carried out according to General Procedure C from **344** (124 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded an impure fraction (3 mg), in which a minor component was tentatively identified as 1-benzyl-2-propyl-1*H*-indole **346** by GC-MS (*m/z* = 249.1, retention time = 15.458 min). Key signals in the ^{1}H-NMR are (400 MHz, $CDCl_3$) 1.03 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.76 (sxt, *J* = 7.6 Hz, 1 H, CH_2), 2.75 (t, *J* = 7.5 Hz, 2 H, CH_2), 6.25 (m, 1 H, ArH). The aromatic signals were found to over-integrate due to impurities in the sample. However, no benzylic CH_2 was observed in the ^{1}H NMR, so it is not clear if the true structure of this compound is **346** or an isomer of **346**. This could be followed up in future work in this project. Also isolated was 2-cyclopropyl-1*H*-indole **345**, with data consistent with those reported above (57 mg, 73 %).

Treatment of 1-Benzyl-2-cyclopropyl-1*H*-indole (**344**) with KO^{t}Bu Alone

344

This reaction was carried out according to General Procedure D from **344** (48 mg, 0.19 mmol, 1.0 equiv.) and KO^{t}Bu (65 mg, 0.58 mmol, 3.1 equiv.). No reaction was found to occur, and starting material **344** was recovered, with data consistent with those reported previously (41 mg, 85 %).

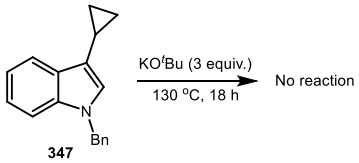
Treatment of 1-Benzyl-3-cyclopropyl-1*H*-indole (**347**) with Et_3SiH/KO^tBu



347 **349**, trace **348**, 65 %

This reaction was carried out according to General Procedure C from **347** (124 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded an impure fraction (1 mg), in which a major component was tentatively identified as 3-propyl-1*H*-indole **349**. The ^{1}H signals for this compound are consistent with the literature data.[258] The major signals in the ^{1}H-NMR are (400 MHz, $CDCl_3$) 0.97 - 1.05 (m, 3 H, CH_3), 1.75 (sxt, *J* = 7.4 Hz, 2 H, CH_2), 2.75 (td, *J* = 7.3, 0.7 Hz, 2 H, CH_2), 6.96 - 7.02 (m, 1 H, ArH), 7.08 - 7.16 (m, 1 H, ArH), 7.16 - 7.23 (m, 1 H, ArH), 7.33 - 7.40 (m, 1 H, ArH), 7.62 (d, *J* = 7.8 Hz, 1 H, ArH), 7.90 (br. s., 1 H, NH). This compound was also detected by GC-MS (*m/z* = 159.0, retention time = 12.158 min). Also isolated was 3-cyclopropyl-1*H*-indole **348**, with data consistent with those reported previously (51 mg, 65 %).

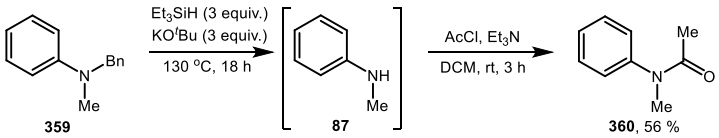
Treatment of 1-Benzyl-3-cyclopropyl-1*H*-indole (**347**) with KO^tBu Alone



347

This reaction was carried out according to General Experimental Procedure D from **347** (124 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and starting material **347** was recovered, with data consistent to those reported previously (121 mg, 98 %).

Treatment of *N*-Benzyl-*N*-methylaniline (**359**) with Et_3SiH/KO^tBu

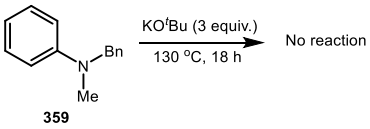


359 **87** **360**, 56 %

N-benzyl-*N*-methylaniline **359** (99 mg, 0.50 mmol, 1.0 equiv.), Et_3SiH (0.24 mL, 1.50 mmol, 3.0 equiv.) and KO^tBu (168 mg, 1.50 mmol, 3.0 equiv.) were sealed in a pressure tube in a glovebox under nitrogen. The tube was removed and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the reaction was quenched with 1 mL of water and 1,3,5-trimethoxybenzene (10 mol %, 8.4 mg) in $CDCl_3$ (3 mL) was added as an internal NMR standard. *N*-methylaniline **87** was detected by ^{1}H NMR and by GC-MS [*m/z* = 107.2 (M^+, 76) 106.2 (100), retention time = 8.018 min], with data consistent with those reported in the literature.[259] **^{1}H NMR** (400 MHz, $CHCl_3$) 2.85 (d, *J* = 5.5 Hz, 3 H, CH_3), 3.71 (br. s., 1 H, NH), 6.64 (dd, *J* = 8.7,

0.9 Hz, 2 H, 2 x ArH), 6.73 (app. tt, *J* = 7.3, 1.0 Hz, 1 H, ArH). The remaining signal at 7.20 was found to overlap with impurities in the crude sample. The ^{1}H NMR of the crude mixture indicated that the yield of *N*-methylaniline **87** was 65 %, as determined by comparison of the integration of the methoxy peaks of the internal standard (3.79 ppm, set to 9 integral units), to the methyl group of **368** (2.85 ppm, 19.63 integral units). To aid isolation, acetylation was carried out according to a literature procedure.[260] The crude mixture was dissolved in DCM and triethylamine (0.08 mL, 0.55 mmol) was added. This solution was cooled to 0 °C and acetyl chloride (0.04 mL, 0.56 mmol) was added dropwise. After 10 min, the solution was warmed to room temperature and stirred at this temperature for 3 h before quenching with 1 M HCl and extracting into DCM. The resulting organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Recrystallisation from hexane afforded *N*-methyl-*N*-phenylacetamide **360** as off-white crystals (42 mg, 56 %). **Mp** = 86-88 °C (lit. mp = 94- 95 °C).[261] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.88 (s, 3 H) 3.28 (s, 3 H) 7.20 (d, *J* = 7.0 Hz, 2 H) 7.34 (app. t, *J* = 7.3 Hz, 1 H) 7.43 (app. t, *J* = 7.3 Hz, 2 H). **^{13}C-NMR** (101 MHz, $CDCl_3$) 22.4, 37.1, 127.1, 127.7, 129.7, 144.6, 170.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3043, 1647, 1595, 1492, 1417, 1382, 1296, 1139, 1083, 1028, 970, 773, 623. ***m/z* (EI)** 149.1 (M^+, 30), 106.1 (100), 77.0 (30), 65.0 (9), 51.0 (20). The data for this compound are consistent with those reported in the literature.[262]

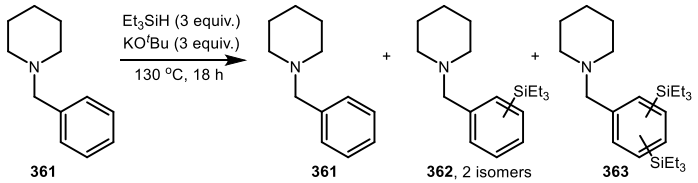
Treatment of *N*-Benzyl-*N*-methylaniline (359) with KO^{t}Bu Alone



359

This reaction was carried out according to General Procedure D from **359** (99 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **359** was recovered, with data consistent with those reported previously (96 mg, 97 %).

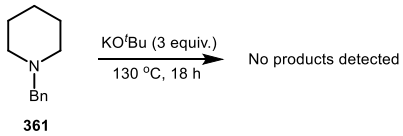
Treatment of *N*-Benzylpiperidine (361) with Et_3SiH/KO^{t}Bu



361 **361** **362**, 2 isomers **363**

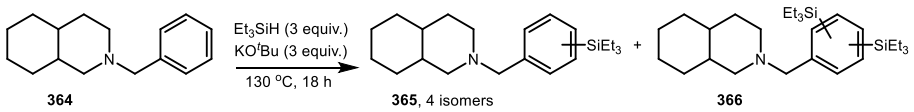
This reaction was carried out according to General Procedure C from **361** (88 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products resulted from which starting material **361** could be detected by GC-MS. Also tentatively identified by GC-MS were silylated compounds **362** (*m/z* = 289.2, retention times = 13.79 and 14.15 min) and **363** (*m/z* = 403.6, retention time = 15.53 min).

Treatment of *N*-Benzylpiperidine (**361**) with KO^{t}Bu Alone



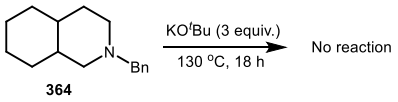
This reaction was carried out according to General Procedure D from **361** (88 mg, 0.50 mmol, 1.0 equiv.). No products could be detected by crude ^{1}H NMR.

Treatment of 2-Benzyldecahydroisoquinoline (**364**) with Et$_3$SiH/KO^{t}Bu



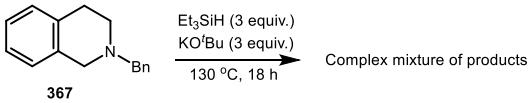
This reaction was carried out according to General Procedure C from **364** (115 mg, 0.50 mmol, 1.0 equiv.). The crude reaction mixture was treated under modified literature acetylation conditions to try to aid isolation of the products.[260] The crude mixture was dissolved in DCM and triethylamine (0.08 mL, 0.55 mmol) was added. This solution was cooled to 0 °C and acetyl chloride (0.04 mL, 0.56 mmol) was added dropwise. After 10 min, the solution was warmed to room temperature and stirred at this temperature for 3 h before quenching with 1 M HCl and extracting into DCM. The resulting organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. A complex mixture of products was produced, from which starting material **364** could be detected by GC-MS. Also tentatively identified were four isomers of monosilylated **365** (*m/z* = 343.3, retention times = 16.631, 16.777, 16.866 and 17.174 min) and an isomer of disilylated compound **366** (*m/z* = 457.4, retention time = 18.186 min).

Treatment of 2-Benzyldecahydroisoquinoline (**364**) with KO^{t}Bu Alone



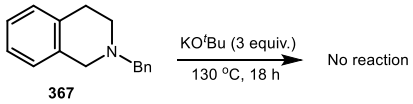
This reaction was carried out according to General Procedure D from **364** (115 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **364** was recovered, with data consistent with those reported previously (55 mg, 48 %). It is not clear what happened to the rest of the starting material, as no other products were detected.

Treatment of 2-Benzyl-1,2,3,4-tetrahydroisoquinoline (**367**) with Et$_3$SiH/KO^{t}Bu



This reaction was carried out according to General Procedure C from **367** (112 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products resulted from which nothing could be isolated or identified.

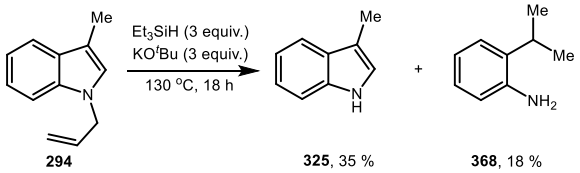
Treatment of 2-Benzyl-1,2,3,4-tetrahydroisoquinoline (367) with KO^{t}Bu Alone



367

This reaction was carried out according to General Procedure D from **367** (112 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **367** was recovered, with data consistent with those reported previously (97 mg, 87 %).

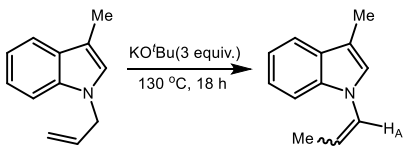
Treatment of 1-Allyl-3-methyl-1*H*-indole (294) with Et_3SiH/KO^{t}Bu



294 **325**, 35 % **368**, 18 %

This reaction was carried out according to General Procedure C from **294** (86 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded 3-methyl-1*H*-indole **325** as a yellow solid, with data consistent with those reported above (23 mg, 35 %), and 2-isopropylaniline **368** as a yellow oil (12 mg, 18 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.28 (d, *J* = 7.0 Hz, 6H, 2 x CH_3), 2.85 - 2.99 (spt, *J* = 6.8 Hz, 1H, CH), 3.66 (br. s., 2H, NH_2), 6.69 (dd, *J* = 7.8, 1.3 Hz, 1H, ArH), 6.80 (app. td, *J* = 8.0, 1.3 Hz, 1H, ArH), 6.98 - 7.07 (m, 1H, ArH), 7.16 (dd, *J* = 7.5, 1.5 Hz, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 22.3, 27.6, 115.8, 119.0, 125.4, 126.5, 132.7, 143.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3456, 3369, 2956, 2927, 2870, 1618, 1494, 1454, 1381, 1361, 1292, 1261, 1155, 1033, 929, 721. ***m/z* (EI)** 135.1 (M^+, 26), 120.1 (100), 103.1 (11), 93.1 (18), 77.1 (20), 65.0 (19), 51.0 (10). The data for this compound are consistent with those reported in the literature.[263]

Treatment of 1-Allyl-3-methyl-1*H*-indole (294) with KO^{t}Bu Alone



294 **385**, 71 % 2.4:1 *E*:*Z*

This reaction was carried out according to General Procedure D from **294** (86 mg, 0.50 mmol, 1.0 equiv.). An inseparable mixture of isomers of **385** was isolated (61 mg, 71 %, 2.4:1 *E*:*Z* ratio).

^{1}H-NMR (400 MHz, $CDCl_3$) 1.85 (dd, *J* = 7.5, 1.5 Hz, 3 H, CH_3 minor), 1.88 (dd, *J* = 6.8, 1.8 Hz, 3 H, CH_3 major), 2.34 (d, *J* = 1.3 Hz, 3 H, CH_3 major), 2.36 (d, *J* = 1.0 Hz, 3 H, CH_3 minor), 5.44 (dq, *J* = 8.5, 7.0 Hz, 1 H, CH minor), 5.55 - 5.80 (m, 1 H, CH major), 6.79 (dq, *J* = 8.7, 1.7 Hz, 1 H, CH minor), 6.96 (dq, *J* = 14.1, 1.6 Hz, 1 H, CH major), 7.05 - 7.09 (m, 1 H, ArH minor), 7.11 - 7.19 (m, 1 x ArH minor + 2 x ArH major), 7.21 - 7.27 (m, 1 x ArH minor + 1 x ArH major), 7.28 - 7.31 (m, 1 H, ArH minor), 7.41 (d, *J* = 8.3 Hz, 1 H, ArH major), 7.52 - 7.57 (m, 1 H, ArH major), 7.57 - 7.61 (m, 1 H, ArH minor). The ratio of isomers was determined by the relative ratio of the H_A signal for the *Z*-isomer [6.79 ppm (dq, *J* = 8.7, 1.7 Hz, 1 integral unit)] relative to the signal for H_A in the *E*-isomer [6.96 ppm (dq, *J* = 14.1, 1.6 Hz, 2.4 integral units)]. The relevant part of the ^{1}H NMR spectrum is shown below.

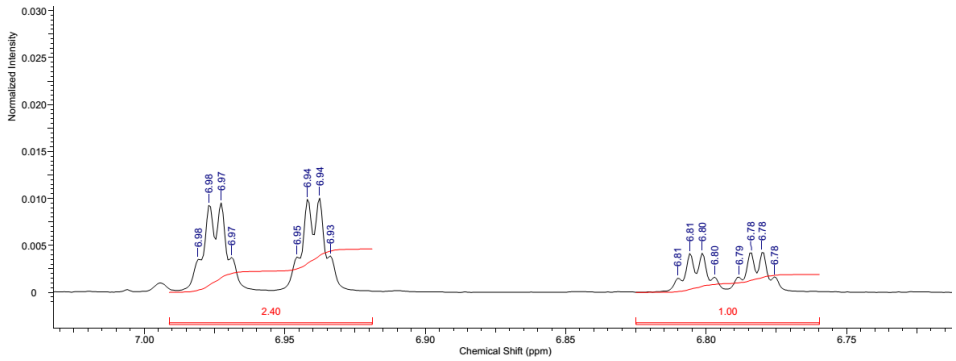
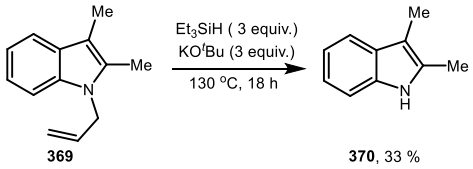


Figure 8 - ^{1}H NMR Spectrum of Isomerisation Products from 1-Allyl-3-methyl-1H-indole ***294***

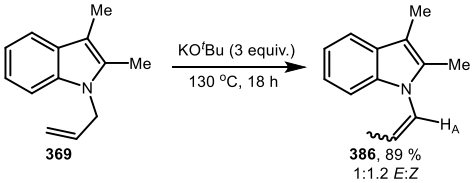
Treatment of 1-Allyl-2,3-dimethyl-1*H*-indole (369) with Et_3SiH/KO^tBu



369 **370**, 33 %

This reaction was carried out according to General Procedure C from **369** (93 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded 2,3-dimethyl-1*H*-indole **370**, with data consistent with those reported above (24 mg, 33 %).

Treatment of 1-Allyl-2,3-dimethyl-1*H*-indole (369) with KO^tBu Alone



369 **386**, 89 %
1:1.2 *E*:*Z*

This reaction was carried out according to General Procedure D from **369** (93 mg, 0.50 mmol, 1.0 equiv.). An inseparable mixture of isomers of **386** was isolated (83 mg, 89 %, 1:1.2 *E*:*Z* ratio). **^{1}H-NMR** (500 MHz, $CDCl_3$) 1.60 (dd, *J* = 6.9, 1.7 Hz, 3 H, CH_3 major), 1.96 (dd, *J* = 6.7, 1.7 Hz,

3 H, CH_3 minor), 2.23 - 2.41 (m, 2 x CH_3 major and 2 x CH_3 minor), 5.84 - 5.98 (m, CH minor and CH major), 6.54 - 6.62 (dq, *J* = 7.9, 1.7 Hz, 1 H, CH major), 6.73 (dq, *J* = 14.0, 1.6 Hz, 1 H, CH minor), 7.07 - 7.53 (overlapping signals, 4 x ArH minor and 4 x ArH major). The ratio of isomers was determined by the relative ratio of the H_A signal for the *Z*-isomer [6.59 ppm (dq, *J* = 7.9, 1.7 Hz, 1.2 integral units)] relative to the signal for H_A in the *E*-isomer [6.73 (dq, *J* = 14.0, 1.6 Hz, 1 integral unit)]. The relevant part of the ^{1}H NMR spectrum is shown below. Three isomers were also detected by GC-MS (*m/z* = 185.2, retention times = 12.249, 12.452 and 12.868 min).

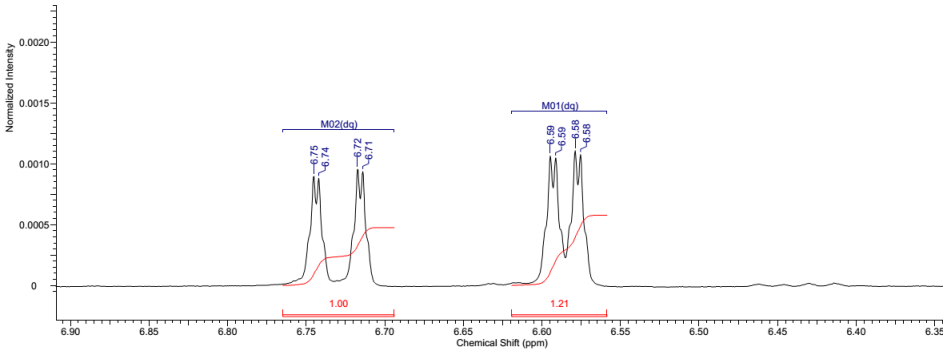
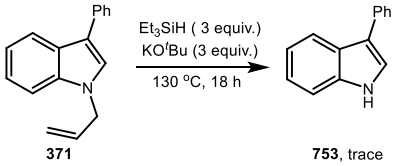


Figure 9 - 1H NMR Spectrum of Isomerisation Products from 1-Allyl-2,3-dimethyl-1H-indole ***369***

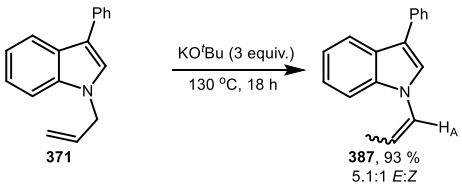
Treatment of 1-Allyl-3-phenyl-1*H*-indole (371) with Et_3SiH/KO^tBu



371 **753**, trace

This reaction was carried out according to General Procedure C from **371** (117 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 3:1) afforded a complex mixture of products. 3-Phenyl-1*H*-indole **753** was detected by ^{1}H NMR (<1 mg), which was consistent with that reported above.

Treatment of 1-Allyl-3-phenyl-1*H*-indole (371) with KO^tBu Alone



371 **387**, 93 %
5.1:1 *E*:*Z*

This reaction was carried out according to General Procedure D from **371** (117 mg, 0.50 mmol, 1.0 equiv.). An inseparable mixture of isomers **387** was isolated (109 mg, 93 %, 5.1:1 *E*:*Z* ratio). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.90 (dd, *J* = 7.0, 1.8 Hz, 3 H, CH_3 minor), 1.93 (dd, *J* = 6.8, 1.8 Hz, 3 H, CH_3 major), 5.61 (dq, *J* = 8.5, 7.1 Hz, 1 H, CH minor), 5.78 - 5.91 (m, 1 H, CH major), 6.87 (dq, *J* = 8.5, 1.8 Hz, 1 H, CH minor), 7.06 (dq, *J* = 14.1, 1.8 Hz, 1 H, CH major), 7.19 - 7.26 (m,

ArH minor + ArH major), 7.28 - 7.36 (m, 2 x ArH minor + 2 x ArH major), 7.42 - 7.55 (m, 4 x ArH minor + 4 x ArH major), 7.65 - 7.73 (m, 2 x ArH minor + 2 x ArH major), 7.93 (app. dt, *J* = 7.8, 1.0 Hz, 1 H, ArH major), 7.96 (app. dt, *J* = 7.8, 1.0 Hz, 1 H, ArH minor). The ratio of isomers was determined by the comparison of the integrals of the H_A signal for the *Z*-isomer [6.87 ppm (dq, *J* = 8.5, 1.8 Hz, 1 integral unit)] relative to the signal for H_A in the *E*-isomer [7.06 ppm (dq, *J* = 14.1, 1.8 Hz, 5.1 integral units, CH major)]. The relevant part of the ^{1}H NMR spectrum is shown below. Two isomers were also detected by GC-MS (*m/z* = 233.2, retention times = 15.263 and 15.685 min).

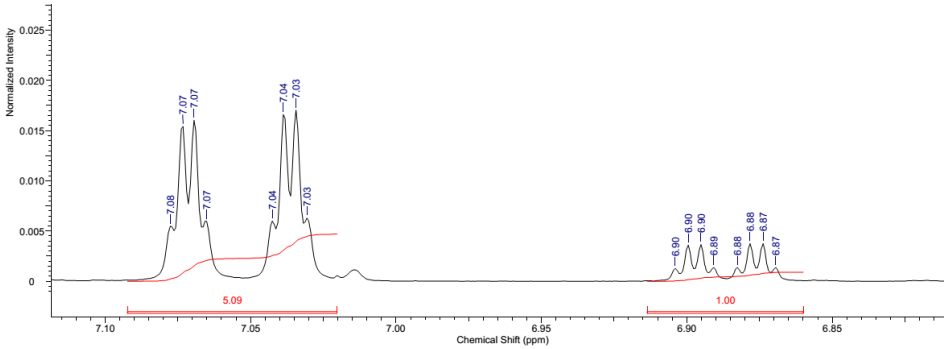
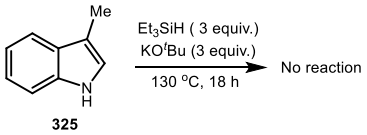


Figure 10 - 1H NMR Spectrum of Isomerisation Products from 1-Allyl-3-phenyl-1H-indole ***371***

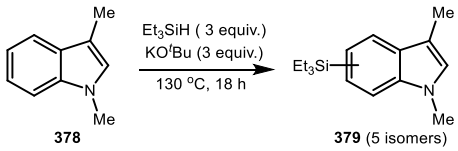
Treatment of 3-Methyl-1*H*-indole (325) with Et_3SiH/KO^tBu



325

This reaction was carried out according to General Procedure C from **325** (66 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to have occurred by ^{1}H NMR of the crude reaction mixture.

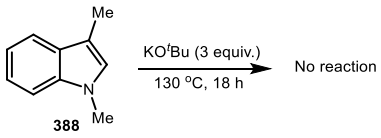
Treatment of 1,3-Dimethyl-1*H*-indole (378) with Et_3SiH/KO^tBu



378 **379** (5 isomers)

This reaction was carried out according to General Procedure C from **378** (73 mg, 0.50 mmol, 1.0 equiv.). A mixture of **379** (5 isomers) and starting material **378** was found which could not be purified (63 mg). Determination of the ratio of products was difficult due to overlapping peaks in the ^{1}H NMR. Five isomers of silylated compounds **379** were detected by GC-MS (*m/z* = 259.2, retention times = 13.381, 13.930, 14.153, 14.243 and 14.301 min).

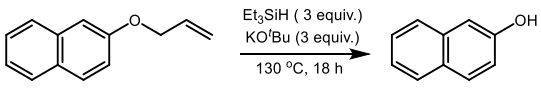
Treatment of 1,3-Dimethyl-1*H*-indole (**378**) with KO^{t}Bu Alone



388

This reaction was carried out according to General Procedure D from **378** (73 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **378** was recovered with data consistent with those reported above (56 mg, 77 %).

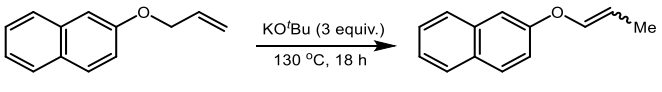
Treatment of 2-(Allyloxy)naphthalene (**380**) with Et_3SiH/KO^{t}Bu



380 **161**, 50 %

This reaction was carried out according to General Procedure C from **380** (92 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded naphthalen-2-ol **161** as a brown solid (36 mg, 50 %). **Mp** = 117-119 °C (lit. mp = 121-123 °C).[264] **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.95 (s, 1 H, OH), 7.11 (dd, *J* = 8.9, 2.6 Hz, 1 H, ArH), 7.16 (d, *J* = 2.5 Hz, 1 H, ArH), 7.34 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1 H, ArH), 7.44 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1 H, ArH), 7.70 (d, *J* = 8.5 Hz, 1 H, ArH), 7.77 (dd, *J* = 8.0, 6.0 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 109.5, 117.7, 123.6, 126.3, 126.5, 127.8, 129.0, 129.8, 134.6, 153.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3296, 3051, 1627, 1598, 1508, 1463, 1406, 1377, 1274, 1240, 1215, 1170, 1138, 1161, 958, 904, 877, 842, 713. ***m/z* (EI)** 144.1 (M^+, 49), 115.1 (100), 89.0 (24), 74.0 (14), 63.0 (33), 51.0 (17). The data for this compound are consistent with those reported in the literature.[265]

Treatment of 2-(Allyloxy)naphthalene (**380**) with KO^{t}Bu Alone



380 **388**, 84 %
1:8.1 *E*:*Z*

This reaction was carried out according to General Procedure D from **380** (92 mg, 0.50 mmol, 1.0 equiv.). A mixture of isomers of **388** was isolated (77 mg, 84 %, 1:8.1 *E*:*Z* ratio). The ratio of isomers was determined by comparison of the integration of the CH_3 groups for the *E*-isomer [1.74 (dd, *J* = 7.0, 1.5 Hz, 1 integral unit)] to the *Z*-isomer [1.78 (dd, *J* = 6.9, 1.6 Hz, 8.1 integral units)]. The identity of each isomer was determined by comparison to the literature.[266] The relevant part of the ^{1}H NMR spectrum is shown below. Two isomers were also detected by GC-MS (*m/z* = 184.1, retention times = 12.351 and 12.476 min).

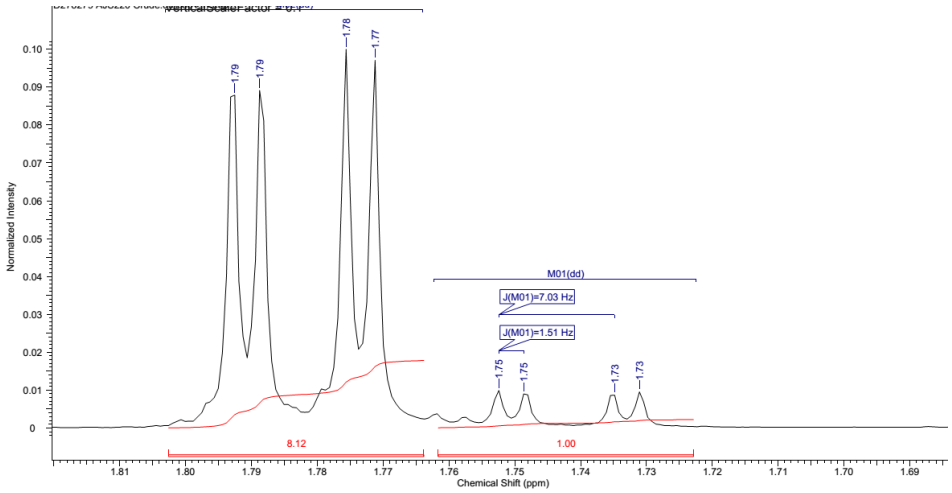
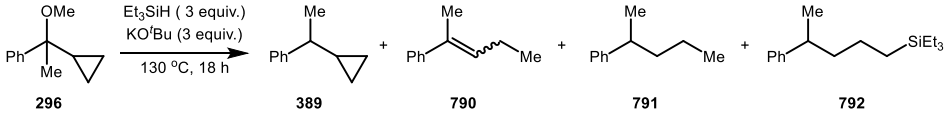


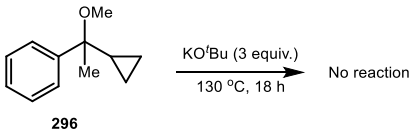
*Figure 11 - ^{1}H NMR Spectrum of Isomerisation Products from 2-(Allyloxy)naphthalene **380***

Treatment of (1-Cyclopropyl-1-methoxyethyl)benzene (296) with Et_3SiH/KO^tBu



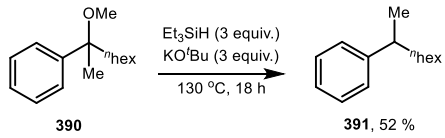
This reaction was carried out according to General Procedure C from **296** (88 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was obtained, from which nothing could be isolated, however, from GC-MS analysis, compounds **389** and **790**-**792** or isomers of these compounds were tentatively identified. The mass of compound **389** and/or **790** was detected under four peaks on the GC-MS spectrum (*m/z* = 146.1, retention times = 8.951, 9.096, 9.567 and 9.834 min). The mass of compound **791** was also detected (*m/z* = 148.1, retention time = 8.746 min), as was the mass of two isomers of **792** (*m/z* = 262.2, retention time = 12.665 and 13.026 min).

Treatment of (1-Cyclopropyl-1-methoxyethyl)benzene (296) with KO^tBu Alone



This reaction was carried out according to General Procedure D from **296** (88 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **296** was recovered with data consistent with those reported above (64 mg, 73 %).

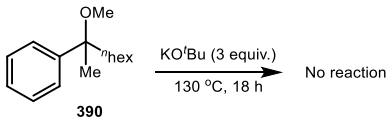
Treatment of (2-Methoxyoctan-2-yl)benzene (390) with Et_3SiH/KO^tBu



390 **391**, 52 %

This reaction was carried out according to General Procedure C from **390** (110 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane) afforded octan-2-ylbenzene **391** which co-eluted with some silyl by-products (combined yield = 70 mg). This mixture was dissolved in diethyl ether (3 mL) and conc. hydrochloric acid (3 mL) added. This mixture was stirred overnight at room temperature before being diluted with water, extracted into DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford octan-2-ylbenzene **391** as a colourless oil (49 mg, 52 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.87 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.16 - 1.33 (m, 11 H, 4 x CH_2 + CH_3), 1.55 - 1.64 (m, 2 H, CH_2), 2.68 (sxt, *J* = 7.1 Hz, 1 H, CH), 7.13 - 7.23 (m, 3 H, 3 x ArH), 7.27 - 7.33 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.1, 22.3, 22.6, 27.7, 29.4, 31.8, 38.5, 39.9, 125.7, 127.0, 128.2, 148.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 2954, 1922, 2852, 1492, 1452, 1375, 1014, 759, 719, 698. ***m/z* (EI)** 190.2 (M^+, 16), 105.2 (100), 91.1 (17), 77.1 (9). The data for this compound are consistent with those reported in the literature.[267]

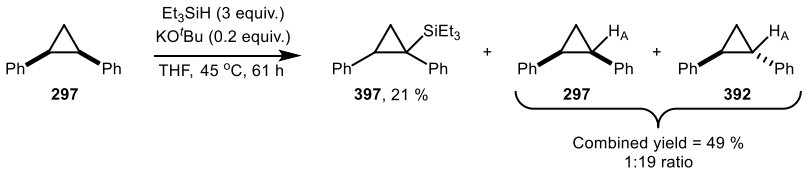
Treatment of (2-Methoxyoctan-2-yl)benzene (390) with KO^tBu Alone



390

This reaction was carried out according to General Procedure D from **390** (110 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **390** was recovered with data consistent with those reported above (68 mg, 62 %).

Treatment of *cis*-1,2-Diphenylcyclopropane (297) with Et_3SiH/KO^tBu



Substrate **297** (97 mg, 0.50 mmol, 1.0 equiv.), Et_3SiH (0.24 mL, 1.50 mmol, 3.0 equiv.) and KO^tBu (11 mg, 0.10 mmol, 0.2 equiv.) were dissolved in THF (0.5 mL) in a pressure tube in a glovebox under nitrogen. The tube was sealed and removed from the glovebox, and heated at 45 °C for 61 h. The mixture was then diluted with diethyl ether and concentrated under reduced pressure. Purification by column chromatography (petroleum ether) afforded (1,2-diphenylcyclopropyl)triethylsilane **397** as a waxy white solid (32 mg, 21 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.52 (q, *J* = 7.8 Hz, 6 H, 3 x CH_2), 0.98 (t, *J* = 7.9 Hz, 9 H, 3 x CH_3),

1.41 - 1.52 (m, 2 H, 2 x CH), 2.35 (dd, *J* = 7.8, 5.8 Hz, 1 H, CH), 6.62 - 6.70 (m, 2 H, 2 x ArH), 6.81 - 6.89 (m, 2 H, 2 x ArH), 6.96 - 7.10 (m, 6 H, 6 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 2.0, 7.5, 16.8, 25.5, 29.7, 124.7, 125.1, 127.3, 127.5, 127.6, 131.1, 139.4, 141.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3061, 3028, 2922, 1602, 1498, 1463, 1450, 1211, 1114, 1070, 1029, 906, 775, 734. ***m/z* (EI)** 308.4 (M^+, 13), 279.3 (10), 192.2 (14), 178.2 (14), 165.2 (7), 135.2 (10), 115.2 (100), 87.2 (71), 77.0 (5), 59.1 (33). **HRMS (CI)** calcd. for $C_{21}H_{28}Si^+$ (M): 308.1960, found: 308.1962. Also isolated was an inseparable mixture of *cis*-1,2-diphenylcyclopropane **297** and *trans*-1,2-diphenylcyclopropane **392** as a colourless oil (48 mg, 49 %). Only the data corresponding to the major *trans*-isomer are reported here. The data for the *cis*-isomer are consistent with those reported above. **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.49 (dd, *J* = 8.8, 7.3 Hz, 2 H, 2 x CH), 2.21 (t, *J* = 7.5 Hz, 2 H, 2 x CH), 7.16 - 7.20 (m, 4 H, 4 x ArH), 7.22 (app. tt, *J* = 7.5, 1.3 Hz, 2 H, 2 x ArH), 7.29 - 7.38 (m, 4 H, 4 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 18.2, 28.0, 125.7, 125.8, 128.4, 142.5. A shift in retention time of the major isomer of 1,2-diphenylcyclopropane was also observed relative to the starting material, from 11.944 min to 12.649 min. The ratio of isomers was determined by comparison of the relative integrations of H_A in the *cis*-isomer [2.52 (dd, *J* = 8.7, 6.4 Hz, 1 integral unit)] and the *trans*-isomer [2.21 (t, *J* = 7.5 Hz, 19 integral units)]. The isomers were identified by comparison to the literature data.[138] The relevant part of the ^{1}H NMR spectrum is shown below.

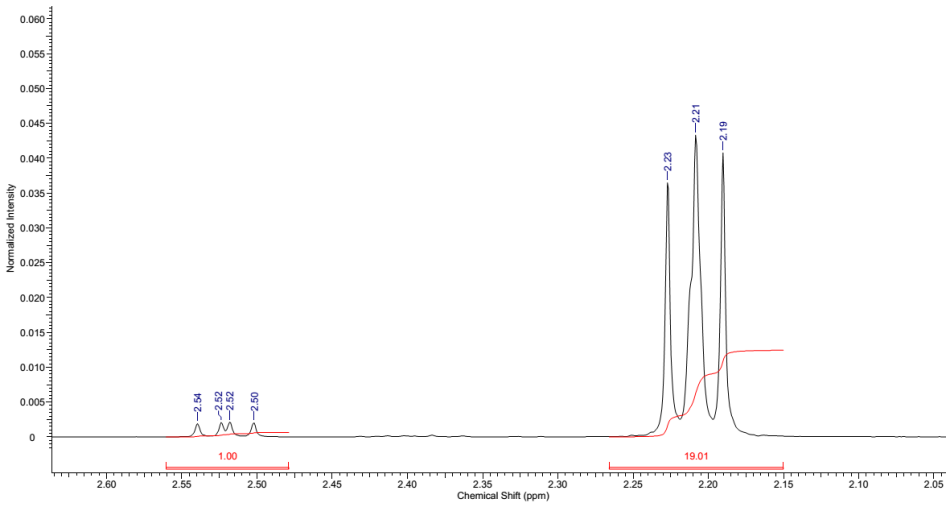
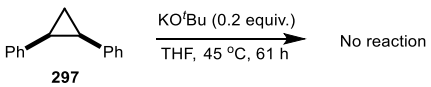


Figure 12 - ^{1}H NMR Spectrum of 1,2-Diphenylcyclopropane (cis and trans)

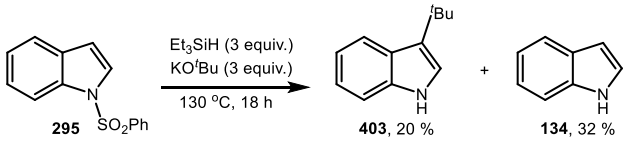
Treatment of *cis*-1,2-Diphenylcyclopropane (297) with KO^{t}Bu Alone



Substrate **297** (40 mg, 0.20 mmol, 1.0 equiv.) and KO^{t}Bu (4 mg, 0.04 mmol, 0.20 equiv.) were dissolved in THF (0.5 mL) in a pressure tube in a glovebox under nitrogen. The tube was sealed and removed from the glovebox, and heated at 45 °C for 61 h. The mixture was then diluted with

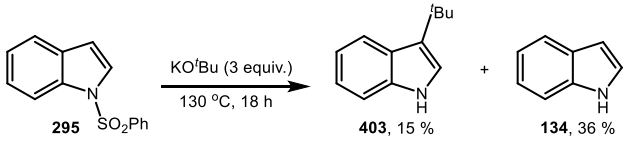
diethyl ether and concentrated under reduced pressure. No reaction was found to occur, and **297** was recovered with data consistent with those reported above (20 mg, 50 %).

Treatment of 1-(Phenylsulfonyl)-1H-indole (295) with Et_3SiH/KO^tBu



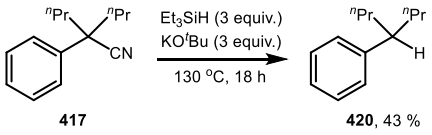
This reaction was carried out according to General Procedure C from **295** (129 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (petroleum ether:diethyl ether, 9:1) afforded 3-*tert*-butyl-1*H*-indole **403** as a brown oil (17 mg, 20 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.48 (s, 9 H, 3 x CH_3), 6.95 (d, *J* = 2.5 Hz, 1 H, ArH), 7.11 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H, ArH), 7.18 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1 H, ArH), 7.37 (app. dt, *J* = 8.0, 0.9 Hz, 1 H, ArH), 7.84 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.86 (br. s, 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 30.7, 31.6, 111.3, 118.8, 119.2, 121.3, 121.4, 125.9, 126.8, 137.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3394, 2958, 1676, 1616, 1460, 1359, 1334, 1244, 1207, 1176, 1101, 1010, 808, 763. ***m/z* (EI)** 173.1 (M^+, 26), 158.1 (100), 143.0 (14), 130.1 (16), 117.1 (12), 103.1 (2), 89.0 (5), 77.1 (4), 65.0 (4), 51.1 (2). **HRMS (CI)** calcd. for $C_{12}H_{16}N^+$ ($[M+H]^+$): 174.1283, found: 174.1287. Also isolated was 1*H*-indole **134**, with data consistent with those reported above (19 mg, 32 %).

Treatment of 1-(Phenylsulfonyl)-1H-indole (295) with KO^tBu Alone



This reaction was carried out according to General Procedure D from **295** (129 mg, 0.50 mmol, 1.0 equiv.) Purification by column chromatography (petroleum ether:diethyl ether, 9:1) afforded 3-*tert*-butyl-1*H*-indole **403**, with data consistent with those reported above (13 mg, 15 %) and 1*H*-indole **134**, with data consistent with those reported above (21 mg, 36 %).

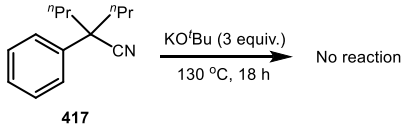
Treatment of 2-Phenyl-2-propylpentanenitrile (417) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from **417** (101 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane) afforded 4-phenylheptane **420** which was inseparable from some silyl-derived by-products. This crude mixture was then

dissolved in diethyl ether (3 mL) and conc. HCl (3 mL) added. This mixture was stirred at room temperature for 48 h under air before diluting with water and extracting into hexane. The combined organic layers were washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated to afford 4-phenylheptane **420** as a colourless oil (38 mg, 43 %) **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.86 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.11 - 1.25 (m, 4 H, 2 x CH_2), 1.48 - 1.70 (m, 4 H, 2 x CH_2), 2.47 - 2.59 (m, 1 H, CH), 7.11 - 7.22 (m, 3 H, 3 x ArH), 7.26 - 7.33 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.1, 20.7, 39.2, 45.5, 125.7, 127.7, 128.1, 146.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 2953, 2924, 2870, 1610, 1492, 1452, 1377, 1099, 1066, 1029, 1008, 759, 731, 665. ***m/z* (EI)** 176.2 (M^+, 13), 133.1 (25), 91.1 (100). **HRMS (CI)** calcd. for $C_{13}H_{20}^+$ ([M]$^+$): 176.1560, found: 176.1562.

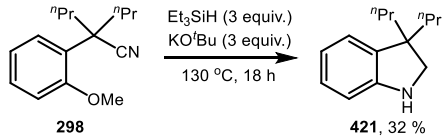
Treatment of 2-Phenyl-2-propylpentanenitrile (417) with KO^{t}Bu Alone



417

This reaction was carried out according to General Procedure D from **417** (101 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **417** was recovered with data consistent with those reported above (101 mg, 100 %).

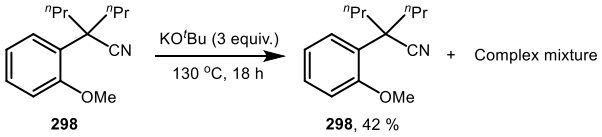
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with Et_3SiH/KO^{t}Bu



298 **421**, 32 %

This reaction was carried out according to General Procedure C from **298** (116 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded 3,3-dipropylindoline **421** as a colourless oil (33 mg, 32 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.89 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.11 - 1.25 (m, 2 H, 2 x CH), 1.27 - 1.47 (m, 2 H, 2 x CH), 1.55 (ddd, *J* = 13.7, 12.2, 4.4 Hz, 2 H, 2 x CH), 1.68 (ddd, *J* = 13.7, 12.2, 4.4 Hz, 2 H, 2 x CH), 3.37 (s, 2 H, CH_2), 6.62 (d, *J* = 7.8 Hz, 1 H, ArH), 6.72 (app. td, *J* = 7.3, 1.0 Hz, 1 H, ArH), 6.99 (dd, *J* = 7.3, 1.0 Hz, 1 H, ArH), 7.03 (app. td, *J* = 7.3, 1.5 Hz, 1 H, ArH). **^{13}C NMR** (101 MHz, $CDCl_3$) 14.8, 17.6, 41.3, 48.8, 57.6, 109.4, 118.2, 123.3, 127.2, 136.0, 151.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3383, 2953, 2927, 2868, 1604, 1487, 1462, 1377, 1311, 1232, 1180, 1151, 1116, 1028, 896, 707. ***m/z* (EI)** 203.2 (M^+, 13) 160.2 (100), 144.1 (3), 130.1 (27), 118.1 (55), 103.1 (4), 91.1 (9), 77.1 (5), 65.1 (2), 51.1 (2). **HRMS (CI)** calcd. for $C_{14}H_{22}N^+$ ([M+H]$^+$): 204.1747, found: 204.1745.

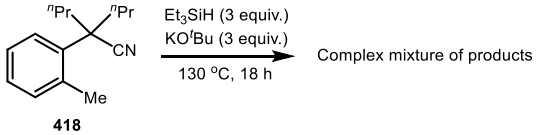
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with KO^{t}Bu Alone



298 **298**, 42 %

This reaction was carried out according to General Procedure D from **298** (116 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded a complex mixture of products from which nothing could be identified (19 mg), and starting material **298**, with data consistent with those reported above (49 mg, 42 %).

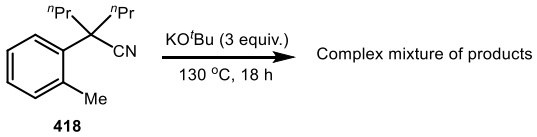
Treatment of 2-(2-Methylphenyl)-2-propylpentanenitrile (418) with Et_3SiH/KO^{t}Bu



418

This reaction was carried out according to General Procedure C from **418** (108 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was produced, from which nothing could be isolated or identified.

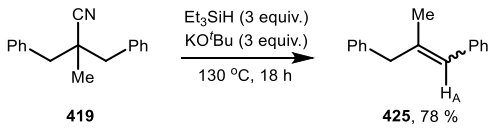
Treatment of 2-(2-Methylphenyl)-2-propylpentanenitrile (418) with KO^{t}Bu Alone



418

This reaction was carried out according to General Procedure D from **418** (108 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was produced, from which nothing could be isolated or identified. This mixture of products produced very similar ^{1}H NMR and GC-MS data to the case above where **418** was treated with Et_3SiH/KO^{t}Bu.

Treatment of 2-Benzyl-2-methyl-3-phenylpropanenitrile (419) with Et_3SiH/KO^{t}Bu



419 **425**, 78 %
2.5:1 E:Z

This reaction was carried out according to General Procedure C from **419** (118 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane) afforded an inseparable mixture of isomers of (*E*/*Z*)-(2-methylprop-1-ene-1,3-diyl)dibenzene **425** as a colourless oil (81 mg, 78 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.83 (d, *J* = 1.3 Hz, 3 H, CH_3 major), 1.84 (d, *J* = 1.5 Hz, 3 H, CH_3

minor), 3.51 (s, 2 H, CH_2 major), 3.63 (s, 2 H, CH_2 minor), 6.41 (s, 1 H, CH major), 6.55 (s, 1 H, CH minor), 7.16 - 7.40 (m, 10 x ArH major + 10 x ArH minor). **^{13}C-NMR** (101 MHz, $CDCl_3$) 17.6, 24.0, 38.5, 47.1, 126.0, 126.1, 126.2, 126.3, 126.8, 127.4, 128.0, 128.2, 128.3, 128.4, 128.4, 128.6, 128.9, 129.0, 137.0, 138.1, 138.3, 139.7, 139.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3024, 2922, 1597, 1492, 1452, 1074, 1028, 916, 732, 696. ***m/z* (EI)** 208.2 (M^+, 73), 193.1 (57), 178.1 (30), 165.1 (10), 152.1 (4), 130.1 (25), 115.1 (100), 103.1 (5), 91.1 (52), 77.1 (10), 65.1 (20), 51.1 (14). Two isomers were detected by GC-MS (*m/z* = 208.1, retention times = 12.809 and 13.038 min) The *E*:*Z* ratio was determined by comparison of the integral of H_A for the *Z*-isomer [6.55 ppm (s, 1 integral unit)] to the integral of H_A for the *E*-isomer [6.41 ppm (s, 2.5 integral units)]. The relevant part of the ^{1}H NMR spectrum is shown below. The data for these compounds are consistent with those reported in the literature.[268]

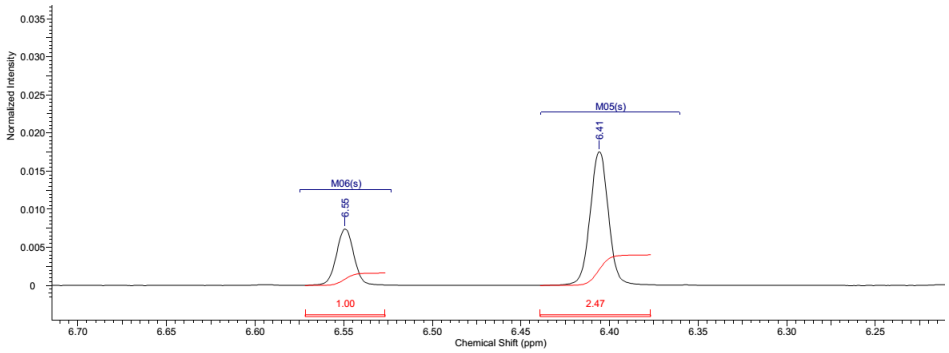
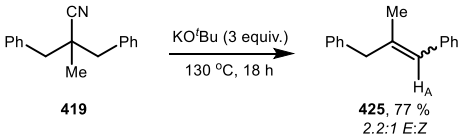


*Figure 13 - ^{1}H NMR Spectrum Showing the Ratio of E/Z Isomers of **425***

Treatment of 2-Benzyl-2-methyl-3-phenylpropanenitrile (**419**) with KO^{t}Bu Alone

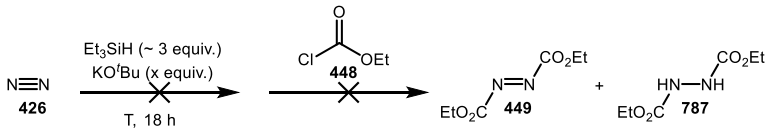


419

425, 77 %
2.2:1 E:Z

This reaction was carried out according to General Procedure D from **419** (118 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane) afforded an inseparable mixture of isomers of (*E*/*Z*)-(2-methylprop-1-ene-1,3-diyl)dibenzene **425** as a colourless oil (80 mg, 77 %), with data consistent to those reported above.

Attempted Reduction of Nitrogen (**426**) with Et_3SiH/KO^{t}Bu

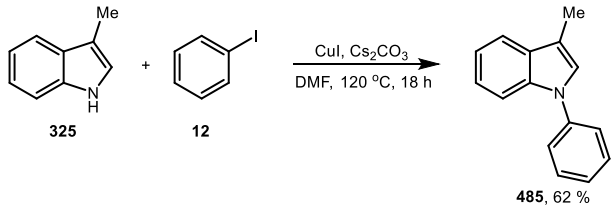


Entry	X	T/ °C	**449**	**787**
1	~ 3	130	0	0
2	~ 0.2	130	0	0
3	~ 3	150	0	0
4	~ 3	180	0	0

To a 10 mL microwave vial in a glovebox under nitrogen was added Et_3SiH (0.22 mL, 1.35 mmol, ~3.0 equiv.) and KO^{t}Bu [(151 mg, 1.35 mmol, ~3.0 equiv.) or (10 mg, 0.09 mmol, ~0.2 equiv.). The volume of nitrogen gas was estimated (~10 mL, ~0.45 mmol, ~1.0 equiv.) at atmospheric temperature and pressure. The tube was sealed and removed from the glovebox, and then heated at the specified temperature above for 18 h behind a shield. After a short period of cooling (~10 min), ethyl chloroformate (0.13 mL, 1.35 mmol, ~3.0 equiv.) was added to the warm reaction mixture behind a shield, and the mixture was stirred whilst cooling to room temperature. After cooling to room temperature, the mixture was diluted with water and extracted into diethyl ether. The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. ^{1}H NMR analyses of the crude reaction mixtures were compared to the spectra obtained from **449** and **787** above. These compounds were not detected in the reaction mixture in any case.

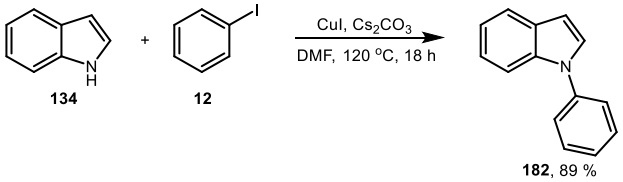
8.5 – Preparation of Substrates for Chapter 4

Preparation of 3-Methyl-1-phenyl-1*H*-indole (485)



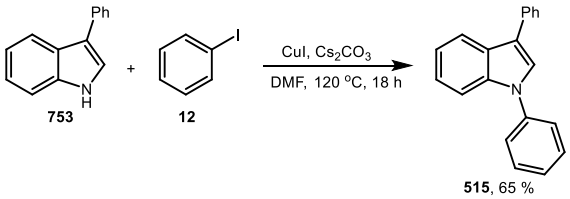
This substrate was prepared according to General Procedure F from 3-methyl-1*H*-indole **325** (367 mg, 2.80 mmol, 1.4 equiv.) and iodobenzene **12** (0.22 mL, 1.97 mmol, 1.0 equiv.) with copper(I) iodide (76 mg, 0.4 mmol, 0.2 equiv.) and cesium carbonate (1.30 g, 3.99 mmol, 2.0 equiv.) in DMF (4 mL). Purification by column chromatography (hexane) afforded 3-methyl-1-phenyl-1*H*-indole **485** as a yellow oil (257 mg, 62 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.49 (d, *J* = 1.3 Hz, 3 H, $ArCH_3$), 7.22 (q, *J* = 1.0 Hz, 1 H, ArH), 7.28 (app. td, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.32 (app. td, *J* = 8.0, 1.5 Hz, 1 H, ArH), 7.36 - 7.43 (m, 1 H, ArH), 7.57 (m, 4 H, 4 x ArH), 7.66 (app. dt, *J* = 8.2, 0.9 Hz, 1 H, ArH), 7.71 - 7.76 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 110.3, 112.8, 119.2, 119.8, 122.3, 124.0, 125.4, 125.9, 129.5, 129.8, 135.9, 140.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3045, 2912, 1597, 1499, 1454, 1371, 1227, 1125, 1070, 1015, 904, 773, 692, 655. ***m/z* (EI)** 207.1 (M^+, 92), 206.1 (100), 178.1 (8), 128.1 (18), 102.1 (9), 77.1 (44), 63.1 (6), 51.1 (24). The data for this compound are consistent with those reported in the literature.[238]

Preparation of 1-Phenyl-1*H*-indole (**182**)



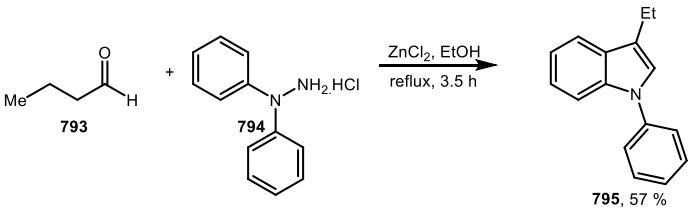
This substrate was prepared according to General Procedure F from 1*H*-indole **134** (1.64 g, 14.0 mmol, 1.4 equiv.) and iodobenzene **12** (1.12 mL, 10.0 mmol, 1.0 equiv.) with copper (I) iodide (381 mg, 2.00 mmol, 0.2 equiv.) and cesium carbonate (6.52 g, 20.0 mmol, 2.0 equiv.) in DMF (20 mL). Purification by column chromatography (hexane) afforded 1-phenyl-1*H*-indole **182** as a colourless oil (1.72 g, 89 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 6.71 (dd, *J* = 3.3, 0.8 Hz, 1 H, ArH), 7.15 - 7.22 (m, 1 H, ArH), 7.22 - 7.27 (m, 1 H, ArH), 7.34 - 7.43 (m, 2 H, 2 x ArH), 7.50 - 7.56 (m, 4 H, 4 x ArH), 7.57 - 7.63 (m, 1 H, ArH), 7.69 - 7.74 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 103.5, 110.5, 120.3, 121.1, 122.3, 124.3, 126.4, 127.9, 129.2, 129.6, 135.8, 139.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3051, 1595, 1512, 1494, 1454, 1329, 1230, 1211, 1134, 1072, 1012, 950, 906, 881, 781. ***m/z* (EI)** 193.1 (M^+, 100), 165.1 (28), 89.1 (17), 77.1 (7), 63.1 (7), 51.1 (12). The data for this compound are consistent with those reported in the literature.[269]

Preparation of 1,3-Diphenyl-1*H*-indole (**515**)



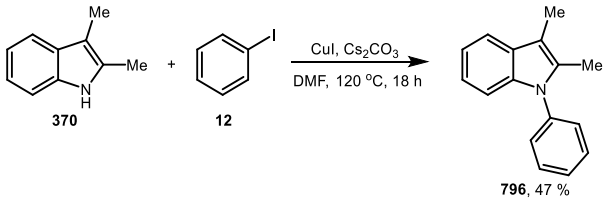
This substrate was prepared according to General Procedure F from 3-phenyl-1*H*-indole **753** (1.06 g, 5.49 mmol, 1.1 equiv.), and iodobenzene **12** (0.56 mL, 5.02 mmol, 1.0 equiv.), with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.), and cesium carbonate (3.26 g, 10.0 mmol, 2.0 equiv.) in DMF (10 mL). Purification by column chromatography (hexane:diethyl ether, 49:1) afforded 1,3-diphenyl-1*H*-indole **515** as a white solid (878 mg, 65 %). **Mp** = 105-108 °C (lit. mp = 107-108.5 °C).[270] **^{1}H-NMR** (400 MHz, $CDCl_3$) 7.25 - 7.33 (m, 2 H, 2 x ArH), 7.33 - 7.39 (m, 1 H, ArH), 7.39 - 7.45 (m, 1 H, ArH), 7.47 - 7.53 (m, 2 H, 2 x ArH), 7.53 - 7.56 (m, 1 H, ArH), 7.56 - 7.62 (m, 4 H, 4 x ArH), 7.62 - 7.67 (m, 1 H, ArH), 7.72 - 7.78 (m, 2 H, 2 x ArH), 8.01 - 8.05 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 110.8, 119.1, 120.1, 120.9, 122.8, 124.5, 125.5, 126.2, 126.7, 127.1, 127.6, 128.8, 129.7, 135.1, 136.7, 139.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3018, 1593, 1552, 1500, 1454, 1379, 1226, 1076, 1022, 972, 908, 810, 734, 639. ***m/z* (EI)** 269.2 (M^+, 94), 190.1 (14), 165.1 (86), 139.1 (11), 77.1 (100), 51.1 (53). The data for this compound are consistent with those reported in the literature.[207]

Preparation of 3-Ethyl-1-phenyl-1*H*-indole (795)



This substrate was prepared according to a modified literature procedure.[198] A mixture of butyraldehyde **793** (0.45 mL, 4.99 mmol, 1.0 equiv.) and 1,1-diphenylhydrazine hydrochloride **794** (1.10 g, 4.98 mmol, 1.0 equiv.) were stirred for 1 h under argon. The reaction mixture was then heated to 100 °C and heated for a further 30 min at this temperature. A solution of zinc chloride (1.23 g, 9.02 mmol, 1.8 equiv.) in ethanol (5.5 mL) was then added and the mixture stirred at reflux for 2 h. After cooling to room temperature, the mixture was filtered, and the solvent was removed under reduced pressure. 1 M HCl was added to the residue and organic material was extracted into DCM. The combined organic layers were then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 49:1) afforded 3-ethyl-1-phenyl-1*H*-indole **795** as a yellow oil (627 mg, 57 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.41 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.88 (qd, *J* = 7.5, 1.0 Hz, 2 H, CH_2), 7.15 - 7.17 (m, 1 H, ArH), 7.17 - 7.22 (m, 1 H, ArH), 7.22 - 7.27 (m, 1 H, ArH), 7.30 - 7.38 (m, 1 H, ArH), 7.48 - 7.55 (m, 4 H, 4 x ArH), 7.56 - 7.62 (m, 1 H, ArH), 7.65 - 7.72 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.3, 18.3, 110.5, 119.3, 119.7, 119.8, 122.3, 124.0, 124.4, 125.9, 129.0, 129.5, 136.1, 140.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3049, 2960, 1595, 1499, 1454, 1377, 1315, 1298, 1223, 1132, 1072, 1014, 960, 925, 904, 773, 694. ***m/z* (EI)** 221.1 (M^+, 47) 206.1 (100), 178.1 (9), 128.0 (14), 115.1 (12), 102.1 (10), 89.0 (5), 77.1 (40), 63.0 (4), 51.1 (19). The data for this compound are consistent with those reported in the literature.[238]

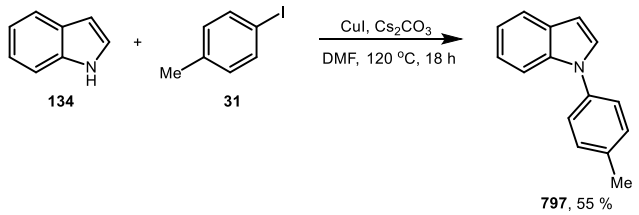
Preparation of 2,3-Dimethyl-1-phenyl-1*H*-indole (796)



This substrate was prepared according to General Procedure F from 2,3-dimethyl-1*H*-indole **370** (290 mg, 2.00 mmol, 1.0 equiv.) and iodobenzene **12** (0.22 mL, 1.97 mmol, 1.0 equiv.) with copper (I) iodide (76 mg, 0.4 mmol, 0.2 equiv.) and cesium carbonate (1.30 g, 3.99 mmol, 2.0 equiv.) in DMF (4 mL). Purification by column chromatography (hexane) afforded 2,3-dimethyl-1-phenyl-1*H*-indole **796** as a colourless oil (207 mg, 47 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.26 (s, 3 H, $ArCH_3$), 2.35 (d, *J* = 0.5 Hz, 3 H, $ArCH_3$), 7.08 - 7.18 (m, 3 H, 3 x ArH), 7.32 - 7.38 (m, 2 H, 2 x ArH), 7.45 (app. tt, *J* = 7.5, 2.0 Hz, 1 H, ArH), 7.50 - 7.59 (m, 3 H, 3 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 8.9, 11.0, 107.9, 109.7, 117.8, 119.4, 121.1, 127.4, 128.0, 128.7, 129.3, 132.8, 137.2, 138.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3041, 2915, 2858, 1597, 1499, 1458, 1400, 1361, 1234, 1217, 1134, 1072, 1015,

914. ***m/z* (EI)** 221.1 (M^+, 100), 206.1 (38), 178.1 (6), 143.1 (9), 128.1 (9), 115.0 (15), 102.1 (12), 77.0 (57), 63.0 (8), 51.0 (34). The data for this compound are consistent with those reported in the literature.[271]

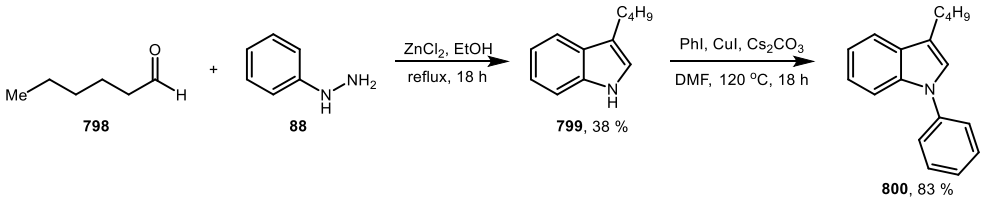
Preparation of 1-(*p*-Tolyl)-1*H*-indole (797)



134 31 **797**, 55 %

This substrate was prepared according to General Procedure F from 1*H*-indole **134** (234 mg, 2.00 mmol, 1.0 equiv.) and 4-iodotoluene **31** (436 mg, 2.00 mmol, 1.0 equiv.) with copper (I) iodide (76 mg, 0.4 mmol, 0.2 equiv.) and cesium carbonate (1.30 g, 3.99 mmol, 2.0 equiv.) in DMF (4 mL). Purification by column chromatography (hexane) afforded 1-(*p*-tolyl)-1*H*-indole **797** as a yellow oil (226 mg, 55 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.46 (s, 3 H, $ArCH_3$), 6.70 (dd, *J* = 3.3, 0.8 Hz, 1 H, ArH), 7.16 - 7.21 (m, 1 H, ArH), 7.22 - 7.27 (m, 1 H, ArH), 7.31 - 7.37 (m, 3 H, 3 x ArH), 7.39 - 7.44 (m, 2 H, 2 x ArH), 7.53 - 7.59 (m, 1 H, ArH), 7.69 - 7.75 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 21.0, 103.2, 110.5, 120.2, 121.0, 122.2, 124.3, 128.0, 129.2, 130.1, 136.0, 136.3, 137.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3030, 2916, 1606, 1514, 1454, 1330, 1315, 1230, 1211, 1134, 1107, 1012, 952, 881, 817, 710. ***m/z* (EI)** 207.1 (M^+,100), 191.1 (7), 178.1 (8), 165.1 (11), 116.1 (10), 102.5 (8), 89.0 (29), 77.0 (5), 63.0 (15), 51.0 (7). The data for this compound are consistent with those reported in the literature.[199]

Preparation of 3-Butyl-1-phenyl-1*H*-indole (800)

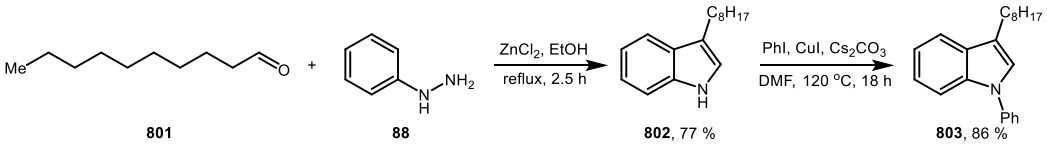


798 88 **799**, 38 % **800**, 83 %

Step 1 was carried out according to General Procedure E from hexanal **798** (1.23 mL, 10.0 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1 → 9:1) afforded 3-butyl-1*H*-indole **799** as an orange oil (665 mg, 38 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.97 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.44 (sxt, *J* = 7.3 Hz, 2 H, CH_2), 1.58 - 1.81 (m, 2 H, CH_2), 2.57 - 2.87 (m, 2 H, CH_2), 6.96 - 7.00 (m, 1 H, ArH), 7.09 - 7.16 (m, 1 H, ArH), 7.20 (app. td, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.36 (app. dt, *J* = 8.1, 1.0 Hz, 1 H, ArH), 7.60 - 7.65 (m, 1 H, ArH), 7.88 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 22.7, 24.8, 32.3, 111.0, 117.2, 119.0 (2 carbons), 121.0, 121.8, 127.7, 136.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3414, 2954, 2926, 2845, 1618, 1454, 1419, 1338, 1222, 1089, 1008, 802, 763. ***m/z* (EI)** 173.2 (M^+, 71), 143.1 (21), 130.2 (100), 115.1 (26), 103.1 (42), 89.1 (15), 77.1 (51), 63.1 (11), 51.1 (11). The data for this compound are consistent with those reported in the literature.[272]

Step 2 was carried out according to General Procedure F from 3-butyl-1*H*-indole **799** (665 mg, 3.83 mmol, 1.1 equiv.), and iodobenzene **12** (0.39 mL, 3.45 mmol, 1.0 equiv.), with copper (I) iodide (131 mg, 0.69 mmol, 0.2 equiv.), and cesium carbonate (2.25 g, 6.91 mmol, 2.0 equiv.) in DMF (7 mL). Purification by column chromatography (hexane) afforded 3-butyl-1-phenyl-1*H*-indole **800** as an off-white solid (715 mg, 83 %). **Mp** = 44-45 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.99 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.48 (sxt, *J* = 7.5 Hz, 2 H, CH_2), 1.70 - 1.84 (m, 2 H, CH_2), 2.76 - 2.88 (m, 2 H, CH_2), 7.13 - 7.20 (m, 2 H, 2 x ArH), 7.20 - 7.26 (m, 1 H, ArH), 7.33 (m, 1 H, ArH), 7.51 (m, 4 H, 4 x ArH), 7.55 - 7.61 (m, 1 H, ArH), 7.67 (app. dt, *J* = 8.1, 0.8 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 22.7, 24.7, 32.2, 110.4, 118.2, 119.3, 119.7, 122.3, 124.0, 124.9, 125.9, 129.2, 129.5, 136.0, 140.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3053, 2956, 2870, 1593, 1500, 1454, 1373, 1311, 1213, 1132, 1074, 1016, 898, 773, 686, 669. ***m/z* (EI)** 249.2 (M^+, 20), 206.2 (100), 178.2 (11), 128.1 (19), 115.0 (8), 102.3 (7), 89.0 (5), 77.1 (30), 51.0 (8). **HRMS (CI)** calcd. for $C_{18}H_{20}N^+$ ([M+H]$^+$): 250.1596, found: 250.1595.

Preparation of 3-Octyl-1-phenyl-1*H*-indole (803)



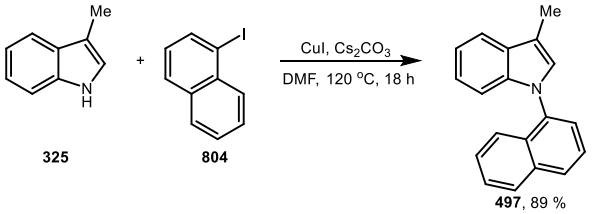
801 **88** **802**, 77 % **803**, 86 %

Step 1 was carried out according to General Procedure E from decanal **801** (1.88 mL, 9.99 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded 3-octyl-1-phenyl-1*H*-indole **802** as orange crystals (1.76 g, 77 %). **Mp** = 30-32 °C (lit. mp = 32 °C)[272]. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.90 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.16 - 1.46 (m, 10 H, 5 x CH_2), 1.73 (quin, *J* = 7.5 Hz, 2 H, CH_2), 2.76 (td, *J* = 7.3, 0.8 Hz, 2 H, CH_2), 6.96 - 7.01 (m, 1 H, ArH), 7.12 (ddd, *J* = 7.85, 7.0, 1.0 Hz, 1 H, ArH), 7.20 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H, ArH), 7.36 (app. dt, *J* = 8.0, 0.9 Hz, 1 H, ArH), 7.56 - 7.69 (m, 1 H, ArH), 7.89 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.1, 22.7, 25.1, 29.3, 29.5, 29.7, 30.2, 31.9, 111.0, 117.1, 119.0 (2 carbons), 121.0, 121.8, 127.6, 136.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3419, 3001, 2922, 1595, 1496, 1454, 1309, 1220, 1134, 1074, 1020, 871, 773, 694. ***m/z* (EI)** 229.3 (M^+, 9), 143.1 (5), 130.1 (100), 103.1 (7), 77.7 (7). The data for this compound are consistent with those reported in the literature.[272]

Step 2 was carried out according to General Procedure F from 3-octyl-1-phenyl-1*H*-indole **802** (1.26 g, 5.49 mmol, 1,1 equiv.) and, iodobenzene **12** (0.56 mL, 5.02 mmol, 1.0 equiv.), copper (I) iodide (190 mg, 1.0 mmol, 0.2 equiv.), and cesium carbonate (3.26 g, 10.0 mmol, 2 equiv.) in DMF (10 mL). Purification by column chromatography (hexane) afforded 3-octyl-1-phenyl-1*H*-indole **803** as an orange oil (1.32 g, 86 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.91 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.22 - 1.52 (m, 10 H, 5 x CH_2), 1.78 (quin, *J* = 7.5 Hz, 2 H, CH_2), 2.82 (t, *J* = 7.5 Hz, 2 H, CH_2), 7.14 - 7.17 (m, 1 H, ArH), 7.19 (dd, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.24 (app. td, *J* = 7.0, 1.3 Hz,

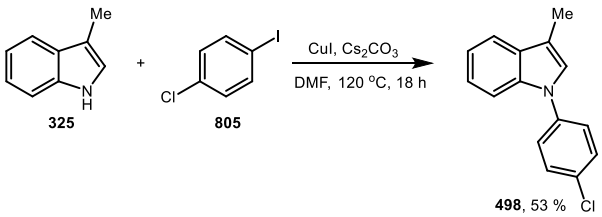
1 H, ArH), 7.33 (m, 1 H, ArH), 7.52 (m, 4 H, 4 x ArH), 7.59 (d, *J* = 8.0 Hz, 1 H, ArH), 7.68 (d, *J* = 7.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.1, 22.7, 25.1, 29.3, 29.5, 29.7, 30.1, 31.9, 110.4, 118.3, 119.3, 119.7, 122.3, 124.0, 124.9, 125.9, 129.2, 129.5, 136.0, 140.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 2920, 2850, 1595, 1498, 1454, 1377, 1317, 1224, 1132, 773, 694. ***m/z* (EI)** 305.3 (M^+, 33), 206.2 (100), 178.1 (18), 128.1 (20), 77.1 (14), 57.1 (7). **HRMS (CI)** calcd. for $C_{22}H_{28}N^+$ ($[M+H]^+$): 306.2216, found: 306.2213.

Preparation of 3-Methyl-1-(naphthalen-1-yl)-1*H*-indole (497)



This substrate was prepared according to General Procedure F from 3-methyl-1*H*-indole **325** (918 mg, 7.00 mmol, 1.4 equiv.) and 1-iodonaphthalene **804** (0.73 mL, 5.00 mmol, 1.0 equiv.) with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.26 g, 10.0 mmol, 2 equiv.) in DMF (10 mL). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 3-methyl-1-(naphthalen-1-yl)-1*H*-indole **497** as an orange solid (1.14 g, 89 %). **Mp** = 93-95 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.47 (d, *J* = 1.0 Hz, 3 H, $ArCH_3$), 6.98 - 7.05 (m, 1 H, ArH), 7.09 - 7.23 (m, 3 H, 3 x ArH), 7.42 (app. td, *J* = 7.3, 1.3 Hz, 1 H, ArH), 7.49 - 7.62 (m, 4 H, 4 x ArH), 7.67 - 7.74 (m, 1 H, ArH), 7.90 - 8.01 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.7, 110.7, 112.0, 119.0, 119.5, 122.1, 123.5, 124.9, 125.5, 126.5, 126.7, 127.4, 128.0, 128.2, 128.9, 130.5, 134.4, 136.2, 138.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3043, 2912, 1595, 1573, 1506, 1469, 1452, 1406, 1303, 1232, 1008, 862, 800, 761, 686, 642. ***m/z* (EI)** 257.2 (M^+, 100), 241.2 (33), 127.1 (34), 102.1 (15), 77.1 (35), 63.1 (11), 51.1 (13). **HRMS (CI)** calcd. for $C_{19}H_{16}N^+$ ($[M+H]^+$): 258.1283, found: 258.1282.

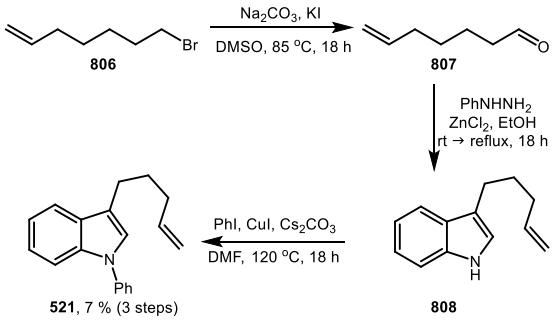
Preparation of 1-(4-Chlorophenyl)-3-methyl-1*H*-indole (498)



This substrate was prepared according to General Procedure F from 3-methyl-1*H*-indole **325** (918 mg, 7.00 mmol, 1.4 equiv.) and 4-chloro-1-iodobenzene **805** (1.19 g, 4.99 mmol, 1.0 equiv.) with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.26 g, 10.0 mmol, 2 equiv.) in DMF (10 mL). Purification by column chromatography (hexane) afforded 3-methyl-1-(naphthalen-1-yl)-1*H*-indole **498** as a colourless oil (641 mg, 53 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.40 (d, *J* = 1.0 Hz, 3 H, CH_3), 7.09 - 7.12 (m, 1 H, ArH), 7.20 (app. td, *J* = 7.5, 1.5 Hz, 1 H, ArH),

7.25 (app. td, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.41 - 7.50 (m, 4 H, 4 x ArH), 7.50 - 7.54 (m, 1 H, ArH), 7.61 - 7.67 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.5, 110.1, 113.3, 119.3, 120.0, 122.6, 125.1, 125.2, 129.7, 129.9, 131.3, 135.9, 138.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3049, 2914, 1595, 1490, 1454, 1386, 1371, 1355, 1309, 1228, 1091, 1070, 831, 734. ***m/z* (EI)** 243.1 (M^+, 47), 242.1 (65), 241.1 (M^+, 98), 240.1 (100), 204.1 (40), 191.1 (7), 176.1 (7), 165.1 (4), 151.1 (4), 139.1 (2), 128.1 (36), 111.0 (23), 102.2 (48), 89.1 (10), 75.1 (53), 63.1 (15), 51.1 (19). **HRMS (CI)** calcd. for $C_{15}H_{13}NCl^+$ ([M+H]$^+$): 242.0737 and 244.0711, found: 242.0733 and 244.0709 (3:1 ratio), and 241.0660 and 243.0693 (M^+). The data for this compound are consistent with those reported in the literature.[273]

Preparation of 3-(Pent-4-en-1-yl)-1-phenyl-1*H*-indole (521)



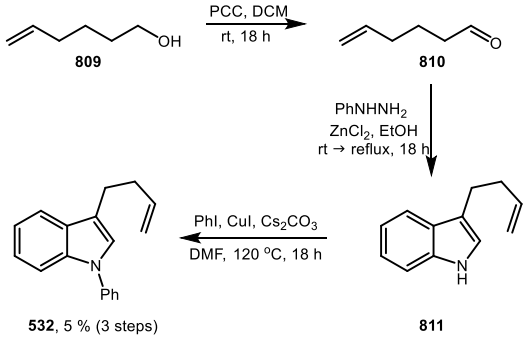
The first step was carried out according to a literature procedure.[274] A solution of 7-bromoheptene **806** (1.52 mL, 9.97 mmol, 1.0 equiv.), sodium carbonate (1.06 g, 10.0 mmol, 1.0 equiv.) and potassium iodide (1.66 g, 10.0 mmol, 1.0 equiv.) in DMSO (50 mL) was heated at 85 °C for 18 h. After cooling to room temperature, the mixture was diluted with diethyl ether and washed with sodium carbonate, water and brine. The combined organic layers were dried over Na_2SO4 and filtered. Careful removal of solvent under reduced pressure afforded 6-heptenal **807** as a colourless oil which was used with no further purification.

To a three-necked flask under argon, equipped with a stirrer bar and fitted with a condenser was added crude 6-heptenal **807** and phenylhydrazine **88** (0.98 mL, 9.95 mmol, 1.0 equiv.). This mixture was stirred for 1 h at room temperature then for 30 min at 100 °C. Zinc chloride (2.45 g, 18 mmol, 1.8 equiv.) in ethanol (11 mL) was then added and the mixture was refluxed for 18 h. After cooling to room temperature, the mixture was filtered and the solvent was removed under reduced pressure. Hydrochloric acid (2 M) was added to the crude residue and the organic products were extracted into DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 19:1 → 9:1) afforded 3-(pent-4-en-1-yl)-1*H*-indole **808** as an impure orange oil (395 mg) which was used without purification. The crude ^{1}H NMR and GC-MS data of this compound were consistent with those reported in the literature.[275] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.76 - 1.94 (m, 2 H, CH_2), 2.12 - 2.30 (m, 2 H, CH_2), 2.73 - 2.89 (m, 2 H, CH_2), 5.00 - 5.06 (m, 1 H, CH), 5.10 (app. dq, *J* = 17.2, 1.7 Hz, 1 H, CH), 5.93 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1 H, CH), 6.97 - 7.01 (m, 1 H,

ArH), 7.13 - 7.19 (m, 1 H, ArH), 7.21 - 7.26 (m, 1 H, ArH), 7.60 - 7.71 (m, 1 H, ArH), 7.88 (br. s., 1 H, NH). GC-MS (*m/z* = 185.2, retention time = 13.727 min).

The Ullmann coupling was carried out according to General Procedure F from 3-(pent-4-en-1-yl)-1*H*-indole **808** (395 mg, 2.13 mmol, 1.1 equiv.) and iodobenzene (0.22 mL, 1.94 mmol, 1.0 equiv.) with copper (I) iodide (74 mg, 0.39 mmol, 0.2 equiv.) and cesium carbonate (1.26 g, 3.88 mmol, 2.0 equiv.) in DMF (4 mL). Purification by column chromatography (hexane) afforded 3-(pent-4-en-1-yl)-1-phenyl-1*H*-indole **521** as a colourless oil (184 mg, 7 % over three steps). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.88 (quin, *J* = 7.5 Hz, 2 H, CH_2), 2.14 - 2.31 (m, 2 H, CH_2), 2.75 - 2.92 (m, 2 H, CH_2), 5.01 (ddt, *J* = 10.3, 2.1, 1.2 Hz, 1 H, CH), 5.08 (dm, *J* = 17.2, 1.7 Hz, 1 H, CH), 5.77 - 6.01 (m, 1 H, CH), 7.16 (s, 1 H, ArH), 7.19 (dd, *J* = 7.7, 1.1 Hz, 1 H, ArH), 7.21 - 7.26 (m, 1 H, ArH), 7.30 - 7.39 (m, 1 H, ArH), 7.49 - 7.55 (m, 4 H, 4 x ArH), 7.58 (app. dt, *J* = 8.1, 1.0 Hz, 1 H, ArH), 7.67 (app. dq, *J* = 7.7, 0.7 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 24.5, 29.2, 33.6, 110.5, 114.7, 117.7, 119.3, 119.7, 122.3, 124.0, 125.0, 125.9, 129.1, 129.5, 136.1, 138.8, 140.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3057, 2926, 1637, 1595, 1498, 1454, 1377, 1317, 1228, 1132, 1014, 989, 906, 773, 694. ***m/z* (EI)** 261.2 (M^+, 17), 219.1 (11), 206.2 (100), 178.2 (14), 128.1 (21), 115.1 (9), 102.2 (7), 77.1 (27), 55.1 (36). **HRMS (CI)** calcd. for $C_{19}H_{20}N^+$ ([M+H]$^+$): 262.1590, found: 262.1595.

Preparation of 3-(But-3-en-1-yl)-1-phenyl-1*H*-indole (532)



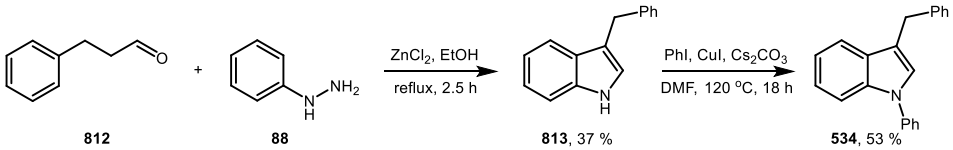
The first step was carried out according to a literature procedure.[276] A solution of 5-hexen-1-ol **809** (5.0 mL, 42 mmol, 1.0 equiv.) in DCM (20 mL) was added to a suspension of pyridinium chlorochromate (13.4 g, 62.0 mmol, 1.5 equiv.) in DCM (60 mL) at 0 °C. The mixture was then stirred at room temperature for 18 h before diluting with diethyl ether and filtering through a pad of silica gel. Careful removal of solvent under reduced pressure afforded 5-hexenal **810** as a colourless oil, which was used crude with no further purification.

To a three-necked flask under argon and equipped with a stirrer bar and fitted with a condenser was added crude 5-hexenal **810** and phenylhydrazine **88** (4.13 mL, 41.9 mmol, 1.0 equiv.). This mixture was stirred for 1 h at room temperature then for 30 min at 100 °C. Zinc chloride (10.3 g, 75.6 mmol, 1.8 equiv.) in ethanol (46 mL) was then added and the mixture was refluxed for 18 h. After cooling to room temperature, the mixture was filtered and the solvent was removed under

reduced pressure. Hydrochloric acid (2 M) was added to the crude residue and the organic products were extracted into DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 19:1 → 9:1) afforded 3-(but-3-en-1-yl)-1*H*-indole **811** as an impure red oil (526 mg). The crude ^{1}H NMR and GC-MS data were consistent with those reported in the literature.[277] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.51 (m, 2 H, CH_2), 2.85 - 2.95 (m, 2 H, CH_2), 5.02 (ddt, *J* = 10.1, 2.1, 1.2 Hz, 1 H, CH), 5.11 (app. dq, *J* = 17.2, 1.7 Hz, 1 H, CH), 5.97 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1 H, CH), 6.98 - 7.03 (m, 1 H, ArH), 7.11 - 7.17 (m, 1 H, ArH), 7.18 - 7.25 (m, 1 H, ArH), 7.37 (app. dt, *J* = 8.1, 0.8 Hz, 1 H, ArH), 7.61 - 7.67 (m, 1 H, ArH), 7.92 (br. s., 1 H, NH). GC-MS (*m/z* = 171.2, retention time = 13.2 min).

Ullmann coupling was carried out according to General Procedure F from 3-(but-3-en-1-yl)-1*H*-indole **811** (526 mg, 3.07 mmol, 1.1 equiv.) and iodobenzene **12** (0.31 mL, 2.79 mmol, 1.0 equiv.) with copper (I) iodide (106 mg, 0.56 mmol, 0.2 equiv.) and cesium carbonate (1.82 g, 5.58 mmol, 2 equiv.) in DMF (6 mL). Purification by column chromatography (hexane) afforded 3-(but-3-en-1-yl)-1-phenyl-1*H*-indole **532** as a colourless oil (438 mg, 5 % over three steps). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.48 - 2.62 (m, 2 H, CH_2), 2.88 - 2.99 (m, 2 H, CH_2), 5.04 (ddt, *J* = 10.3, 2.1, 1.1, Hz, 1 H, CH), 5.14 (dm, *J* = 17.1, 1.8 Hz, 1 H, CH), 5.99 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1 H, CH), 7.16 - 7.21 (m, 2 H, 2 x ArH), 7.22 - 7.27 (m, 1 H, ArH), 7.29 - 7.39 (m, 1 H, ArH), 7.48 - 7.54 (m, 4 H, 4 x ArH), 7.56 - 7.61 (m, 1 H, ArH), 7.68 (app. dq, *J* = 7.8, 0.7 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 24.6, 34.1, 110.5, 114.8, 117.3, 119.2, 119.8, 122.4, 124.1, 125.1, 126.0, 129.0, 129.5, 136.0, 138.6, 140.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3057, 2918, 1639, 1595, 1498, 1454, 1379, 1379, 1317, 1228, 1134, 1072, 1014, 993, 906, 773, 694. ***m/z* (EI)** 247.2 (M^+, 12), 206.2 (100), 178.2 (13), 128.1 (21), 115.1 (6), 102.1 (8), 77.1 (34), 51.0 (18). **HRMS (CI):** calcd. for $C_{18}H_{18}N^+$ ([M+H]$^+$): 248.1439, found: 248.1435.

Preparation of 3-Benzyl-1-phenyl-1*H*-indole (534)



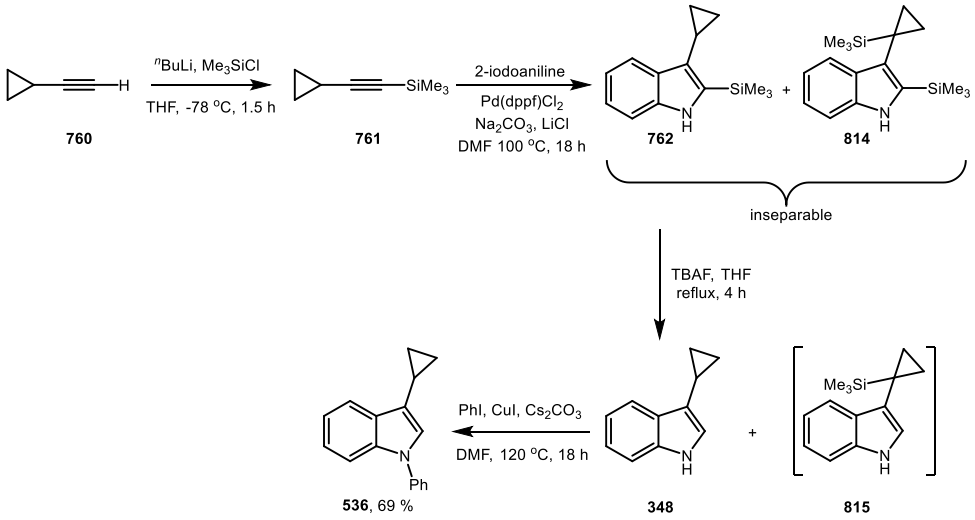
812 **88** **813**, 37 % **534**, 53 %

Step 1 was carried out according to General Procedure E from 3-phenylpropionaldehyde **812** (1.32 mL, 9.94 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) followed by recrystallisation from hexane afforded 3-benzyl-1*H*-indole **813** as a red solid (762 mg, 37 %). **Mp** = 96-98 °C (lit. mp = 101-102 °C).[278] **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.14 (s, 2 H, CH_2), 6.91 - 6.95 (m, 1 H, ArH), 7.06 - 7.13 (m, 1 H, ArH), 7.16 - 7.23 (m, 2 H, 2 x ArH), 7.28 - 7.33 (m, 4 H, 4 x ArH), 7.37 (app. dt, *J* = 8.2, 0.8 Hz, 1 H, ArH), 7.54 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 7.96 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 31.6, 111.0, 115.9, 119.1, 119.3, 122.0, 122.3, 125.9, 127.5, 128.3, 128.7, 136.5, 141.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3396, 3051, 3022, 2904, 1598, 1490, 1454, 1336, 1220, 1087, 1074, 987, 925, 908, 798, 756, 707, 694. ***m/z* (EI)** 207.2

(M^+, 52), 178.2 (13), 130.1 (100), 102.2 (15), 89.0 (15), 77.1 (48), 63.1 (20), 51.1 (26). The data for this compound are consistent with those reported in the literature.[224]

Step 2 was carried out according to General Procedure F from 3-benzyl-1*H*-indole **813** (750 mg, 3.61 mmol, 1.1 equiv.), and iodobenzene **12** (0.37 mL, 3.29 mmol, 1.0 equiv.), with copper (I) iodide (126 mg, 0.66 mmol, 0.2 equiv.) and cesium carbonate (2.14 g, 6.58 mmol, 2 equiv.) in DMF (6 mL). Purification by column chromatography (hexane) afforded 3-benzyl-1-phenyl-1*H*-indole **534** as a yellow oil (493 mg, 53 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.19 (s, 2 H, CH_2), 7.09 (s, 1 H, ArH), 7.16 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H, ArH), 7.20 - 7.27 (m, 2 H, 2 x ArH), 7.29 - 7.40 (m, 5 H, 5 x ArH), 7.48 - 7.54 (m, 4 H, 4 x ArH), 7.60 (app. ddt, *J* = 8.2, 6.3, 0.9, 0.9 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 31.5, 110.5, 116.9, 119.5, 120.0, 122.5, 124.1, 126.0, 126.1, 126.1, 128.4, 128.8, 128.9, 129.5, 136.2, 139.9, 140.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3022, 2899, 1595, 1496, 1452, 1367, 1317, 1296, 1222, 1072, 1028, 1014, 906, 767, 734, 688. ***m/z* (EI)** 283.2 (M^+, 91), 206.1 (100), 178.2 (24), 152.1 (8), 128.1 (19), 91.0 (13), 77.1 (77), 51.1 (42). The data for this compound are consistent with those reported in the literature.[238]

Preparation of 3-Cyclopropyl-1-phenyl-1*H*-indole (536)



The first three steps were carried out according to a literature procedure.[4] To a stirring solution of cyclopropylacetylene **760** (1.27 mL, 15.0 mmol, 1.00 equiv.) in dry THF (5 mL) at -78 °C was added ^{n}BuLi (10.7 mL of a 1.45 M solution in hexane, 15.45 mmol, 1.03 equiv.) dropwise. The solution was allowed to stir for 30 min at this temperature, after which chlorotrimethylsilane (1.98 mL, 15.6 mmol, 1.04 equiv.) was added. The reaction mixture was then stirred at -78 °C for 1 h. The reaction mixture was then warmed to room temperature, diluted with Et_2O and filtered through a pad of Na_2SO_4 layered on silica gel, eluting with pentane: diethyl ether (4:1). The filtrate was concentrated under reduced pressure to afford (cyclopropylethynyl)trimethylsilane **761**, which was used without further purification.

Pd(dppf)Cl_2 (817 mg, 10.0 mmol, 0.10 equiv.), (cyclopropylethynyl)trimethylsilane **761** (1.52 g, 11.0 mmol, 1.10 equiv.), 2-iodoaniline (2.19 g, 10.0 mmol, 1.00 equiv.), sodium carbonate (3.18 g, 30.0 mmol, 3.00 equiv.) and lithium chloride (445 mg, 10.5 mmol, 1.05 equiv.) in DMF (200 mL) under argon were heated at 100 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O and washed with aqueous ammonium chloride and water. The organic layer was then dried over Na_2SO_4, filtered and concentrated to afford an inseparable mixture of 2-(trimethylsilyl)-3-(1-(trimethylsilyl)cyclopropyl)-1*H*-indole **814** and 3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole **762** (1.5:1 ratio, 777 mg) which was carried on to the next step as a mixture (GC-MS retention times 15.105 and 14.276 min respectively). The ratio was calculated by comparing the integration of aromatic doublets in the proton NMR (7.70-7.75 ppm and 7.30-7.36 ppm). The relevant part of the ^{1}H NMR spectrum is shown below.

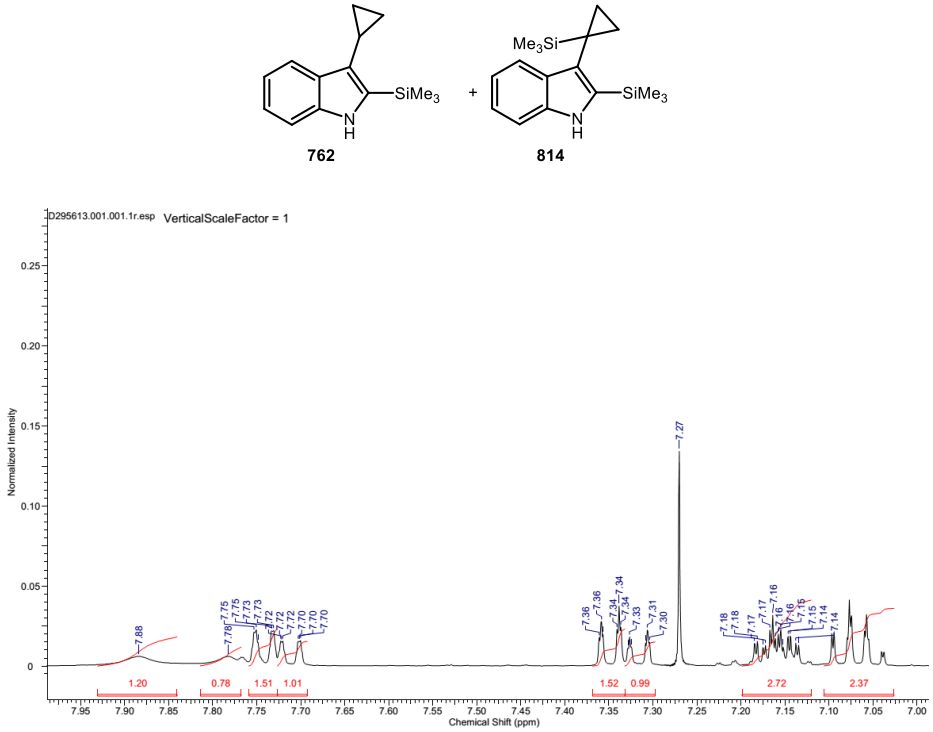


*Figure 14 - ^{1}H NMR Spectrum of the Mixture of **762** and **814***

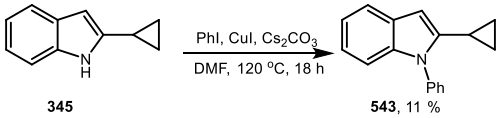
Also isolated after column chromatography was 3-cyclopropyl-1*H*-indole **348** as an orange solid (97 mg, 6 %). The data for this compound were consistent with those reported above.

To the inseparable mixture of 2-(trimethylsilyl)-3-(1-(trimethylsilyl)cyclopropyl)-1*H*-indole **814** and 3-cyclopropyl-2-(trimethylsilyl)-1*H*-indole **762** (777 mg, ~3.39 mmol, 1.0 equiv.) was added tetra-*n*-butylammonium fluoride (464 mg, 4.98 mmol, 1.5 equiv.) in THF (7 mL). This mixture was refluxed for 4 h before quenching with water and extracting into DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 49:1 → 19:1) afforded 3-(1-(trimethylsilyl)cyclopropyl)-1H-indole **815** as a yellow solid (141 mg, 6 %). **Mp** = 100-103 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) –0.03 (s, 9 H, $SiMe_3$), 0.77 - 0.90 (m, 4 H, 2 x CH_2), 6.94 (d, *J* = 2.3 Hz,

1 H, ArH), 7.12 (app. t, *J* = 7.5 Hz, 1 H, ArH), 7.19 (app. t, *J* = 7.5 Hz, 1 H, ArH), 7.33 (d, *J* = 8.1 Hz, 1 H, ArH), 7.73 (d, *J* = 7.9 Hz, 1 H, ArH), 7.82 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) –2.9, 4.2, 9.3, 110.9, 118.8, 120.1, 121.4, 121.6, 123.0, 128.4, 135.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3414, 3068, 2995, 2953, 2895, 1616, 1454, 1328, 1242, 1157, 1089, 904, 804, 763. ***m/z* (EI)** 229.2 (M^+, 36), 214.2 (13), 200.1 (6), 174.1 (15), 156.2 (98), 141.1 (7), 129.1 (38), 115.1 (15), 73.1 (100), 58.1 (13). **HRMS (CI)** calcd. for $C_{14}H_{20}NSi^+$ ($[M+H]^+$): 230.1365, found: 230.1366. Also isolated was 3-cyclopropyl-1*H*-indole **348** (160 mg, 10 % over three steps), with data consistent with those reported above.

The Ullmann coupling was carried out according to General Procedure F from 3-cyclopropyl-1*H*-indole **348** (250 mg, 1.59 mmol, 1.1 equiv.) and iodobenzene **12** (0.16 mL, 1.44 mmol, 1.0 equiv.), with copper (I) iodide (94.0 mg, 0.29 mmol, 0.2 equiv.) and cesium carbonate (548 mg, 2.88 mmol, 2.0 equiv.) in DMF (1.5 mL). Purification by column chromatography (hexane) afforded 3-cyclopropyl-1-phenyl-1*H*-indole **536** as a colourless oil, which solidified to a waxy solid (233 mg, 69 %). **Mp** = 37-40 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.67 - 0.75 (m, 2 H, CH_2), 0.89 - 1.00 (m, 2 H, CH_2), 1.94 - 2.08 (m, 1 H, CH), 7.06 (d, *J* = 1.0 Hz, 1 H, ArH), 7.19 (app. td, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.24 (app. td, *J* = 7.0, 1.5 Hz, 1 H, ArH), 7.30 - 7.37 (m, 1 H, ArH), 7.45 - 7.54 (m, 4 H, 4 x ArH), 7.56 (app. dt, *J* = 8.2, 0.9 Hz, 1 H, ArH), 7.76 - 7.83 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 6.0, 6.1, 110.5, 119.5, 119.8, 120.2, 122.5, 124.0, 124.2, 126.0, 129.5, 129.6, 136.1, 139.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3041, 3001, 1595, 1496, 1454, 1398, 1373, 1309, 1220, 1134, 1020, 869, 773, 648. ***m/z* (EI)** 233.2 (M^+, 70), 218.2 (7), 206.2 (37), 154.1 (20), 128.1 (45), 116.1 (13), 104.1 (15), 89.1 (15), 77.1 (100), 63.0 (12), 51.1 (66). **HRMS (CI)** calcd. for $C_{17}H_{16}N^+$ ($[M+H]^+$): 234.1283, found: 234.1280.

Preparation of 2-Cyclopropyl-1-phenyl-1*H*-indole (**543**)

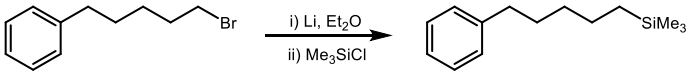


345 **543**, 11 %

This substrate was prepared according to General Procedure F from 2-cyclopropyl-1*H*-indole **345** (865 mg, 5.50 mmol, 1.1 equiv.) and iodobenzene **12** (0.56 mL, 5.02 mmol, 1.0 equiv.) with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.26 g, 10.0 mmol, 2.0 equiv.) in DMF (10 mL). Purification by column chromatography (hexane) afforded 2-cyclopropyl-1-phenyl-1*H*-indole **543** as a yellow oil (146 mg, 11 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.74 - 0.83 (m, 2 H, CH_2), 0.83 - 0.94 (m, 2 H, CH_2), 1.65 - 1.77 (m, 1 H, CH), 6.21 (app. br. s., 1 H, ArH), 7.06 - 7.17 (m, 3 H, 3 x ArH), 7.41 - 7.51 (m, 3 H, 3 x ArH), 7.52 - 7.60 (m, 3 H, 3 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 8.3, 8.3, 97.3, 109.9, 119.8, 120.0, 121.1, 127.5, 128.0, 128.1, 129.3, 138.2, 138.2, 144.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3080, 3051, 3007, 1595, 1552, 1498, 1454, 1400, 1346, 1296, 1217, 1153, 1014, 883, 827, 758, 744, 715, 663, 628. ***m/z* (EI)** 233.1 (M^+, 100), 218.1 (29), 206.1 (49), 190.1 (3), 178.1 (4), 165.1 (4), 154.1 (8), 140.1 (3), 130.0 (13), 118.1 (10), 108.6 (16),

89.0 (6), 77.0 (16), 63.0 (7), 51.0 (12). The data for this compound are consistent with those reported in the literature.[279]

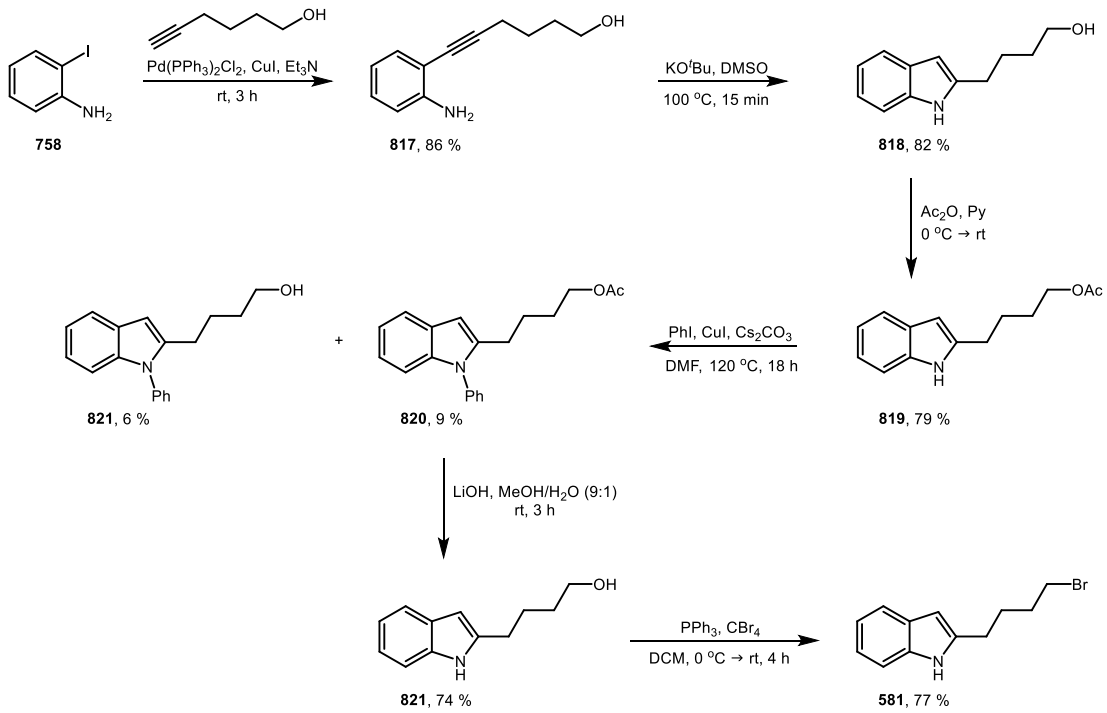
Preparation of Trimethyl(5-phenylpentyl)silane (569)



816 569

This substrate was prepared according to a literature procedure.[280] To a flask under nitrogen, equipped with a stirrer bar and a reflux condenser, was added lithium (38.0 mg, 5.50 mmol, 1.1 equiv.) and dry diethyl ether (10 mL) at room temperature. A few drops of (5-bromopentyl)benzene **816** (0.92 mL, 5.00 mmol, 1.0 equiv.) were added via syringe, and the reaction mixture was cooled to – 41 °C. The remaining alkyl bromide **816** was added dropwise with vigorous stirring, and the resulting mixture was stirred for 2 h at this temperature. Trimethylchlorosilane (0.70 mL, 5.50 mmol, 1.1 equiv.) was then added at room temperature via syringe and the mixture was allowed to reflux for 30 min, before quenching with saturated sodium chloride solution. The organic phase was separated, and the aqueous phase extracted twice more with diethyl ether. The combined ether phases were washed with water until neutral, then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane), afforded trimethyl(5-phenylpentyl)silane **569** as a colourless oil (143 mg, 13 %). **^{1}H-NMR** (400 MHz, CDCl3) – 0.02 (s, 9 H, $SiMe_3$), 0.46 - 0.54 (m, 2 H, CH_2), 1.29 - 1.43 (m, 4 H, 2 x CH_2), 1.64 (quin, *J* = 6.9 Hz, 2 H, CH_2), 2.61 (t, *J* = 7.8 Hz, 2 H, CH_2), 7.15 - 7.22 (m, 3 H, 3 x ArH), 7.28 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) –1.7, 16.6, 23.8, 31.2, 33.2, 35.9, 125.5, 128.2, 128.4, 143.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3027, 2923, 2854, 1604, 1496, 1453, 1246, 860, 832, 744, 696. ***m/z* (EI)** 220.0 (M^+, 6), 205.2 (28), 204.1 (26), 146.2 (28), 117.1 (6), 104.1 (16), 91.1 (82), 73.1 (100), 59.1 (67). **HRMS (CI)** calcd. for $C_{14}H_{25}Si^+$ ($[M+H]^+$): 221.1720, found: 221.1716.

Preparation of 2-(4-Bromobutyl)-1-phenyl-1H-indole (**581**)



The first step was carried out according to a modified literature procedure.[213] 5-Hexyn-1-ol (2.43 mL, 22.0 mmol, 1.1 equiv.) was added to a suspension of 2-iodoaniline **758** (4.38 g, 20.0 mmol, 1.0 equiv.), copper (I) iodide (46.0 mg, 0.24 mmol, 1.2 mol %), and $Pd(PPh_3)_2Cl_2$ (351 mg, 0.50 mmol, 2.5 mol %) in Et_3N (100 mL). The resulting mixture was stirred at room temperature for 3 h. Et_3N was then removed under reduced pressure, and the mixture was diluted with DCM and water. The organic layer was separated and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 4:1 → 1:1) afforded 6-(2-aminophenyl)hex-5-yn-1-ol **817** as an orange oil (3.26 g, 86 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.65 - 1.82 (m, 4 H, 2 x CH_2), 2.53 (t, *J* = 6.7 Hz, 2 H, CH_2), 3.19 (br. s., 3 H, NH_2 + OH), 3.72 (t, *J* = 6.0 Hz, 2 H, OCH_2), 6.64 - 6.75 (m, 2 H, 2 x ArH), 7.09 (app. td, *J* = 8.0, 1.5 Hz, 1 H, ArH), 7.25 (dd, *J* = 7.7, 1.4 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 19.4, 25.2, 31.9, 62.4, 95.3, 109.0, 114.4, 118.1, 128.9, 132.0, 147.3 – one carbon not observed due to overlap with the $CDCl_3$ signals.[281] **ATR-IR** ν_{max} (neat)/cm^{-1} 3367 (NH_2 not observed due to large, broad OH signal), 2935, 2864, 2243, 1612, 1490, 1454, 1305, 1157, 1056, 906, 727. ***m/z* (CI)** 190.1 ([M+H]$^+$). The data for this compound are consistent with those reported in the literature.[281]

The second step was carried out according to a modified literature procedure.[215] A solution of 6-(2-aminophenyl)hex-5-yn-1-ol **817** (3.16 g, 16.7 mmol, 1.0 equiv.) and KO^{t}Bu (4.68 g, 41.7 mmol, 2.5 equiv.) in DMSO (17 mL) were stirred under argon at 100 °C for 15 min. After cooling to room temperature, brine was added to the reaction mixture and the products were extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 3:7) afforded 4-(1*H*-indol-2-yl)butan-1-ol **818** as an orange oil (2.59 g, 82 %).

^{1}H-NMR (400 MHz, $CDCl_3$) 1.68 (quin, *J* = 6.3 Hz, 2 H, CH_2), 1.84 (quin, J=7.5 Hz, 2 H, CH_2), 2.83 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.71 (t, *J* = 6.5 Hz, 2 H, OCH_2), 6.25 (app. br. s., 1 H, ArH), 7.08 (app. t, *J* = 6.8 Hz, 1 H, ArH), 7.13 (app. td, *J* = 7.0, 1.0 Hz, 1 H, ArH), 7.31 (d, *J* = 7.8 Hz, 1 H, ArH), 7.53 (d, *J* = 7.5 Hz, 1 H, ArH), 8.03 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 25.5, 27.9, 32.0, 62.6, 99.7, 110.3, 119.6, 119.8, 121.0, 128.8, 135.9, 139.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3390, 3321, 2933, 1456, 1413, 1340, 1286, 1055, 950, 779, 748. ***m/z* (CI)** 190.1 ($[M+H]^+$). The data for this compound are consistent with those reported in the literature.[282]

Step three was carried out according to a modified literature procedure.[283] 4-(1*H*-Indol-2-yl)butan-1-ol **818** (2.59 g, 13.7 mmol, 1.0 equiv.) was dissolved in pyridine (5 mL) and the solution was cooled to 0 °C. Acetic anhydride (1.68 mL, 17.8 mmol, 1.3 equiv.) was added and the mixture was stirred at 0 °C for 10 min, and then at room temperature for 18 h. Incomplete conversion was observed, so another portion of acetic anhydride (0.25 mL, 2.64 mmol, 0.2 equiv.) was added and the reaction mixture was stirred for 6 h. A further portion of acetic anhydride (0.25 mL, 2.64 mmol, 0.2 equiv.) was then added, and the reaction was stirred overnight. Again, incomplete conversion was observed, so a further portion of acetic anhydride (0.25 mL, 2.64 mmol, 0.2 equiv.) was added and the reaction mixture was stirred for 2 h. The reaction mixture was then quenched with water and extracted into EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 4:1) afforded 4-(1*H*-indol-2-yl)butyl acetate **819** as a yellow oil (2.50 g, 79 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.68 - 1.88 (m, 4 H, 2 x CH_2), 2.07 (s, 3 H, CH_3), 2.82 (t, *J* = 7.3 Hz, 2 H, CH_2), 4.13 (t, *J* = 6.4 Hz, 2 H, OCH_2), 6.26 (s, 1 H, ArH), 7.03 - 7.10 (m, 1 H, ArH), 7.13 (app. td, *J* = 7.0, 1.3 Hz, 1 H, ArH), 7.31 (d, *J* = 8.0 Hz, 1 H, ArH), 7.54 (d, *J* = 7.8 Hz, 1 H, ArH), 7.95 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 21.0, 25.6, 27.7, 28.1, 64.1, 99.8, 110.3, 119.6, 119.8, 121.1, 128.8, 135.9, 139.0, 171.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3388, 2943, 1716, 1550, 1456, 1363, 1238, 1037, 779, 748. ***m/z* (EI)** 231.1 (M^+, 49), 188.1 (5), 170.1 (16), 156.1 (4), 144.1 (34), 130.0 (100), 117.1 (7), 103.1 (11), 89.0 (4), 77.0 (9), 63.0 (2), 51.0 (1). **HRMS (CI)** calcd. for $C_{14}H_{18}NO_2^+$ ($[M+H]^+$): 232.1338, found: 232.1339.

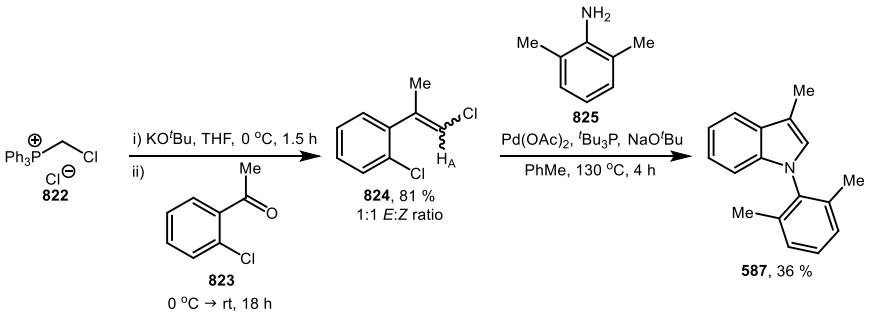
Step four was carried out according to General Procedure F from 4-(1*H*-indol-2-yl)butyl acetate **819** (2.24 g, 9.68 mmol, 1.1 equiv.) and iodobenzene (0.98 mL, 8.79 mmol, 1.0 equiv.), with copper (I) iodide (335 mg, 1.76 mmol, 0.2 equiv.) and cesium carbonate (5.73 g, 17.6 mmol, 2 equiv.) in DMF (19 mL). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 0:100) afforded 4-(1-phenyl-1*H*-indol-2-yl)butyl acetate **820** as a yellow oil (251 mg, 9 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.59 - 1.68 (m, 4 H, 2 x CH_2), 2.02 (s, 3 H, CH_3), 2.62 - 2.73 (m, 2 H, CH_2), 3.97 - 4.05 (m, 2 H, OCH_2), 6.44 (s, 1 H, ArH), 7.05 - 7.15 (m, 3 H, 3 x ArH), 7.32 - 7.38 (m, 2 H, 2 x ArH), 7.44 - 7.50 (m, 1 H, ArH), 7.52 - 7.58 (m, 2 H, 2 x ArH), 7.58 - 7.63 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 20.9, 24.9, 26.7, 28.1, 64.1, 100.5, 110.0, 119.7, 120.0, 121.2, 127.9, 128.0, 128.2, 129.5, 137.9, 138.3, 141.0, 171.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3053, 2949, 1734, 1595,

1545, 1496, 1456, 1390, 1363, 1234, 1037, 1014, 761, 746, 698. ***m/z* (EI)** 307.2 (M^+, 48), 264.1 (3), 246.2 (11), 220.1 (31), 206.1 (100), 191.1 (5), 178.1 (6), 165.1 (2), 152.1 (1), 130.1 (8), 117.1 (4), 102.1 (4), 89.0 (2), 77.0 (6), 63.0 (1), 51.0 (2). **HRMS (CI)** calcd. for $C_{20}H_{22}NO_2^+$ ($[M+H]^+$): 308.1651, found: 308.1649. Also isolated was 4-(1-phenyl-1*H*-indol-2-yl)butan-1-ol **821** as a yellow oil (180 mg, 6 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.53 - 1.62 (m, 2 H, CH_2), 1.62 - 1.73 (m, 2 H, CH_2), 2.68 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.59 (t, *J* = 6.3 Hz, 2 H, OCH_2), 6.44 (app. br. s., 1 H, ArH), 7.02 - 7.16 (m, 3 H, 3 x ArH), 7.31 - 7.40 (m, 2 H, 2 x ArH), 7.43 - 7.50 (m, 1 H, ArH), 7.51 - 7.56 (m, 2 H, 2 x ArH), 7.56 - 7.62 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 24.7, 26.8, 32.2, 62.6, 100.4, 110.0, 119.7, 120.0, 121.1, 127.9, 128.0, 128.3, 129.5, 138.0, 138.3, 141.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3336, 2935, 2862, 1595, 1545, 1496, 1456, 1392, 1315, 1209, 1149, 1070, 1014, 906, 731, 698. ***m/z* (EI)** 265.1 (M^+, 55), 220.1 (39), 206.1 (100), 194.1 (11), 178.1 (8), 165.1 (2), 152.1 (2), 140.1 (1), 128.1 (6), 117.1 (10), 102.1 (4), 89.0 (3), 77.0 (6), 63.0 (2), 51.0 (3). **HRMS (CI)** calcd. for $C_{18}H_{20}NO^+$ ($[M+H]^+$): 266.1545, found: 266.1545.

4-(1-Phenyl-1*H*-indol-2-yl)butyl acetate **820** (251 mg, 0.82 mmol, 1.0 equiv.) and LiOH (98.0 mg, 4.09 mmol, 5.0 equiv.) were dissolved in MeOH/H_2O (1 mL, 9:1) and the resulting mixture was stirred at room temperature for 3 h. The mixture was then diluted with water and extracted into DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 3:1) afforded 4-(1-phenyl-1*H*-indol-2-yl)butan-1-ol **821**, with data consistent with those reported above (160 mg, 74 %).

The final step was carried out according to a modified literature procedure.[284] 4-(1-Phenyl-1*H*-indol-2-yl)butan-1-ol **821** (340 mg, 1.28 mmol, 1.0 equiv.) and PPh_3 (367 mg, 1.40 mmol, 1.1 equiv.) were dissolved in DCM (2.5 mL) and the mixture was cooled to 0 °C. Carbon tetrabromide (463 mg, 1.40 mmol, 1.1 equiv.) was added, and the reaction was stirred at room temperature for 4 h and then concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 19:1) afforded 2-(4-bromobutyl)-1*H*-indole **581** as a pink oil (323 mg, 77 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.67 - 1.80 (m, 2 H, CH_2), 1.80 - 1.94 (m, 2 H, CH_2), 2.68 (t, *J* = 7.3 Hz, 2 H, CH_2), 3.34 (t, *J* = 6.7 Hz, 2 H, CH_2), 6.44 (s, 1 H, ArH), 7.04 - 7.15 (m, 3 H, 3 x ArH), 7.33 - 7.39 (m, 2 H, 2 x ArH), 7.44 - 7.51 (m, 1 H, ArH), 7.52 - 7.58 (m, 2 H, 2 x ArH), 7.58 - 7.62 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 26.2, 27.1, 32.1, 33.3, 100.6, 110.0, 119.7, 120.1, 121.3, 128.0, 128.2, 129.5, 137.9, 138.4, 140.7 – one carbon not observed due to overlap. **ATR-IR** ν_{max} (neat)/cm^{-1} 3053, 2939, 1595, 1496, 1454, 1392, 1313, 1219, 1151, 1072, 1016, 761, 746, 698. ***m/z* (EI)** 329.1 (M^+, 13), 327.1 (M^+, 13), 248.2 (33), 219.1 (28), 206.1 (100), 191.1 (7), 178.1 (7), 165.1 (3), 152.1 (3), 128.1 (7), 115.1 (7), 102.2 (7), 77.0 (14), 63.1 (3), 51.1 (10). **HRMS (CI)** calcd. for $C_{18}H_{19}NBr^+$ ($[M+H]^+$): 328.0701 and 330.0682, found: 328.0701 and 330.0682.

Preparation of 1-(2,6-Dimethylphenyl)-3-methyl-1*H*-indole (**587**)



This substrate was prepared according to a modified literature procedure.[285] To a suspension of (chloromethyl)triphenylphosphonium chloride **822** (1.60 g, 4.60 mmol, 1.2 equiv.) in dry THF (4 mL) at 0 °C was added a solution of potassium *tert*-butoxide (516 mg, 4.60 mmol, 1.2 equiv.) in dry THF (17 mL). The solution was stirred at this temperature for 1.5 h, and then 2'-chloroacetophenone **823** (0.50 mL, 3.84 mmol, 1.0 equiv.) was added. The reaction was stirred at room temperature for 18 h. Petroleum ether was added to the reaction mixture, and the contents were passed through a celite plug, eluting with petroleum ether. The mixture was then concentrated under reduced pressure. Purification by column chromatography (hexane) afforded (*E*/*Z*)-1-chloro-2-(1-chloroprop-1-en-2-yl)benzene **824** as a colourless oil (581 mg, 81 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.07 (d, *J* = 1.8 Hz, 3 H, CH_3 of *Z*-isomer), 2.16 (d, *J* = 1.3 Hz, 3 H, CH_3 of *E*-isomer), 6.09 (q, *J* = 1.3 Hz, 1 H, CH of *E*-isomer), 6.18 (q, *J* = 1.0 Hz, 1 H, CH of *Z*-isomer), 7.13 - 7.21 (m, ArH [two signals]), 7.21 - 7.27 (m, ArH [two signals]), 7.27 - 7.33 (m, ArH [two signals]), 7.36 - 7.41 (m, ArH [one signal]), 7.41 - 7.46 (m, ArH [one signal]). **^{13}C-NMR** (101 MHz, $CDCl_3$) 18.2, 22.3, 115.2, 118.1, 126.8, 126.9, 128.9, 129.0, 129.6, 129.4, 129.8, 130.1, 132.0, 132.6, 137.6, 138.1, 138.3, 140.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3068, 2970, 2919, 1631, 1591, 1566, 1471, 1427, 1375, 1325, 1257, 1232, 1205, 1126, 1089, 1041, 985, 943, 831, 806, 746, 727, 682, 669. ***m/z* (EI)** 188.0 (M^+, 34), 186.0 (M^+, 53), 153.0 (17), 151.0 (51), 137.0 (29), 125.0 (4), 115.1 (100), 101.1 (13), 89.0 (16), 75.0 (23), 63.0 (18), 51.0 (15). The *E*:*Z* ratio was determined by comparison of the integrals for H_A for the *Z*-isomer [6.18 ppm (q, *J* = 1.0 Hz, 1 integral units)] to the *E*-isomer [6.09 ppm (q, *J* = 1.3 Hz, 1 integral unit]. The relevant part of the ^{1}H NMR spectrum is shown below. The data for this compound are consistent with those reported in the literature.[270] Also isolated was recovered starting material **823**, with data consistent with the commercial material (116 mg, 19 %).

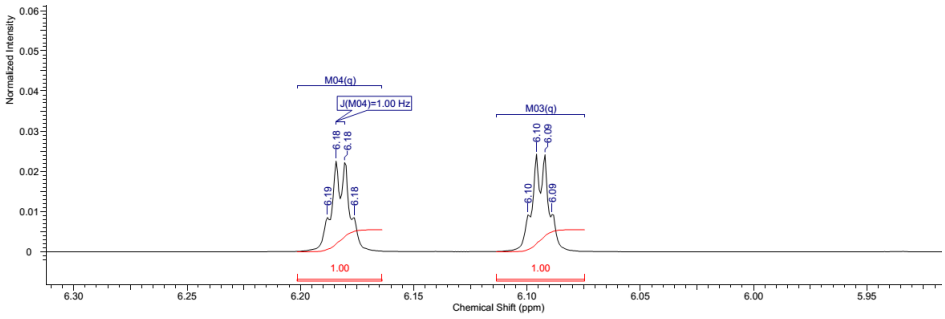
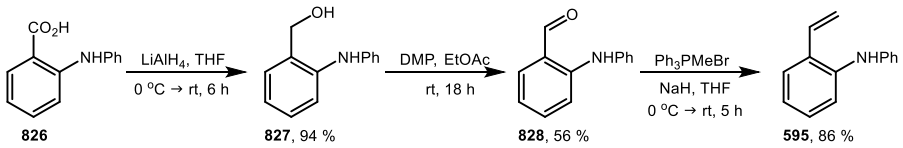


*Figure 15 - ^{1}H NMR Spectrum Showing the E/Z Ratio of **824***

To a pressure tube in a glovebox under nitrogen was added (*E*/*Z*)-1-chloro-2-(1-chloroprop-1-en-2-yl)benzene **824** (580 mg, 3.08 mmol, 1 equiv.), palladium (II) acetate (70.0 mg, 0.31 mmol, 0.1 equiv.), tri-*tert*-butylphosphine (188 mg, 0.93 mmol, 0.3 equiv.) and sodium *tert*-butoxide (745 mg, 7.75 mmol, 2.5 equiv.). A solution of 2,6-dimethylaniline **825** (1.15 mL, 9.34 mmol, 3.0 equiv.) in dry toluene (5 mL) was then added, and the tube was sealed and removed from the glovebox. The mixture was stirred at 130 °C for 4 h behind a shield. After cooling to room temperature, the reaction mixture was filtered through celite eluting with toluene and concentrated under reduced pressure. Purification by column chromatography (hexane) afforded 1-(2,6-dimethylphenyl)-3-methyl-1*H*-indole **587** as a yellow oil (266 mg, 36 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.94 (s, 6 H, 2 x CH_3), 2.43 (d, *J* = 1.0 Hz, 3 H, CH_3), 6.80 - 6.87 (m, 2 H, 2 x ArH), 7.11 - 7.17 (m, 2 H, 2 x ArH), 7.17 - 7.22 (m, 2 H, 2 x ArH), 7.24 - 7.30 (m, 1 H, ArH), 7.62 - 7.69 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.7, 17.5, 110.0, 111.5, 118.9, 118.9, 121.9, 125.5, 128.2, 128.2, 128.4, 136.6, 137.2, 137.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3055, 2972, 2916, 1612, 1473, 1452, 1379, 1357, 1300, 1222, 1159, 1134, 1122, 1089, 1064, 1037, 1010, 987, 933, 920, 840, 808, 785, 734. ***m/z* (EI)** 235.1 (M^+, 100), 220.1 (49), 204.1 (27), 194.1 (4), 178.1 (3), 130.1 (7), 115.1 (5), 103.0 (15), 89.0 (4), 77.0 (23), 63.0 (5), 51.0 (7). **HRMS (CI)** calcd. for $C_{17}H_{18}N^+$ ($[M+H]^+$): 236.1439, found: 236.1432, and calcd. for $C_{17}H_{17}N^+$ (M^+): 235.1361, found 235.1357 (M^+).

Preparation of *N*-Phenyl-2-vinylaniline (595)



826 **827**, 94 % **828**, 56 % **595**, 86 %

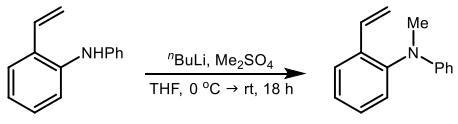
The first step was carried out according to a literature procedure.[286] A solution of *N*-phenylanthranilic acid **826** (2.13 g, 9.99 mmol, 1.0 equiv.) in dry THF (40 mL) was added to a stirred solution of $LiAlH_4$ in THF (10 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 6 h before quenching with EtOAc followed by NaOH. The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 9:1) afforded (2-(phenylamino)phenyl)methanol **827** as an orange solid (1.88 g, 94 %). **Mp** = 55-56 °C (lit. mp = 59-62 °C).[287] **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.74 (s, 2 H, CH_2), 6.87 - 6.98 (m, 2 H, 2 x ArH), 7.06 - 7.12 (m, 2 H, 2 x ArH), 7.19 - 7.33 (m, 4 H, 4 x ArH), 7.39 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 64.6, 117.0, 118.2, 120.5, 120.9, 128.5, 129.2, 129.3, 129.6, 143.0, 143.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3401, 1591, 1516, 1494, 1454, 1294, 1172, 1040, 880, 694. ***m/z* (EI)** 199.1 (M^+, 7), 180.2 (100), 167.0 (6), 101.9 (11), 90.1 (9), 77.0 (27), 64.5 (15), 51.0 (17). The data for this compound are consistent with those reported in the literature.[288]

The second step was carried out according to a modified literature procedure.[286] To a solution of Dess-Martin Periodinane (DMP) (10.0 g, 23.6 mmol, 2.5 equiv.) in EtOAc (190 mL) was added

(2-[(phenylamino)phenyl]methanol **877** (1.88 g, 9.44 mmol, 1.0 equiv.). The resulting mixture was stirred for 18 h at room temperature before being filtered and the solid washed with EtOAc. The filtrate was then concentrated under reduced pressure and purified by column chromatography (hexane:diethyl ether, 19:1) to afford 2-(phenylamino)benzaldehyde **828** as a yellow solid (1.05 g, 56 %). **Mp** = 63-65 °C (lit. mp = 71-72 °C).[288] **^{1}H-NMR** (400 MHz, $CDCl_3$) 6.80 - 6.88, (m, 1 H, ArH), 7.12 - 7.20 (m, 1 H, ArH), 7.24 (d, *J* = 8.5 Hz, 1 H, ArH), 7.27 - 7.33 (m, 2 H, 2 x ArH), 7.34 - 7.43 (m, 3 H, 3 x ArH), 7.58 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArH), 9.92 (d, *J* = 1.0 Hz, 1 H, CHO), 10.02 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 112.9, 117.1, 119.4, 123.2, 124.4, 129.4, 135.5, 136.6, 139.7, 147.8, 194.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3271, 3035, 2835, 1649, 1591, 1572, 1517, 1450, 1421, 1396, 1317, 1184, 1157, 1116, 898, 698, 693. ***m/z* (EI)** 197.2 (M^+, 56), 168.2 (100), 139.1 (10), 115.1 (9), 93.1 (11), 77.1 (26), 65.1 (16), 51.1 (39). The data for this compound are consistent with those reported in the literature.[288]

To a suspension of sodium hydride (312 mg, 13.0 mmol, 2.6 equiv.) in dry THF (50 mL) was added methyltriphenylphosphonium bromide (4.47 g, 12.5 mmol, 2.5 equiv.) at 0 °C. The mixture was then stirred at this temperature for 30 min before the addition of 2-(phenylamino)benzaldehyde **828** (986 mg, 5.00 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature for 5 h before being quenched with water and extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:diethyl ether, 49:1) afforded *N*-phenyl-2-vinylaniline **595** as a yellow oil (835 mg, 86 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 5.33 (dd, *J* = 11.0, 1.5 Hz, 1 H, CH), 5.54 (br. s., 1 H, NH), 5.70 (dd, *J* = 17.4, 1.4 Hz, 1 H, CH), 6.85 - 6.98 (m, 4 H, 3 x ArH + CH), 7.00 - 7.06 (m, 1 H, ArH), 7.18 - 7.29 (m, 4 H, 4 x ArH), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 116.2, 117.1, 120.0, 120.4, 122.5, 127.1, 128.6, 129.3, 130.0, 132.8, 140.0, 144.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 3389, 1593, 1494, 1452, 1298, 1174, 993, 910, 690. ***m/z* (EI)** 195.2 (M^+, 100), 194.2 (100), 180.1 (76), 167.2 (25), 152.1 (7), 139.1 (6), 128.1 (5), 118.1 (41), 102.1 (6), 91.1 (29), 83.7 (8), 77.1 (47), 65.1 (23), 51.1 (54). The data for this compound are consistent with those reported in the literature.[289]

Preparation of *N*-Methyl-*N*-phenyl-2-vinylaniline (599)

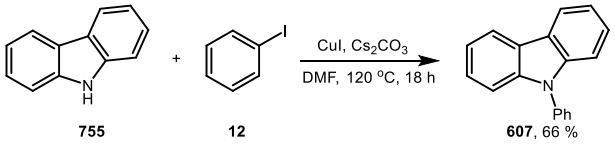


595 **599**, 92 %

This substrate was prepared according to a modified literature procedure.[290] *N*-phenyl-2-vinylaniline **595** was prepared according to the above procedure. Compound **595** (391 mg, 2.00 mmol, 1.0 equiv.) was then dissolved in dry THF (5 mL) under argon, and the flask was cooled to 0 °C. ^{n}BuLi (2.5 M solution in hexanes, 0.88 mL, 2.20 mmol, 1.1 equiv.) was added dropwise, and the mixture was stirred at this temperature for 30 mins. Dimethylsulfate (0.28 mL, 2.95 mmol, 1.5 equiv.) was then added and the mixture was allowed to warm to room temperature

with stirring for 18 h. The mixture was then diluted with water and extracted into diethyl ether. The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 5:95) afforded *N*-methyl-*N*-phenyl-2-vinylaniline **599** as a yellow oil (385 mg, 92 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 3.22 (s, 3 H, NMe), 5.23 (dd, *J* = 11.1, 1.3 Hz, 1 H, CH), 5.75 (dd, *J* = 17.7, 1.2 Hz, 1 H, CH), 6.58 - 6.64 (m, 2 H, 2 x ArH), 6.74 (app. t, *J* = 7.3 Hz, 1 H, ArH), 6.80 (dd, *J* = 17.8, 11.2 Hz, 1 H, CH), 7.14 - 7.22 (m, 3 H, 3 x ArH), 7.27 - 7.36 (m, 2 H, 2 x ArH), 7.68 (dd, *J* = 7.5, 1.8 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 39.7, 113.4, 115.1, 117.2, 126.4, 126.5, 128.5, 128.9, 129.3, 133.1, 136.2, 146.3, 149.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3059, 3024, 2926, 2868, 1591, 1496, 1485, 1448, 1340. 1298, 1249, 1186, 1155, 1186, 1136, 1097, 989, 910, 864, 761, 690. ***m/z* (EI)** 209.2 (M^+, 93), 194.1 (100), 180.1 (11), 167.1 (19), 152.1 (7), 140.1 (3), 132.1 (13), 117.1 (11), 104.1 (6), 91.1 (19), 77.0 (27), 63.0 (7), 51.1 (20). **HRMS (CI)** calcd. for $C_{15}H_{16}N^+$ ($[M+H]^+$): 210.1283, found: 210.1280. The data for this compound are consistent with those reported in the literature.[156]

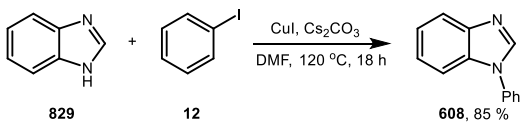
Preparation of 9-Phenyl-9*H*-carbazole (607)



755 **12** **607**, 66 %

This substrate was prepared according to General Procedure F from 9*H*-carbazole **755** (920 mg, 5.50 mmol, 1.1 equiv.) and iodobenzene **12** (0.56 mL, 5.02 mmol, 1.0 equiv.) with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.25 g, 10.0 mmol, 2.0 equiv.) in DMF (10 mL). Purification by column chromatography (petroleum ether) afforded 9-phenyl-9*H*-carbazole **607** as a white solid (805 mg, 66 %). **Mp** = 78-79 °C (lit. mp = 87-88 °C).[291] **^{1}H-NMR** (400 MHz, $CDCl_3$) 7.28 - 7.33 (m, 2 H, 2 x ArH), 7.40 - 7.44 (m, 4 H, 4 x ArH), 7.48 (app. t, *J* = 7.2 Hz, 1 H, ArH), 7.55 - 7.59 (m, 2 H, 2 x ArH), 7.59 - 7.66 (m, 2 H, 2 x ArH), 8.16 (d, *J* = 7.8 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 109.8, 119.9, 120.3, 123.4, 125.9, 127.2, 127.5, 129.9, 137.7, 140.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3061, 2924, 1595, 1498, 1477, 1450, 1334, 1311, 1232, 1178, 1026, 927, 744, 723, 694. ***m/z* (EI)** 243.0 (M^+, 100), 166.0 (11), 140.0 (20), 77.0 (17), 63.0 (4), 51.0 (18). The data for this compound are consistent with those reported in the literature.[292]

Preparation of 1-Phenyl-1*H*-benzo[*d*]imidazole (608)

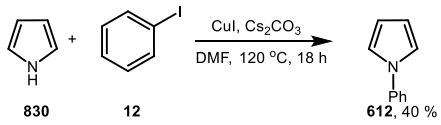


829 **12** **608**, 85 %

This substrate was prepared according to General Procedure F from benzimidazole **829** (650 mg, 5.50 mmol, 1.1 equiv.) and iodobenzene **12** (0.56 mL, 5.02 mmol, 1 equiv.) with copper (I) iodide

(190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.25 g, 10.0 mmol, 2.0 equiv.) in DMF (10 mL). Purification by column chromatography (hexane:ethyl acetate, 4:1 → 1:1) afforded 1-phenyl-1*H*-benzo[*d*]imidazole **608** as a viscous yellow oil (829 mg, 85 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 7.31 - 7.39 (m, 2 H, 2 x ArH), 7.45 - 7.51 (m, 1 H, ArH), 7.51 - 7.64 (m, 5 H, 5 x ArH), 7.87 - 7.93 (m, 1 H, ArH), 8.14 (s, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 110.5, 120.6, 122.8, 123.7, 124.1, 128.1, 130.1, 133.7, 136.4, 142.2, 144.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3055, 1597, 1498, 1452, 1288, 1228, 1203, 974, 785, 738, 692. ***m/z* (EI)** 194.1 (M^+, 100), 166.1 (8), 139.1 (8), 77.1 (14), 66.1 (8), 51.1 (13). The data for this compound are consistent with those reported in the literature.[293]

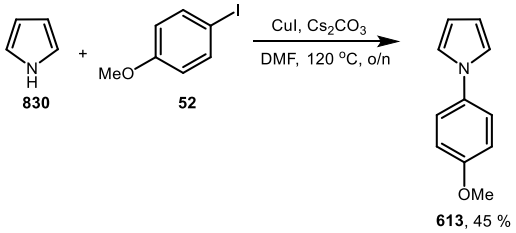
Preparation of 1-Phenyl-1*H*-pyrrole (612)



830 **12** **612**, 40 %

This substrate was prepared according to General Procedure F from 1*H*-pyrrole **830** (0.38 mL, 5.48 mmol, 1.1 equiv.) and iodobenzene **12** (0.56 mL, 5.02 mmol, 1.0 equiv.) with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.25 g, 10.0 mmol, 2.0 equiv.) in DMF (10 mL). Purification by column chromatography (hexane) afforded 1-phenyl-1*H*-pyrrole **612** as a white solid (286 mg, 40 %). **Mp** = 53-54 °C (lit. mp = 55-58 °C).[294] **^{1}H-NMR** (400 MHz, $CDCl_3$) 6.36 (app. t, *J* = 2.1 Hz, 2 H, 2 x ArH), 7.11 (app. t, *J* = 2.1 Hz, 2 H, 2 x ArH), 7.23 - 7.27 (m, 1 H, ArH), 7.36 - 7.48 (m, 4 H, 4 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 110.4, 119.3, 120.5, 125.6, 129.5, 140.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3140, 3045, 1693, 1600, 1508, 1400, 1325, 1188, 1130, 1068, 1014, 918, 756, 717, 678. ***m/z* (EI)** 143.1 (M^+, 100), 115.1 (73), 104.1 (7), 89.0 (8), 77.1 (22), 63.1 (7), 51.1 (22). The data for this compound are consistent with those reported in the literature.[295]

Preparation of 1-(4-Methoxyphenyl)-1H-pyrrole (613)



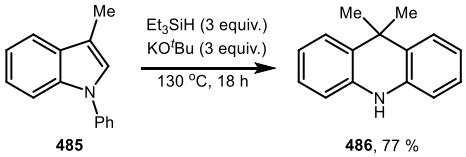
830 **52** **613**, 45 %

This substrate was prepared according to General Procedure F from 1*H*-pyrrole **830** (0.38 mL, 5.48 mmol, 1.1 equiv.) and 4-iodoanisole **52** (1.17 g, 5.00 mmol, 1.0 equiv.) with copper (I) iodide (190 mg, 1.00 mmol, 0.2 equiv.) and cesium carbonate (3.25 g, 10.0 mmol, 2.0 equiv.) in DMF (10 mL). Purification by column chromatography (hexane:ethyl acetate, 49:1) afforded 1-(4-methoxyphenyl)-1*H*-pyrrole **613** as a grey solid (392 mg, 45 %). **Mp** = 99-100 °C (lit. mp = 98-100 °C).[296] **^{1}H-NMR** (400 MHz, $CDCl_3$) 3.85 (s, 3 H, OCH_3), 6.33 (app. t, *J* = 2.1 Hz, 2 H, 2 x ArH), 6.93 - 6.99 (m, 2 H, 2 x ArH), 7.01 (app. t, *J* = 2.3 Hz, 2 H, 2 x ArH), 7.30 - 7.35 (m,

2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 55.6, 109.8, 114.6, 119.7, 122.2, 134.5, 157.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3142, 3012, 2933, 1516, 1400, 1323, 1305, 1257, 1242, 1186, 1128, 1028, 1006, 825, 717. ***m/z* (EI)** 173.1 (M^+, 79), 158.1 (100), 130.1 (55), 115.1 (4), 103.1 (25), 77.0 (24), 63.0 (12), 51.0 (10). The data for this compound are consistent with those reported in the literature.[297]

8.6 – Treating Substrates with Et_3SiH/KO^tBu System from Chapter 4

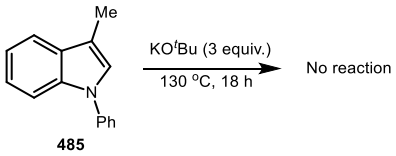
Treatment of 3-Methyl-1-phenyl-1*H*-indole (485) with Et_3SiH/KO^tBu



485 **486**, 77 %

This reaction was carried out according to General Procedure C from 3-methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1 → 4:1) afforded 9,9-dimethyl-9,10-dihydroacridine **486** as a white solid (81 mg, 77 %). **Mp** = 115-118 °C (lit. mp = 120 °C).[298] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.61 (s, 6 H, 2 x CH_3), 6.14 (br. s., 1 H, NH), 6.71 (d, *J* = 7.8 Hz, 2 H, 2 x ArH), 6.94 (app. t, *J* = 7.4 Hz, 2 H 2 x ArH), 7.12 (app. td, *J* = 7.5, 1.5 Hz, 2 H 2 x ArH), 7.40 (dd, *J* = 7.9, 1.4 Hz, 2 H 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 30.5, 36.2, 113.4, 120.6, 125.5, 126.7, 129.1, 138.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3358, 2957, 1605, 1580, 1477, 1450, 1317, 1242, 1213, 1036, 885, 711. ***m/z* (EI)** 209.1 (M^+, 10), 194.2 (100), 179.1 (5), 96.8 (8). The data for this compound are consistent with those reported in the literature.[298]

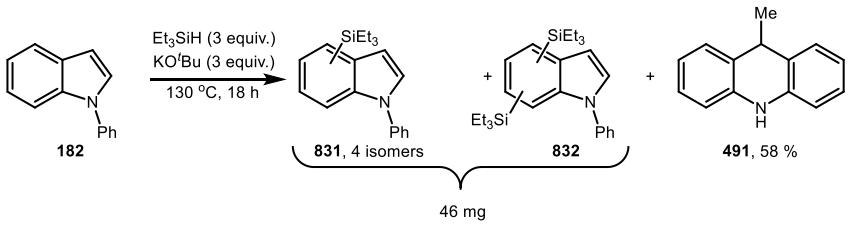
Treatment of 3-Methyl-1-phenyl-1*H*-indole (485) with KO^tBu Alone



485

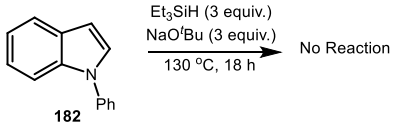
This reaction was carried out according to General Procedure D from 3-methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **485** was recovered with data consistent to those reported above (104 mg, 100 %).

Treatment of 1-Phenyl-1*H*-indole (**182**) with Et_3SiH/KO^tBu



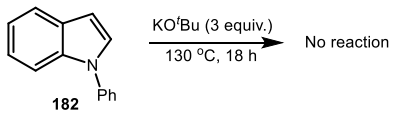
This reaction was carried out according to General Procedure C from 1-phenyl-1*H*-indole **182** (97.0 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded a complex mixture products from which silylated compounds **831** (four isomers) were tentatively identified. These compounds were inseparable from another compound which was tentatively identified as disilylated compound **832** (combined yield of **831** and **832** = 46 mg). These compounds were identified by GC-MS (*m/z* = 307.2, retention times = 15.162, 15.611, 15.743, and 15.962 min), and (*m/z* = 421.3, retention time = 17.564 min). Also isolated was 9-methyl-9,10-dihydroacridine **491** as a yellow solid (57 mg, 58 %). **Mp** = 120-123 °C (lit. mp = 123-125 °C).[299] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.38 (d, *J* = 7.3 Hz, 3 H, CH_3), 4.12 (q, *J* = 7.0 Hz, 1 H, CH), 6.04 (br. s., 1 H, NH), 6.72 (dd, *J* = 8.0, 1.0 Hz, 2 H, 2 x ArH), 6.91 (app. td, *J* = 7.4, 1.3 Hz, 2 H, 2 x ArH), 7.11 (app. td, *J* = 7.5, 1.5 Hz, 2 H, 2 x ArH), 7.19 (dd, *J* = 7.5, 0.8 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 26.4, 36.7, 113.4, 120.8, 125.7, 126.8, 128.2, 139.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3374, 2961, 2918, 1601, 1580, 1477, 1445, 1300, 1254, 1157, 1130, 1032, 887, 739. ***m/z* (EI)** 195.1 (M^+, 7), 193.1 (1), 180.0 (100), 152.1 (7). **HRMS (CI)** calcd. for $C_{14}H_{14}N^+$ ([M+H]$^+$): 196.1121, found: 196.1116.

Treatment of 1-Phenyl-1*H*-indole (**182**) with Et_3SiH/NaO^tBu



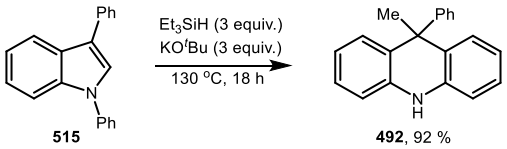
This reaction was carried out according to General Procedure C from 1-phenyl-1*H*-indole **182** (97.0 mg, 0.50 mmol, 1.0 equiv.), with NaO^tBu (144 mg, 1.50 mmol, 3.0 equiv.) instead of KO^tBu. No reaction was found to occur, and after column chromatography (hexane), **182** was recovered with data consistent to those reported above (86 mg, 89 %).

Treatment of 1-Phenyl-1*H*-indole (**182**) with KO^tBu Alone



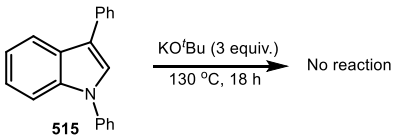
This reaction was carried out according to General Procedure D from 1-phenyl-1*H*-indole **182** (97.0 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **182** was recovered with data consistent to those reported above (95 mg, 98 %).

Treatment of 1,3-Diphenyl-1*H*-indole (515) with Et_3SiH/KO^tBu



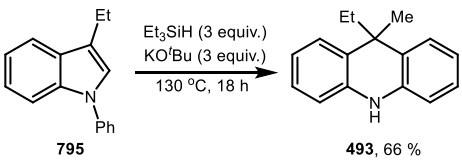
This reaction was carried out according to General Procedure C from 1,3-diphenyl-1*H*-indole **515** (135 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1 → 9:1) afforded 9-methyl-9-phenyl-9,10-dihydroacridine **492** as a yellow solid (125 mg, 92 %). **Mp** = 93-94 °C (lit. mp = 96 °C).[300] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.85 (s, 3 H, CH_3), 6.23 (s, 1 H, NH), 6.73 (dd, *J* = 7.7, 0.9 Hz, 2 H, 2 x ArH), 6.75 - 6.83 (m, 4 H, 4 x ArH), 7.05 - 7.13 (m, 2 H, 2 x ArH), 7.22 (m, 1 H, ArH), 7.28 - 7.34 (m, 2 H, 2 x ArH), 7.34 - 7.39 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 30.7, 45.6, 113.2, 120.5, 125.9, 126.8, 127.8, 128.8, 128.9, 129.3, 138.0, 149.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3365, 3039, 2976, 2904, 1602, 1570, 1465, 1450, 1373, 1309, 1269, 1028, 807, 808, 686, 667, 623. ***m/z* (EI)** 271.2 (M^+, 11), 256.2 (100), 194.2 (80), 179.2 (8), 165.1 (6), 77.1 (77), 51.1 (38). **HRMS (CI)** calcd. for $C_{20}H_{18}N^+$ ($[M+H]^+$): 272.1439, found: 272.1436.

Treatment of 1,3-Diphenyl-1*H*-indole (515) with KO^tBu Alone



This reaction was carried out according to General Procedure D from 1,3-diphenyl-1*H*-indole **515** (135 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **515** was recovered with data consistent to those reported above (130 mg, 97 %).

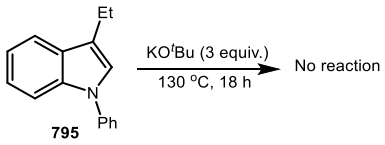
Treatment of 3-Ethyl-1-phenyl-1*H*-indole (795) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from 3-ethyl-1-phenyl-1*H*-indole **795** (111 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1), followed by recrystallisation from hexane, afforded 9-ethyl-9-methyl-9,10-

dihydroacridine **493** as a yellow solid (74 mg, 66 %). **Mp** = 93-94 °C (lit. mp = 93-94 °C).[301] **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.63 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.86 (q, *J* = 7.5 Hz, 2 H, CH_2), 6.04 (br. s., 1 H, NH), 6.65 (d, *J* = 7.0 Hz, 2 H, 2 x ArH), 6.89 (m, 2 H, 2 x ArH), 7.09 (app. t, *J* = 7.2 Hz, 2 H, 2 x ArH), 7.30 (d, *J* = 7.8 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.5, 30.1, 37.5, 40.4, 113.2, 120.3, 126.4, 126.7, 126.9, 138.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3393, 2960, 2918, 1605, 1578, 1474, 1450, 1321, 1144, 1026, 889, 685. ***m/z* (EI)** 222.9 (M^+, 3), 194.1 (100). The data for this compound are consistent with those reported in the literature.[302]

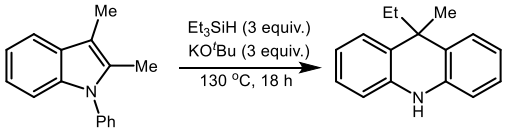
Treatment of 3-Ethyl-1-phenyl-1*H*-indole (795) with KO^{t}Bu Alone



795

This reaction was carried out according to General Procedure D from 3-ethyl-1-phenyl-1*H*-indole **795** (111 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **795** was recovered with data consistent to those reported above (111 mg, 100 %).

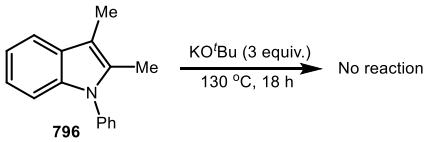
Treatment of 2,3-Dimethyl-1-phenyl-1*H*-indole (796) with Et_3SiH/KO^{t}Bu



796 **493**, 53 %

This reaction was carried out according to General Procedure C from 2,3-dimethyl-1-phenyl-1*H*-indole **796** (111 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 19:1) afforded 9-ethyl-9-methyl-9,10-dihydroacridine **493** as a yellow solid, with data consistent with those reported above (59 mg, 53 %).

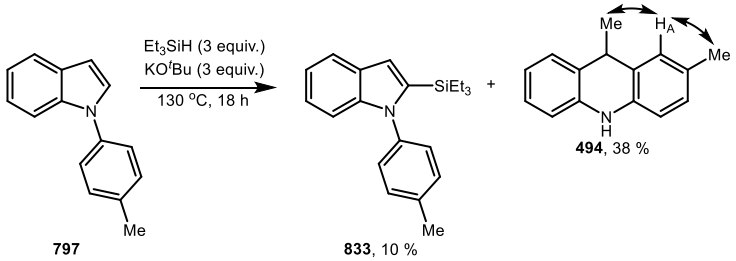
Treatment of 2,3-Dimethyl-1-phenyl-1*H*-indole (796) with KO^{t}Bu Alone



796

This reaction was carried out according to General Procedure D from 2,3-dimethyl-1-phenyl-1*H*-indole **796** (111 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **796** was recovered with data consistent to those reported above (104 mg, 94 %).

Treatment of 1-(*p*-Tolyl)-1*H*-indole (**797**) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from 1-(*p*-tolyl)-1*H*-indole **797** (104 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded an inseparable mixture of silylated compounds **833**. These compounds were tentatively identified by ^{1}H NMR, where the major isomer is likely as drawn above, due to the presence of a C-3 proton [6.89 ppm (d, *J* = 0.8 Hz, 1 H)]. Also isolated was 2,9-dimethyl-9,10-dihydroacridine **494** as a yellow solid (48 mg, 49 %). **Mp** = 94-97 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.36 (d, *J* = 7.0 Hz, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 4.07 (q, *J* = 7.0 Hz, 1 H, CH), 5.96 (br. s., 1 H, NH), 6.63 (d, *J* = 8.0 Hz, 1 H, ArH), 6.70 (dd, *J* = 7.9, 1.1 Hz, 1 H, ArH), 6.88 (app. td, *J* = 7.5, 1.0 Hz, 1 H, ArH), 6.92 (dd, *J* = 8.0, 1.5 Hz, 1 H, ArH), 6.99 (s, 1 H, ArH), 7.10 (app. td, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.17 (d, *J* = 7.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 20.7, 26.4, 36.8, 113.3, 113.4, 120.5, 125.6, 125.6, 126.8, 127.4, 128.2, 128.6, 130.0, 136.7, 139.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3379, 2943, 2914, 2860, 1608, 1585, 1508, 1483, 1448, 1303, 1255, 1155, 1139, 1107, 1033, 929, 889, 867, 854, 808, 700, 613. ***m/z* (EI)** 209.0 (M^+, 6), 207.0 (4), 194.0 (100). **HRMS (CI)** calcd. for $C_{15}H_{16}N^+$ ($[M+H]^+$): 210.1277, found: 210.1274. The presence of this isomer was confirmed by NOESY, where H_A (6.99 pm) correlates to both methyl groups (1.36 and 2.30 ppm).

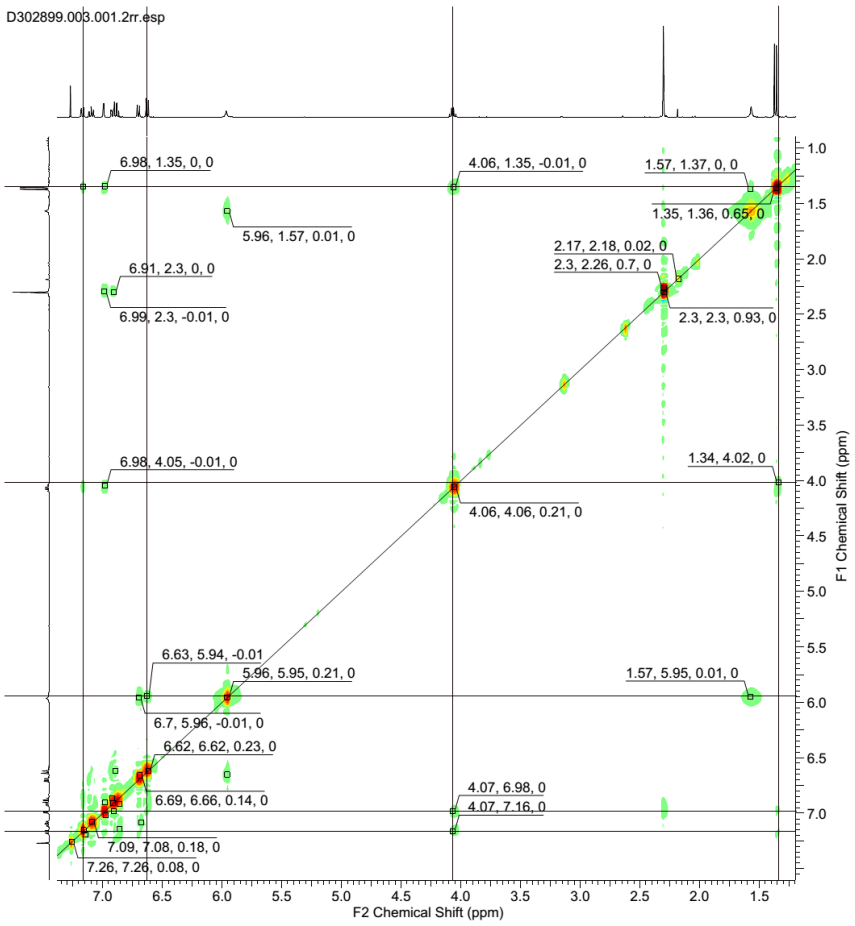
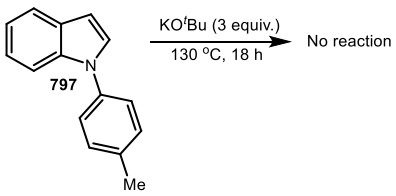


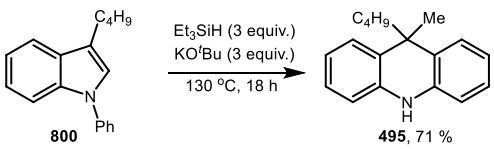
*Figure 16 - NOESY Spectrum of **494***

Treatment of 1-(*p*-Tolyl)-1*H*-indole (797) with KO^{t}Bu Alone



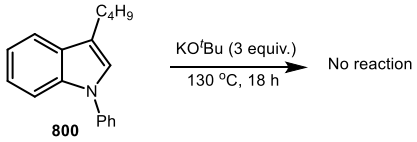
This reaction was carried out according to General Procedure D from 1-(*p*-tolyl)-1*H*-indole **797** (104 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **797** was recovered with data consistent to those reported above (95 mg, 91 %).

Treatment of 3-Butyl-1-phenyl-1*H*-indole (800) with Et_3SiH/KO^{t}Bu



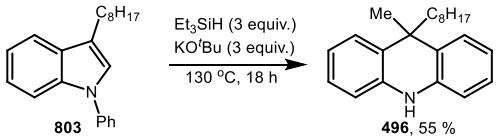
This reaction was carried out according to General Procedure C from 3-butyl-1-phenyl-1*H*-indole **800** (125 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1 → 9:1) afforded 9-butyl-9-methyl-9,10-dihydroacridine **495** as an orange oil (84 mg, 71 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.77 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.95 - 1.06 (m, 2 H, CH_2), 1.17 (sxt, *J* = 7.3 Hz, 2 H, CH_2), 1.66 (s, 3 H, CH_3), 1.80 - 1.89 (m, 2 H, CH_2), 6.04 (br. s., 1 H, NH), 6.65 (dd, *J* = 7.9, 1.1 Hz, 2 H, 2 x ArH), 6.91 (app. td, *J* = 7.5, 1.3 Hz, 2 H, 2 x ArH), 7.05 - 7.14 (m, 2 H, 2 x ArH), 7.32 (dd, *J* = 7.8, 1.0 Hz, 2 H, 2 x ArH). **^{13}C-NMR** 13.9, 23.1, 27.2, 30.7, 39.9, 44.7, 113.2, 120.3, 126.4, 126.6, 127.3, 138.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3404, 2954, 2927, 1606, 1579, 1494, 1323, 1031, 889, 744. ***m/z* (EI)** 251.3 (M^+, 3), 236.3 (2), 194.2 (100), 57.1 (7). **HRMS (CI)** calcd. for $C_{18}H_{22}N^+$ ([M+H]$^+$): 252.1747, found: 252.1749.

Treatment of 3-Butyl-1-phenyl-1*H*-indole (800) with KO^{t}Bu Alone



This reaction was carried out according to General Procedure D from 3-butyl-1-phenyl-1*H*-indole **800** (125 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **800** was recovered with data consistent to those reported above (104 mg, 83 %).

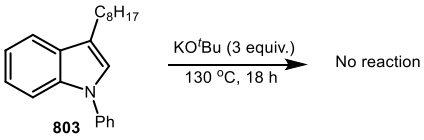
Treatment of 3-Octyl-1-phenyl-1*H*-indole (803) with Et_3SiH/KO^{t}Bu



This reaction was carried out according to General Procedure C from 3-octyl-1-phenyl-1*H*-indole **803** (153 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 19:1) afforded 9-methyl-9-octyl-9,10-dihydroacridine **496** as a yellow oil (85 mg, 55 %). This product was found to oxidise rapidly in air to form a stabilized radical, diagnosed by the broadening of the aromatic peaks in the proton NMR spectrum. This radical was reduced by dissolving the radical species in DCM and shaking with a 1 M solution of aqueous sodium dithionite in a separating funnel. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to recover **496**. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.85 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.94 - 1.06 (m, 2 H, CH_2), 1.07 - 1.25 (m, 10 H, 5 x CH_2), 1.65 (s, 3 H, CH_3), 1.77 - 1.88 (m, 2 H, CH_2), 6.04 (br. s., 1 H, NH), 6.64 (d, *J* = 7.8 Hz, 2 H, 2 x ArH), 6.89 (app. t, *J* = 7.3 Hz, 2 H, 2 x ArH), 7.04 - 7.14 (m, 2 H, 2 x ArH), 7.31 (dd, *J* = 7.9, 1.1 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.1, 22.6, 25.0, 29.2, 29.4, 30.0, 30.7, 31.8, 40.0, 44.9, 113.2, 120.3, 126.4, 126.6, 127.3, 138.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3402, 2922, 2852, 1606, 1579, 1481, 1323,

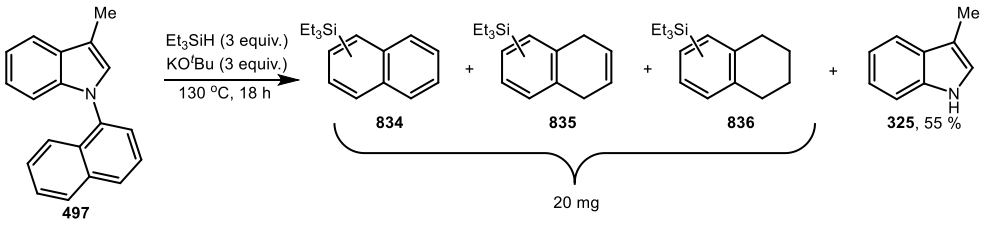
1251, 1097, 1035, 891, 721. ***m/z* (EI)** 307.2 (M^+, 1), 194.2 (100). **HRMS (CI)** calcd. for $C_{22}H_{30}N^+$ ($[M+H]^+$): 308.2373, found: 308.2375.

Treatment of 3-Octyl-1-phenyl-1*H*-indole (803) with KO^{t}Bu Alone



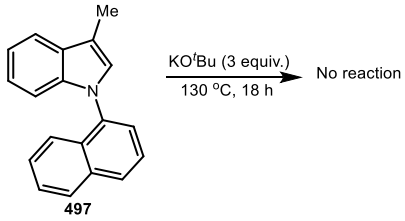
This reaction was carried out according to General Procedure D from 3-octyl-1-phenyl-1*H*-indole **803** (153 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **803** was recovered with data consistent to those reported above (149 mg, 97 %).

Treatment of 3-Methyl-1-(naphthalen-1-yl)-1*H*-indole (497) with Et_3SiH/KO^{t}Bu



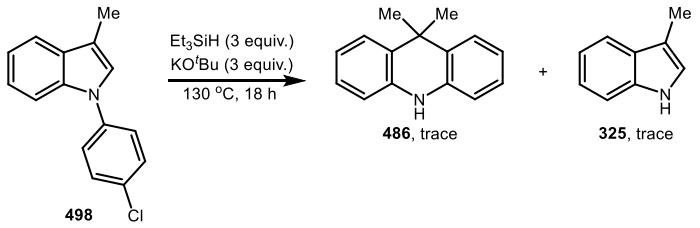
This reaction was carried out according to General Procedure C from 3-methyl-1-(naphthalen-1-yl)-1*H*-indole **497** (129 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded an inseparable mixture of products from which silylated compounds **834**-**836** (20 mg) were tentatively identified by GC-MS (*m/z* = 242.3, retention times = 14.202 and 14.335 min, *m/z* = 244.2, retention times = 13.824 and 14.049 min, and *m/z* = 246.2, retention times = 13.903 and 13.980 min). Also isolated was 3-methyl-1*H*-indole **325** as a white solid, with data consistent with those reported above (36 mg, 55 %).

Treatment of 3-Methyl-1-(naphthalen-1-yl)-1*H*-indole (497) with KO^{t}Bu Alone



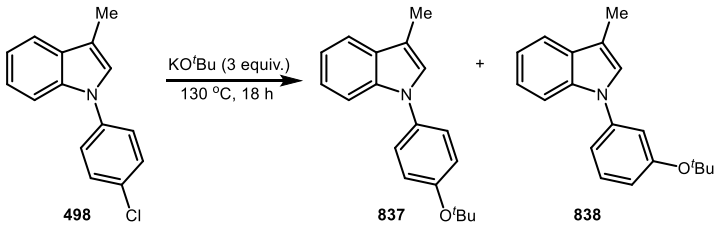
This reaction was carried out according to General Procedure D from 3-methyl-1-(naphthalen-1-yl)-1*H*-indole **497** (129 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **497** was recovered with data consistent to those reported above (129 mg, 100 %).

Treatment of 1-(4-Chlorophenyl)-3-methyl-1*H*-indole (**498**) with Et_3SiH/KO^tBu



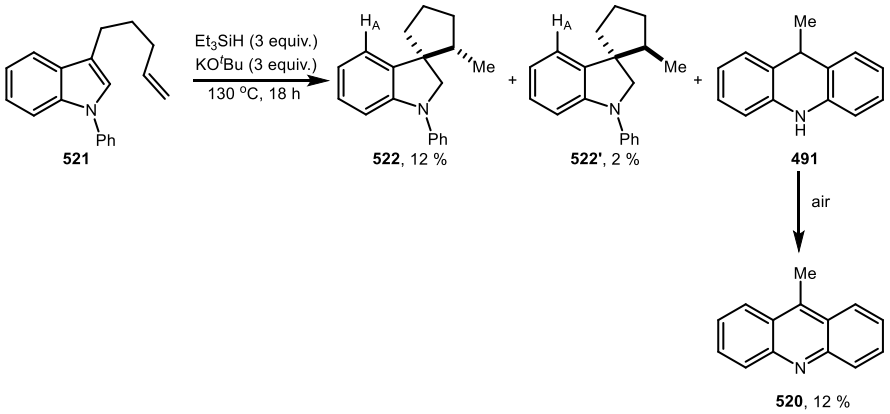
This reaction was carried out according to General Procedure C from 1-(4-chlorophenyl)-3-methyl-1*H*-indole **498** (121 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded a complex mixture of products from which **486** and **325** could be detected in trace amounts by ^{1}H NMR and GC-MS, with data consistent with those reported above.

Treatment of 1-(4-Chlorophenyl)-3-methyl-1*H*-indole (**498**) with KO^tBu Alone



This reaction was carried out according to General Procedure D from 1-(4-chlorophenyl)-3-methyl-1*H*-indole **498** (121 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded a complex mixture of products. No dihydroacridines were detected, nor any compounds where C-N bond cleavage had occurred. ^{1}H NMR of the crude reaction mixture indicated that **837** and **838** may be present due to two singlets present at 1.43 ppm, which may be the *tert*-butyl groups. This is similar to the chemical shift for the *tert*-butyl group in *tert*-butylbenzene, which is produced when halobenzenes are treated with KO^tBu alone (1.35 ppm).[303] However, the aromatic region of the spectrum in quite complex, so it this is not conclusive.

Treatment of 3-(Pent-4-en-1-yl)-1-phenyl-1*H*-indole (**521**) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from 3-(pent-4-en-1-yl)-1-phenyl-1*H*-indole **521** (131 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded 2-methyl-1'-phenylspiro[cyclopentane-1,3'-indoline] **522** and **522'** as a pair of diastereomers, which were inseparable from a small amount of starting material **521** by column chromatography (ratio of **522**:**521** = 10:1 by proton NMR, combined yield = 22 mg), and an impure sample containing 9-methyl-9,10-dihydroacridine **491** as a yellow solid (41 mg), with data consistent with those reported above. The mixture of diastereomers was then dissolved in 1:1 MeOH:DMSO (1 mL) and purified by Open Access Mass Directed AutoPrep on Xbridge column using acetonitrile:water with an ammonium carbonate modifier to afford (1*R**,2*S**)-2-methyl-1'-phenylspiro[cyclopentane-1,3'-indoline] **522** as a colourless oil (16 mg, 12 %); **^{1}H-NMR** (600 MHz, $CDCl_3$) 0.84 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.25 - 1.41 (m, 1 H, CH), 1.65 - 1.77 (m, 1 H, CH), 1.79 - 1.86 (m, 1 H, CH), 1.88 - 1.93 (m, 1 H, CH), 1.95 - 2.01 (m, 1 H, CH), 2.01 - 2.10 (m, 2 H, CH_2), 3.59 (d, *J* = 9.2 Hz, 1 H, CH), 3.85 (d, *J* = 9.5 Hz, 1 H, CH), 6.80 (app. td, *J* = 7.5, 0.7 Hz, 1 H, ArH), 6.95 (app. t, *J* = 7.3 Hz, 1 H, ArH), 7.08 - 7.13 (m, 2 H, 2 x ArH), 7.16 (d, *J* = 8.1 Hz, 1 H, ArH), 7.25 (d, *J* = 7.7 Hz, 2 H, 2 x ArH), 7.29 - 7.44 (m, 2 H, 2 x ArH). **^{13}C-NMR** (151 MHz, $CDCl_3$) 13.8, 21.8, 32.2, 40.1, 44.9, 54.0, 59.6, 108.2, 117.4, 118.9, 120.6, 122.4, 127.2, 129.1, 137.1, 144.0, 146.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 2954, 2875, 1591, 1501, 1484, 1385, 1281, 742, 695. ***m/z* (CI)** 264.0 $(M+H)^+$ **HRMS (CI)** calcd. for $C_{19}H_{22}N^+$ ($[M+H]^+$): 264.1752, found: 264.1757; and (1*R**,2*R**)-2-methyl-1'-phenylspiro[cyclopentane-1,3'-indoline] **522'** as a colourless oil (2 mg, 2 %). **^{1}H-NMR** (600 MHz, $CDCl_3$) 0.79 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.76 - 2.04 (m, 6 H, 3 x CH_2), 2.14 - 2.21 (m, 1 H, CH), 3.70 (d, *J* = 9.2 Hz, 1 H, CH), 3.94 (d, *J* = 9.2 Hz, 1 H, CH), 6.77 (app. td, *J* = 7.8, 0.7 Hz, 1 H, ArH), 6.95 (app. t, *J* = 7.7 Hz, 1 H, ArH), 7.06 - 7.11 (m, 2 H, 2 x ArH), 7.15 (dd, *J* = 8.8, 1.1 Hz, 1 H, ArH), 7.21 - 7.24 (m, 2 H, 2 x ArH), 7.31 - 7.37 (m, 2 H, 2 x ArH). **^{13}C-NMR** (151 MHz, $CDCl_3$) 15.6, 22.3, 32.9, 38.4, 44.6, 53.9, 65.3, 107.9, 117.5, 118.6, 120.7, 124.8, 127.1, 129.1, 136.3, 144.1, 147.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 2954, 2875, 1591, 1501, 1481, 1384, 1286, 742, 695. ***m/z* (CI)** 264.0 $(M+H)^+$. **HRMS (CI)** calcd. for $C_{19}H_{22}N^+$ ($[M+H]^+$): 264.1752, found: 264.1758. The relative stereochemistry of the minor diastereomer **522'** was determined by NOESY, where there is a correlation between H_A and the methyl group as shown in the spectra below (Figure 17). This is not present in the major diastereomer **522** (Figure 18). To facilitate isolation of the 9,10-dihydroacridine **491**, the sample

was intentionally oxidised in air. After stirring in air for 2 weeks, the sample was found to have oxidised to 9-methylacridine **520**. Purification by column chromatography (hexane:diethyl ether, 4:1) afforded 9-methylacridine **520** as an orange solid (12 mg, 12 %). **Mp** = 109-111 °C (lit. mp = 113-114 °C).[304] **^{1}H-NMR** (400 MHz, $CDCl_3$) 3.15 (s, 3 H, CH_3), 7.57 (ddd, *J* = 8.8, 6.5, 1.3 Hz, 2 H, 2 x ArH), 7.78 (ddd, *J* = 8.7, 6.6, 1.3 Hz, 2 H, 2 x ArH), 8.24 (d, *J* = 8.5 Hz, 1 H, 2 x ArH), 8.26 - 8.30 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.6, 124.5, 125.4, 125.5, 129.8, 130.2, 142.3, 148.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3061, 3049, 2922, 1627, 1610, 1556, 1519, 1413, 1379, 1151, 943, 906, 858, 823, 686, 650. ***m/z* (EI)** 193.1 (M^+, 100), 165.2 (12), 89.2 (15), 74.0 (16), 63.0 (26), 52.0 (17). The data for this compound are consistent with those reported in the literature.[304]

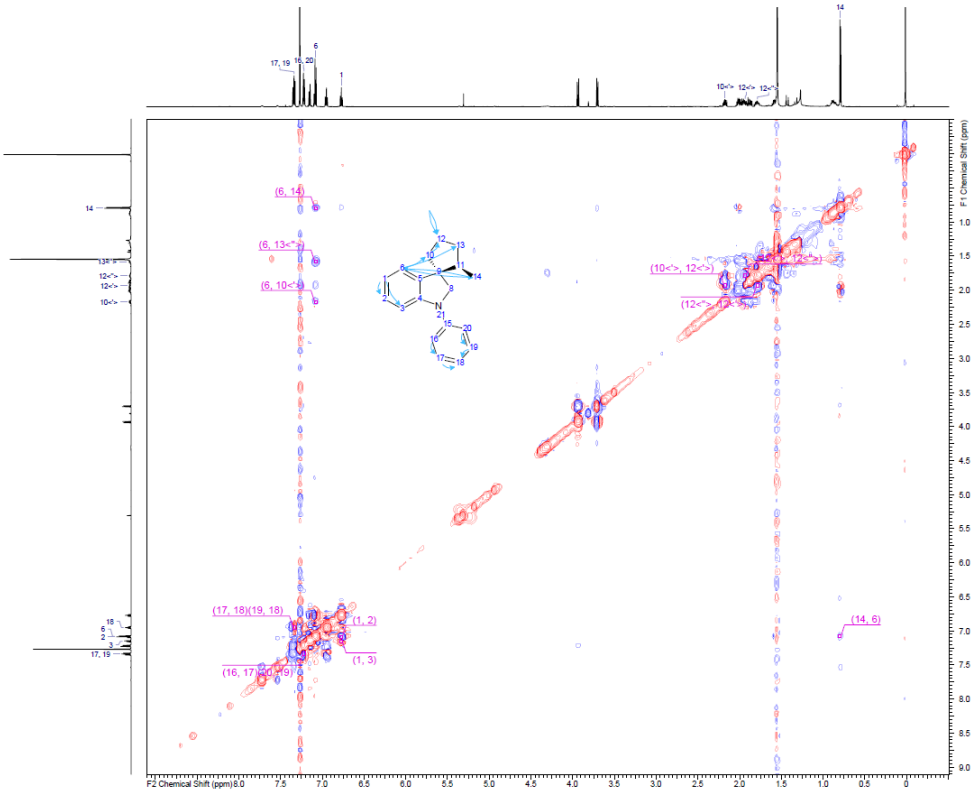


*Figure 17 - NOESY of **522'***

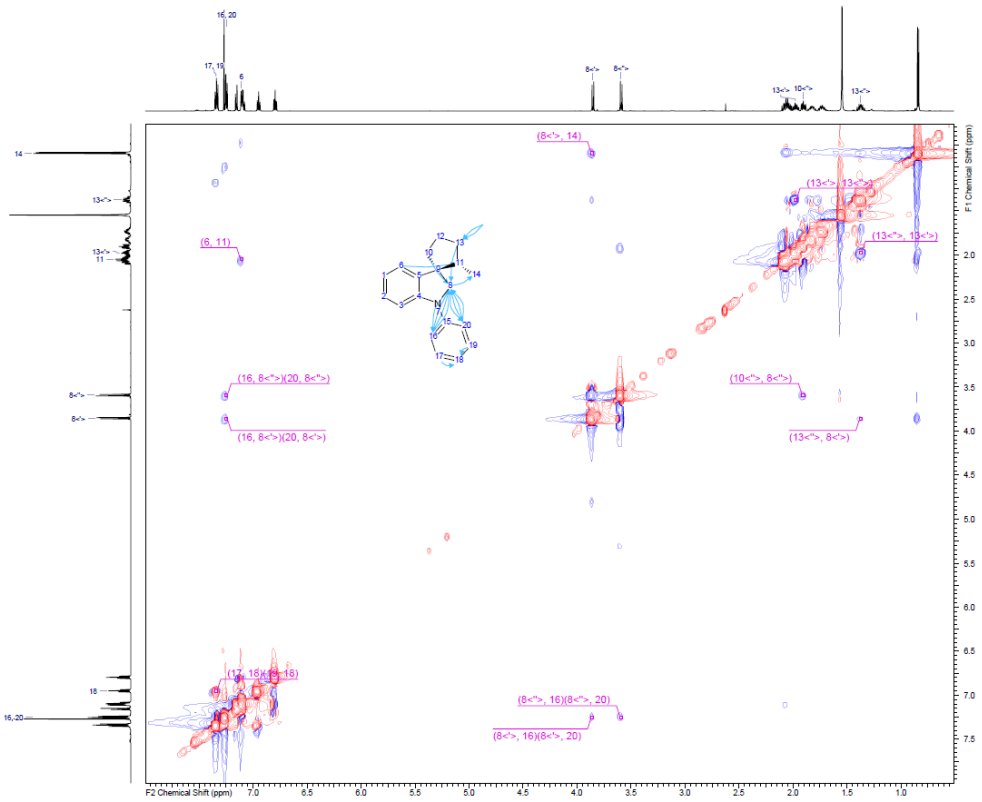
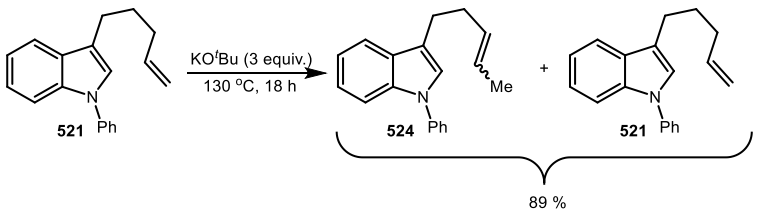


*Figure 18 - NOESY of **522***

Treatment of 3-(Pent-4-en-1-yl)-1-phenyl-1*H*-indole (**521**) with KO^{t}Bu Alone



This reaction was carried out according to General Procedure D from 3-(pent-4-en-1-yl)-1-phenyl-1*H*-indole **521** (131 mg, 0.50 mmol, 1.0 equiv). Purification by column chromatography (hexane) afforded an inseparable mixture of (*E*/*Z*)-3-(pent-3-en-1-yl)-1-phenyl-1*H*-indole **524** and 3-(pent-4-en-1-yl)-1-phenyl-1*H*-indole **521** as a colourless oil (117 mg, 89 %). Evidence for this isomerisation can be seen in the ^{1}H NMR spectra in Figure 19, where the spectrum from this reaction (top) is compared with the spectrum of the starting material (bottom). It can be seen that as well as the terminal alkene present in the starting material, a new peak has developed at 5.6 ppm indicative of an internal alkene.

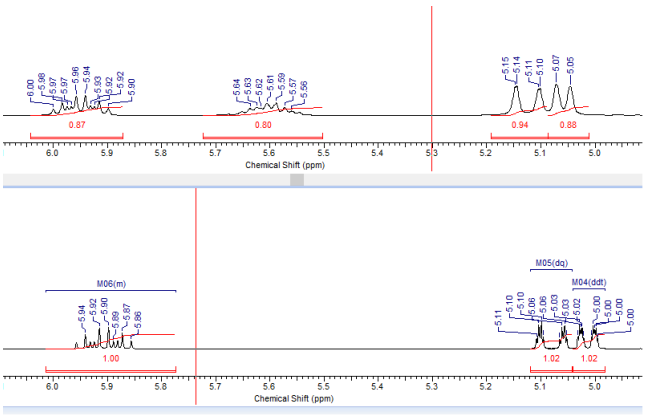


*Figure 19 - ^{1}H NMR Spectrum Showing the Isomerisation of **521** (bottom) to a Mixture of Isomers (top)*

Similarly, in the spectrum from this reaction (Figure 20, top), two isomeric methyl groups (1.68 and 1.74 ppm) can be seen which are not present in the starting material (bottom). This is further evidence for the isomerisation having occurred.

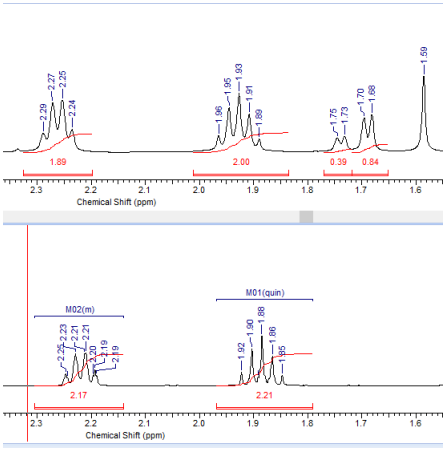
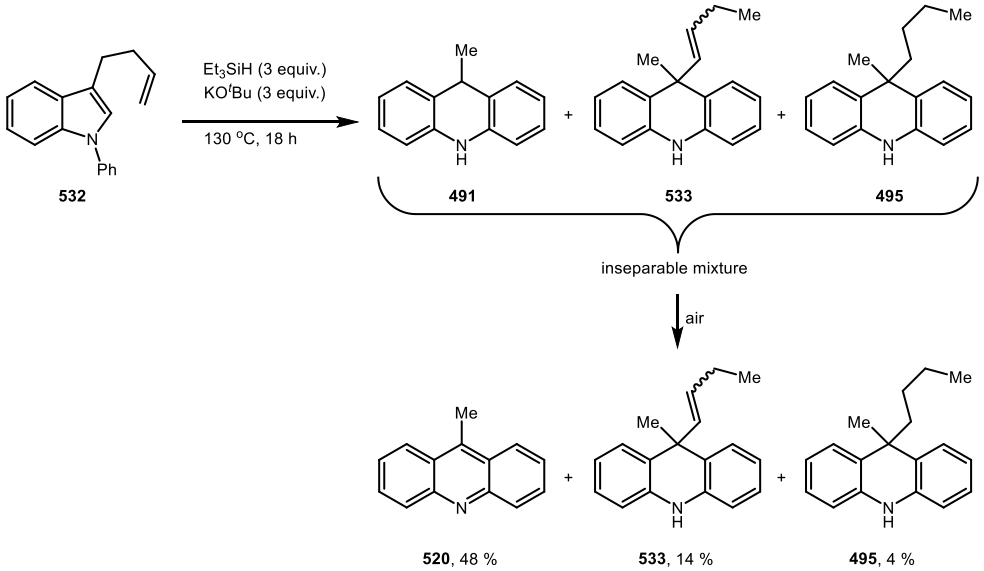


*Figure 20 - ^{1}H NMR Spectrum Showing the Isomerisation of **521** (bottom) to a Mixture of Isomers (top)*

GC-MS also indicates the presence of isomers from this reaction (*m/z* = 261.2), with retention times of 16.096 and 16.158 min. **^{13}C-NMR** (101 MHz, $CDCl_3$) 12.9, 18.0, 24.4, 25.0, 25.3, 27.4, 29.2, 33.0, 33.6, 110.5, 114.7, 117.6, 117.7, 119.2, 119.3, 119.7, 119.8, 120.3, 121.1, 122.3, 124.0, 124.3, 125.0, 125.3, 125.9, 129.1, 129.5, 130.3, 131.1, 136.0, 136.1, 138.7, 140.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3045, 2914, 2846, 1637, 1595, 1498, 1454, 1379, 1317, 1228, 1132, 1014, 906, 773, 694.

Treatment of 3-(But-3-en-1-yl)-1-phenyl-1*H*-indole (**532**) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from 3-(but-3-en-1-yl)-1-phenyl-1*H*-indole **532** (124 mg, 0.50 mmol, 1.0 equiv. Purification by column chromatography (hexane:diethyl ether, 100:0 → 9:1) afforded an impure sample of dihydroacridines **491**, **533** and **495** (67 mg). To facilitate isolation, the sample was intentionally oxidised by stirring in air for two weeks. Purification by column chromatography (hexane:diethyl ether, 4:1) afforded an inseparable mixture containing 9-(but-1-en-1-yl)-9-methyl-9,10-dihydroacridine **533** and 9-butyl-9-methyl-9,10-dihydroacridine **495** (23 mg). To determine the yields of **533** and **495**, 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.1 equiv.) was added as an internal NMR standard. By setting the integration of the three methoxy groups in the internal standard to 9 integral units, the methyl groups in **533** (1.49 ppm) and **495** (1.66 ppm) were found to integrate to 4.31 integral units and 1.16 integral units respectively (compound **495** could be identified by comparison to the data obtained when this isomer was isolated from 3-butyl-1-phenyl-1*H*-indole **800** above). The yield of **533** was determined to be (4.31/3)x10 = 14 %, and the yield of **495** was determined to be (1.16/3)x10 = 4 %. The relevant part of the ^{1}H NMR spectrum is shown below in Figure 21. ***m/z* (EI)** for **533** (retention time = 15.642 min) 249.3 (M^+, 10), 234.1 (99), 217.2 (30), 204.2 (41), 194.2 (100), 179.2 (7), 165.0 (10), 153.0 (5), 139.9 (7), 126.9 (6), 114.9 (4), 102.3 (5), 89.0 (7), 77.0 (12), 65.0 (7), 55.3 (40), and for **495** (retention time = 15.487 min) 251.1 (M^+, 1), 204.0 (3), 194.2 (100), 179.3 (3), 164.8 (3), 96.8 (5), 77.0 (3), 56.0 (6). Also isolated was 9-methylacridine **520** as a yellow solid, with data consistent with those reported above (46 mg, 48 %).

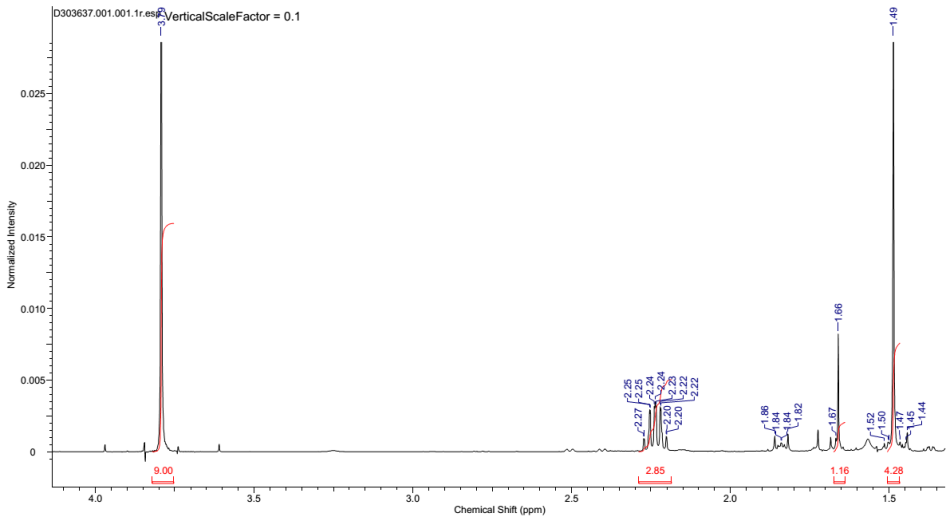
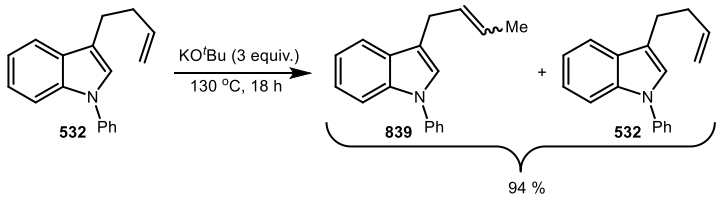


*Figure 21 - Determination of the Yields of **495** and **533** by Addition of an Internal Standard to the ^{1}H NMR*

Treatment of 3-(But-3-en-1-yl)-1-phenyl-1*H*-indole (532) with KO^{t}Bu Alone



This reaction was carried out according to General Procedure D from 3-(but-3-en-1-yl)-1-phenyl-1*H*-indole **532** (124 mg, 0.50 mmol, 1.0 equiv.) to afford a mixture of (*E*/*Z*)-3-(but-2-en-1-yl)-1-phenyl-1*H*-indole **839** and 3-(but-3-en-1-yl)-1-phenyl-1*H*-indole **532** as a colourless oil (117 mg, 94 %). Evidence for this isomerisation can be seen in the ^{1}H-NMR spectra in Figure 22, where the spectrum from this reaction (top) is compared with the spectrum of the starting material (bottom). It can be seen that as well as the terminal alkene present in the starting material, a new peak has developed at 5.75 ppm indicative of an internal alkene.

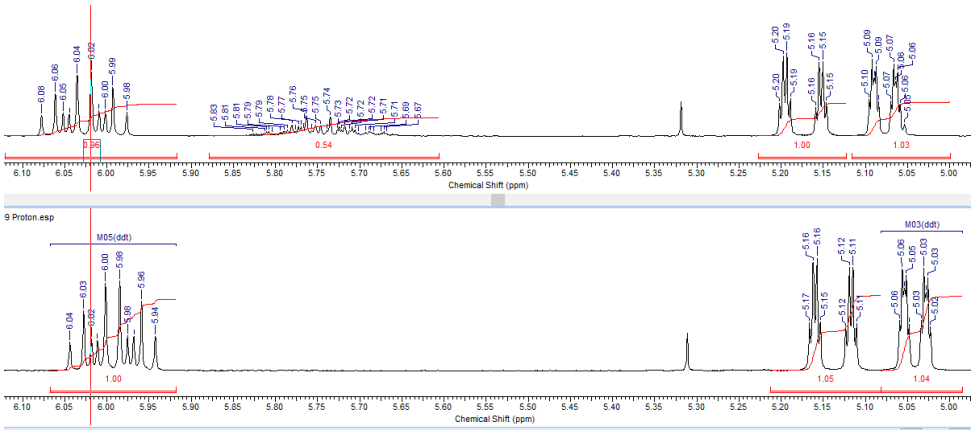


*Figure 22 - Isomerisation of **532** (bottom) to a Mixture of Isomers (top)*

Similarly, in the spectrum from this reaction (Figure 23, top), two isomeric methyl groups (1.76 and 1.85 ppm) can be seen which are not present in the starting material (bottom). This is further evidence for the isomerisation having occurred.

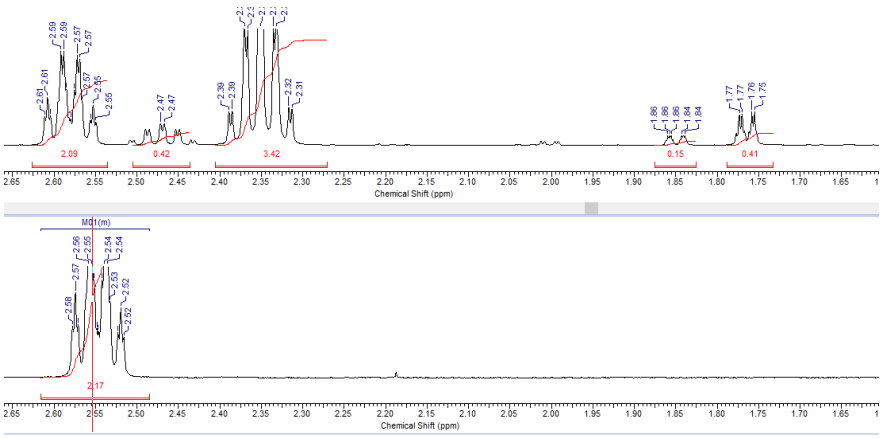
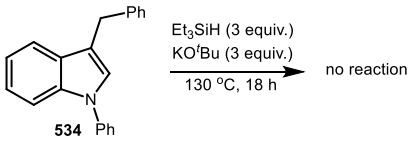


*Figure 23 - Isomerisation of **532** (bottom) to a Mixture of Isomers (top)*

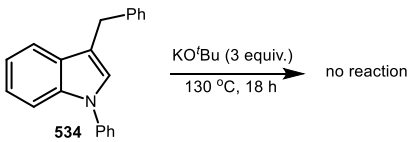
GC-MS also indicates the presence of isomers (*m/z* = 247.2), with retention times of 15.614, 15.721, 15.810 and 16.176 min. **^{13}C-NMR** (101 MHz, $CDCl_3$) 17.9, 23.2, 24.6, 26.6, 28.5, 30.3, 34.1, 110.4, 110.5, 110.6, 114.8, 116.3, 117.3, 118.3, 119.2, 119.3, 119.4, 119.8, 120.2, 120.4, 120.5, 120.6, 122.4, 122.7, 122.8, 124.0, 124.3, 124.4, 125.1, 125.6, 126.0, 126.1, 126.4, 126.5, 127.2, 129.0, 129.5, 129.6, 129.6, 130.6, 132.4, 136.0, 136.6, 138.6, 139.6, 140.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3047, 2960, 2926, 1718, 1595, 1498, 1454 1377, 1319, 1298, 1219, 1134, 1074, 1014, 960, 908, 773, 604.

Treatment of 3-Benzyl-1-phenyl-1*H*-indole (534) with Et_3SiH/KO^tBu



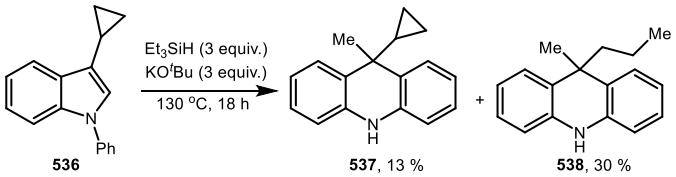
This reaction was carried out according to General Procedure C from 3-benzyl-1-phenyl-1*H*-indole **534** (142 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to have taken place, and after purification by column chromatography (hexane), starting material **534** was recovered (109 mg, 77 %).

Treatment of 3-Benzyl-1-phenyl-1*H*-indole (534) with KO^tBu Alone



This reaction was carried out according to General Procedure D from 3-benzyl-1-phenyl-1*H*-indole **534** (142 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to have taken place, and starting material **534** was recovered (132 mg, 93 %).

Treatment of 3-Cyclopropyl-1-phenyl-1*H*-indole (536) with Et_3SiH/KO^tBu



536 **537**, 13 % **538**, 30 %

This reaction was carried out according to General Procedure C from 3-cyclopropyl-1-phenyl-1*H*-indole **536** (116 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:diethyl ether, 9:1) afforded a yellow oil which consisted of an inseparable mixture (1:2.4 ratio based on integration of CH_3 groups at 1.68 and 1.60 ppm) of 9-cyclopropyl-9-methyl-9,10-dihydroacridine **537** (13 %); **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.18 - 0.26 (m, 2 H, CH_2), 0.32 - 0.40 (m, 2 H, CH_2), 0.95 - 1.14 (m, 1 H, CH), 1.54 (s, 3 H, CH_3), 6.09 (br. s., 1 H, NH), 6.71 (dd, *J* = 8.0, 1.3 Hz, 2 H, 2 x ArH), 6.91 - 6.96 (m, 2 H, 2 x ArH), 7.11 - 7.16 (m, 2 H, 2 x ArH), 7.49 (d, *J* = 7.8 Hz, 2 H, 2 x ArH). ***m/z* (EI)** 235.3 (M^+, 8), 220.2 (18), 207.1 (8), 194.1 (100), 178.9 (7), 165.1 (5). **HRMS (CI)** calcd. for $C_{17}H_{18}N^+$ ($[M+H]^+$): 236.1434, found: 236.1437; and 9-methyl-9-propyl-9,10-dihydroacridine **538** (30 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.75 (t, *J* = 7.5 Hz, 3 H, CH_3), 0.94-1.12 (m, 2H, CH_2), 1.66 (s, 3 H, CH_3), 1.75 - 1.85 (m, 2 H, CH_2), 6.03 (br. s, 1 H, NH), 6.64 (dd, *J* = 7.9, 1.1 Hz, 2 H, 2 x ArH), 6.86 - 6.91 (m, 2 H, 2 x ArH), 7.06 - 7.11 (m, 2 H, 2 x ArH), 7.31 (d, *J* = 7.8 Hz, 2 H, 2 x ArH). ***m/z* (EI)** 237.2 (M^+, 3), 222.2 (3), 194.2 (100). **HRMS (CI)** calcd. for $C_{17}H_{20}N^+$ ($[M+H]^+$): 238.1590, found: 238.1594. The ^{1}H NMR signals for compounds **537** and **538** are separately assigned above from a ^{1}H NMR spectrum of the mixture, making use of integrals to differentiate them. The ^{13}C NMR spectrum represents the peaks from both components. **^{13}C-NMR** (101 MHz, $CDCl_3$) 1.2, 14.4, 18.4, 23.6, 24.3, 30.5, 38.9, 40.0, 47.7, 138.2, 113.3, 120.3, 120.4, 126.4, 126.5, 126.7, 126.8, 127.1, 127.3, 138.6, 139.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3400, 2953, 2927, 2358, 1606, 1577, 1473, 1321, 1029, 694. Compounds **537** and **538** were separated by GC-MS, with retention times of 15.650 and 15.159 min respectively. The yields were calculated by addition of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 10 mol %) as an internal standard to the sample of the mixture. The signal of the three methoxy groups (3.80 ppm) was integrated to 9 integral units, and the relative intensities of the methyl groups of **537** (1.68 ppm, 3.80 integral units) and **538** (1.60 ppm, 8.99 integral units) were used to calculate yields. For **537**, yield = [3.80/3] x 10 = 13 %. For **538**, yield = [8.99/3] x 10 = 30 %.

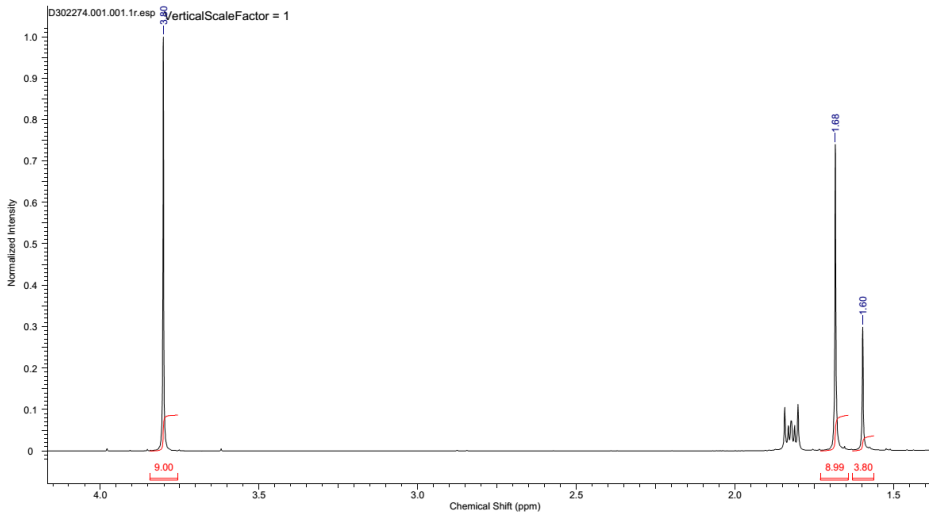
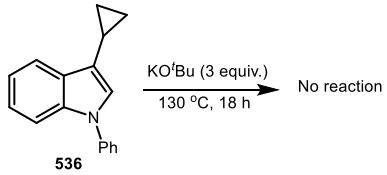


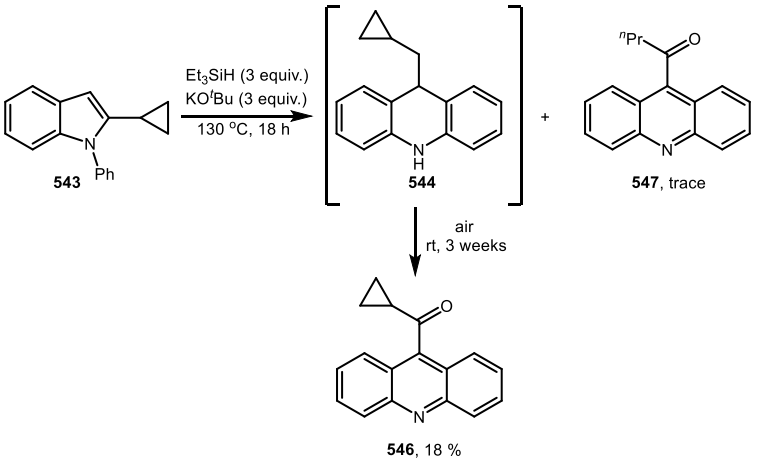
*Figure 24 - Determination of the Yields of **537** and **538** by the Addition of an Internal Standard to the ^{1}H NMR*

Treatment of 3-Cyclopropyl-1-phenyl-1*H*-indole (536) with KO^{t}Bu Alone



This reaction was carried out according to General Procedure D from 3-cyclopropyl-1-phenyl-1*H*-indole **536** (116 mg, 0.50 mmol, 1.0 equiv.). No reaction was found to occur, and **536** was recovered with data consistent to those reported above (116 mg, 100 %).

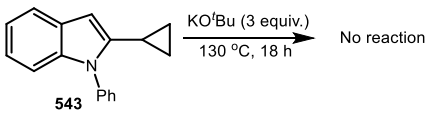
Treatment of 2-Cyclopropyl-1-phenyl-1*H*-indole (543) with Et$_3$SiH/KO^{t}Bu



This reaction was carried out according to General Procedure C from 2-cyclopropyl-1-phenyl-1*H*-indole **543** (117 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded an impure mixture of products which contained 9-(cyclopropylmethyl)-9,10-dihydroacridine **544**. **^{1}H-NMR** (400 MHz, $CDCl_3$) – 0.14 - – 0.05 (m, 2 H, 2 x CH), 0.32 - 0.41 (m, 2 H, 2 x CH), 0.55 - 0.67 (m, 1 H, CH), 1.49 (t, *J* = 7.0 Hz, 2 H, CH_2),

4.03 (t, *J* = 6.9 Hz, 1 H, CH), 6.03 (br. s., 1 H, NH), 6.73 (dd, *J* = 7.8, 1.0 Hz, 2 H, 2 x ArH), 6.90 (app. td, *J* = 7.4, 1.2 Hz, 2 H, 2 x ArH), 7.11 (app. td, *J* = 7.6, 1.5 Hz, 2 H, CH_2), 7.18 (d, *J* = 7.5 Hz, 2 H, 2 x ArH). GC-MS indicated that oxidation had occurred at the temperature of the instrument (300 °C), and showed a mass matching $[M-2H]^+$ (233.1) with a retention time of 15.41 min. The crude mixture was dissolved in EtOAc and stirred at room temperature open to air for three weeks, adding more solvent as necessary. After this time, the mixture was concentrated under reduced pressure and purified by column chromatography (hexane:ethyl acetate, 100:0 → 80:20). This afforded acridin-9-yl(cyclopropyl)methanone **546** as a yellow solid (21 mg, 18 %). **Mp** = 120 – 123 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.29 - 1.37 (m, 2 H, 2 x CH), 1.62 - 1.69 (m, 2 H, 2 x CH), 2.45 - 2.56 (m, 1 H, CH), 7.62 (app. t, *J* = 7.5 Hz, 2 H, 2 x ArH), 7.85 (app. t, *J* = 7.7 Hz, 2 H, 2 x ArH), 7.99 (d, *J* = 8.5 Hz, 2 H, 2 x ArH), 8.25 - 8.44 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 24.9, 121.5, 125.2, 126.9, 129.7, 130.6, 146.2, 148.5, 207.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 247.1 (M^+, 100), 232.1 (11), 218.1 (29), 206.0 (50), 191.1 (9), 178.1 (87), 151.1 (42), 125.0 (8), 101.1 (5), 77.0 (10), 69.0 (14). ***m/z* (EI)** 247.1 (M^+, 100), 232.1 (11), 218.1 (30), 206.0 (51), 191.1 (10), 178.1 (88), 163.0 (4), 151.1 (42), 140.1 (2), 125.0 (7), 114.1 (3), 101.1 (5), 87.0 (4), 77.0 (10), 69.0 (9), 63.0 (4), 51.0 (4). **HRMS (CI)** calcd. for $C_{17}H_{14}NO^+$ ($[M+H]^+$): 248.1075, found: 248.1073. Also isolated was in impure fraction from which compound **547** was tentatively identified by GC-MS, (*m/z* = 249.1), with a retention time of 15.62 min. The propyl group was also detected by ^{1}H NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) 1.11 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.87 - 1.99 (quin, *J* = 7.3 Hz, 2 H, CH_2), 3.06 (t, *J* = 7.3 Hz, 2 H, CH_2). The compound could not be further purified as there was less than 1 mg of the compound present.

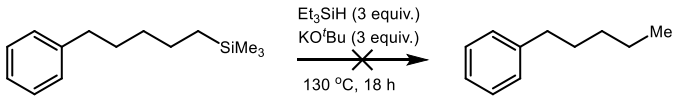
Treatment of 2-Cyclopropyl-1-phenyl-1*H*-indole (543) with KO^{t}Bu Alone



543

This reaction was carried out according to General Procedure D from 2-cyclopropyl-1-phenyl-1*H*-indole **543** (28.0 mg, 0.12 mmol, 1.0 equiv.) and KO^{t}Bu (40.0 mg, 0.36 mmol, 3.0 equiv.). No reaction was found to occur, and **543** was recovered, with data consistent to those reported above (21 mg, 75 %)

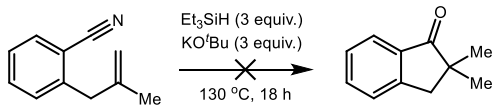
Treatment of Trimethyl(5-phenylpentyl)silane (569) with Et_3SiH/KO^{t}Bu



569 570

This reaction was carried out according to General Procedure C from trimethyl(5-phenylpentyl)silane **569** (110 mg, 0.50 mmol, 1.0 equiv.). No desilylated compounds *e.g.* **570** were detected by ^{1}H NMR or GC-MS of the crude material.

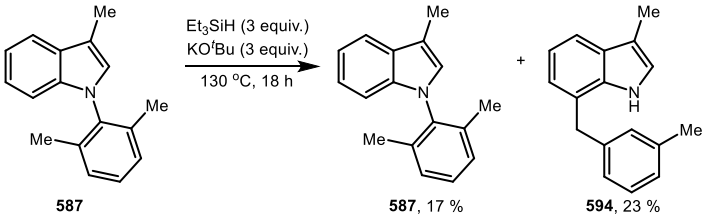
Treatment of 2-(2-Methylallyl)benzonitrile (572) with Et_3SiH/KO^tBu



572 573

To a pressure tube, equipped with a stirrer bar in a glovebox, under nitrogen atmosphere, was added 2-(2-methylallyl)benzonitrile **572** (79.0 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.5 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with 2 M HCl (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. An insoluble orange solid was formed which only consisted of two broad peaks in the ^{1}H NMR spectrum of the crude material. This was assumed to be polymerisation products.

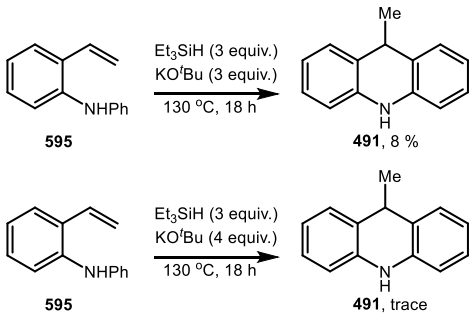
Treatment of 1-(2,6-Dimethylphenyl)-3-methyl-1*H*-indole (587) with Et_3SiH/KO^tBu



587 **587**, 17 % **594**, 23 %

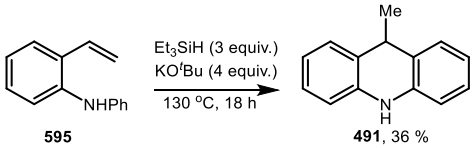
This reaction was carried out according to General Procedure C from 1-(2,6-dimethylphenyl)-3-methyl-1*H*-indole **587** (118 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded starting material **587**, with data consistent to those reported above (20 mg, 17 %), and 3-methyl-7-(3-methylbenzyl)-1*H*-indole **594** as a brown oil (27 mg, 23 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.30 (s, 3 H, CH_3), 2.32 (d, *J* = 1.0 Hz, 3 H, CH_3), 4.19 (s, 2 H, CH_2), 6.86 (s, 1 H, ArH), 7.00 - 7.08 (m, 4 H, 4 x ArH), 7.11 (app. t, *J* = 7.0 Hz, 1 H, ArH), 7.19 (d, *J* = 7.5 Hz, 1 H, ArH), 7.50 (dd, *J* = 7.8, 1.0 Hz, 1 H, ArH), 7.60 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.7, 21.4, 38.3, 111.9, 117.3, 119.3, 121.5, 122.7, 123.1, 125.7, 127.2, 128.5, 128.6, 129.4, 135.5, 138.4, 139.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3448, 2922, 2854, 1718, 1606, 1490, 1458, 1436, 1336, 1083, 908, 732, 648. ***m/z* (EI)** 235.2 (M^+, 100), 220.2 (24), 204.1 (14), 189.1 (3), 178.1 (3), 165.1 (2), 154.1 (2), 144.1 (24), 130.1 (4), 115.1 (17), 102.1 (5), 91.0 (7), 77.0 (6), 65.0 (5), 51.0 (3). **HRMS (CI)** calcd. for $C_{17}H_{18}N^+$ ($[M+H]^+$): 236.1439, found: 236.1437, and calcd. for $C_{17}H_{18}N^+$ (M^+): 235.1361, found 235.1358 (M^+).

Treatment of *N*-Phenyl-2-vinylaniline (595) with Et_3SiH/KO^tBu (Fast Addition)



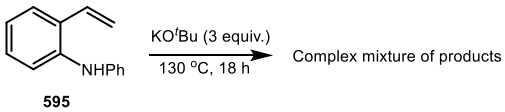
This reaction was carried out according to General Procedure C from *N*-phenyl-2-vinylaniline **595** (98.0 mg, 0.50 mmol, 1.0 equiv) with Et_3SiH (0.24 mL, 1.50 mmol, 3.0 equiv.) and KO^tBu [(168 mg, 1.50 mmol, 3.0 equiv.) or (224 mg, 2.0 mmol, 4.0 equiv.). With three equivalents of KO^tBu, purification by column chromatography afforded 9-methyl-9,10-dihydroacridine **491** as a white solid, with data consistent with those reported above (8 mg, 8 %). With four equivalents of KO^tBu, a complex mixture of products was produced from which **491** was detected by ^1H NMR and GC-MS (trace amount). The major products in each case appear to be polymerisation products as judged by the broad nature of the ^1H NMR spectrum.

Treatment of *N*-Phenyl-2-vinylaniline (595) with Et_3SiH/KO^tBu (Slow Addition)



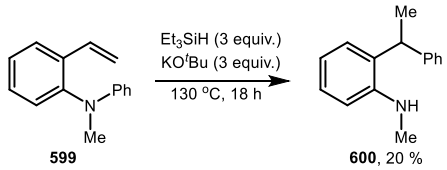
In a glovebox under nitrogen, Et_3SiH (0.24 mL, 1.50 mmol, 3.0 equiv.) and KO^tBu (224 mg, 2.0 mmol, 4.0 equiv.) were sealed in a microwave vial equipped with a stirrer bar. The vial was removed and heated to 130 °C behind a shield. *N*-phenyl-2-vinylaniline **595** (98.0 mg, 0.50 mmol, 1.0 equiv). was added dropwise by needle and syringe over 1 h, and the resulting mixture was stirred for 18 h at this temperature. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1), followed by recrystallisation from hexane afforded 9-methyl-9,10-dihydroacridine **491** as a white solid, with data consistent with those reported above (35 mg, 36 %).

Treatment of *N*-Phenyl-2-vinylaniline (595) with KO^tBu Alone



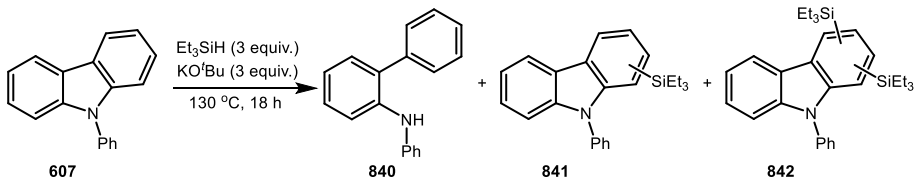
This reaction was carried out according to General Procedure D from *N*-phenyl-2-vinylaniline **595** (98.0 mg, 0.50 mmol, 1.0 equiv). A complex mixture of products was obtained, however, no 9-methyl-9,10-dihydroacridine **491** was detected. It appears as if the major products are polymerisation products as judged by the broad nature of the ^{1}H NMR spectrum.

Treatment of *N*-Methyl-*N*-phenyl-2-vinylaniline (599) with Et_3SiH/KO^tBu



To a microwave vial in the glovebox was added triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The vial was sealed, removed from the glovebox and heated at 130 °C behind a shield. Compound **599** (105 mg, 0.50 mmol, 1.0 equiv.) was added slowly over 1 h, and the mixture was stirred for 18 h at this temperature. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:toluene, 100:0 → 50:50) afforded *N*-methyl-2-(1-phenylethyl)aniline **600** as a yellow oil (21 mg, 20 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.64 (app. dd, *J* = 7.0, 1.3 Hz, 3 H, CH_3), 2.72 (s, 3 H, NCH_3), 4.07 (q, *J* = 7.1 Hz, 1 H, CH), 6.68 (d, *J* = 8.0 Hz, 1 H, ArH), 6.85 (app. t, *J* = 7.5 Hz, 1 H, ArH), 7.16 - 7.26 (m, 4 H, 4 x ArH), 7.27 - 7.35 (m, 3 H, 3 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 22.2, 30.9, 39.8, 110.4, 117.1, 126.4, 126.8, 127.4, 127.4, 128.7, 129.3, 145.7, 146.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3425, 3059, 3043, 2964, 2929, 2870, 2812, 1739, 1602, 1581, 1490, 1448, 1370, 1261, 1165, 1070, 1045, 1024, 908. ***m/z* (EI)** 211.2 (M^+, 100), 196.1 (78), 180.1 (9), 165.1 (13), 152.1 (7), 134.1 (6), 118.1 (54), 103.1 (10), 91.1 (35), 77.0 (25), 65.0 (7), 51.1 (11). The data for this compound are consistent with those reported in the literature.[305]

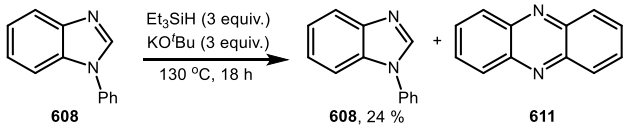
Treatment of 9-Phenyl-9*H*-carbazole (607) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from 9-phenyl-9*H*-carbazole **607** (122 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 4:1) afforded a complex mixture of products. From the ^{1}H NMR of the crude reaction mixture, the major component was starting material **607**, which was also detected by GC-MS (*m/z* = 243.1, retention time = 16.144 min). Also detected was *m/z* = 245.1 (retention time = 15.426 min), which may be a compound such as **840**, although this is not conclusive. Also

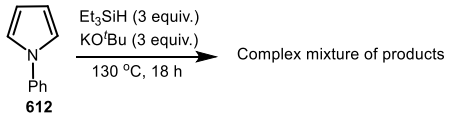
tentatively identified were silylated compounds **841** and **842** (*m/z* = 357.2, retention times = 18.315 and 18.360, and *m/z* = 471.3, retention times = 19.915, 20.805 and 21.261).

Treatment of 1-Phenyl-1*H*-benzo[*d*]imidazole (608) with Et_3SiH/KO^tBu



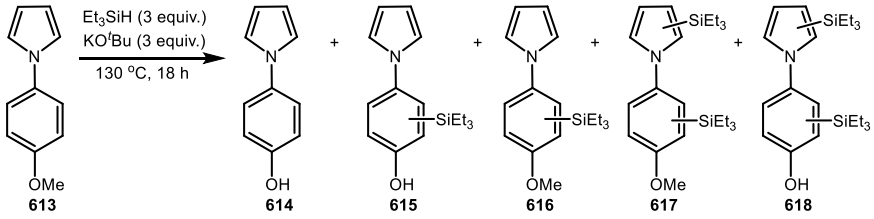
This reaction was carried out according to General Procedure C from 1-phenyl-1*H*-benzo[*d*]imidazole **608** (97.0 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (hexane:ethyl acetate, 100:0 → 3:7) afforded a complex mixture of products from which only starting material **608** could be isolated, with data consistent to those reported above (24 mg, 25 %). Crude GC-MS also indicated that **611** may be present (*m/z* = 180.1, retention time = 13.405 min), although this could not be isolated.

Treatment of 1-Phenyl-1*H*-pyrrole (612) with Et_3SiH/KO^tBu



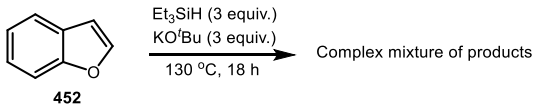
This reaction was carried out according to General Procedure C from 1-phenyl-1*H*-pyrrole **612** (72.0 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was afforded, from which nothing could be identified or isolated.

Treatment of 1-(4-Methoxyphenyl)-1H-pyrrole (613) with Et_3SiH/KO^tBu



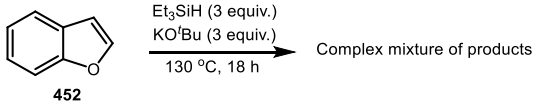
This reaction was carried out according to General Procedure C from 1-(4-methoxyphenyl)-1*H*-pyrrole **613** (87.0 mg, 0.50 mmol, 1.0 equiv.). A complex mixture of products was produced from which nothing could be isolated. Crude GC-MS indicated that compounds **614**-**618** may be present (*m/z* = 159.1, retention time = 12.449 min, *m/z* = 273.2, retention times = 14.539 and 15.327 min, *m/z* = 287.2, retention times = 14.921 and 15.424 min, *m/z* = 401.3, retention times = 16.560, 16.663, 16.702 and 17.345 min, and *m/z* = 387.3, retention time = 17.283 min).

Treatment of Benzofuran (**452**) with Et_3SiH/KO^tBu



This reaction was carried out according to General Procedure C from benzofuran **452** (0.06 mL, 0.54 mmol, 1.0 equiv.). A complex mixture of products was formed from which nothing could be isolated or identified. Polymerisation may have occurred as judged by the broad nature of the ^1H NMR spectrum.

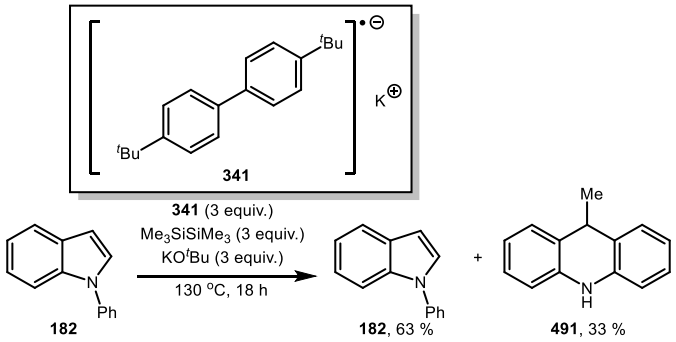
Treatment of Benzofuran (**452**) with KO^tBu Alone



This reaction was carried out according to General Procedure D from benzofuran **452** (0.06 mL, 0.54 mmol, 1.0 equiv.). A complex mixture of products was formed from which nothing could be isolated or identified. Polymerisation may have occurred as judged by the broad nature of the ^1H NMR spectrum.

8.7 – Mechanistic Studies from Chapter 4

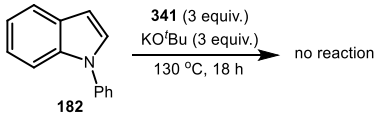
Treatment of 1-Phenyl-1*H*-indole (**508**) with **341**, $Me_3SiSiMe_3$ and KO^tBu



Compound **341** was prepared as described on page 167 Compound **341** (458 mg, 1.50 mmol, 3.0 equiv.), 1-phenyl-1*H*-indole **182** (97.0 mg, 0.50 mmol, 1.0 equiv.), KO^tBu (168 mg, 1.50 mmol, 3.0 equiv.) and hexamethyldisilane (0.31 mL, 1.51 mmol, 3.0 equiv.) were added to a pressure tube equipped with a stirrer bar in the glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography afforded 4,4'-di-*tert*-butylbiphenyl **789** as a white solid with data matching the commercial sample, followed by

1-phenyl-1*H*-indole **182** as a colourless oil (61 mg, 63 %), followed by 9-methyl-9,10-dihydroacridine **491** as a yellow solid (32 mg, 33 %). The data for these compounds are consistent with those reported above.

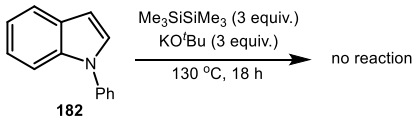
Treatment of 1-Phenyl-1*H*-indole (182) with 341 and KO^{t}Bu



182

Compound **341** (458 mg, 1.50 mmol, 3.0 equiv.), 1-phenyl-1*H*-indole **508** (97.0 mg, 0.50 mmol, 1.0 equiv.) and KO^{t}Bu (168 mg, 1.50 mmol, 3.0 equiv.) were added to a pressure tube equipped with a stirrer bar in the glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. No reaction was found to have taken place by ^{1}H NMR and TLC analysis of the crude reaction mixture.

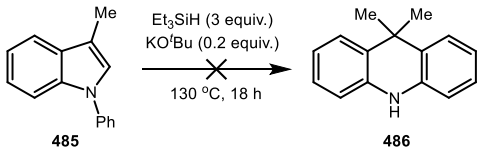
Treatment of 1-Phenyl-1*H*-indole (182) with $Me_3SiSiMe_3$ and KO^{t}Bu



182

Hexamethyldisilane (0.31 mL, 1.51 mmol, 3.0 equiv.), 1-phenyl-1*H*-indole **182** (97.0 mg, 0.50 mmol, 1.0 equiv.) and KO^{t}Bu (168 mg, 1.50 mmol, 3.0 equiv.) were added to a pressure tube equipped with a stirrer bar in the glovebox under nitrogen. The tube was then sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. No reaction was found to have taken place by ^{1}H NMR and TLC analysis of the crude reaction mixture.

Treatment of 3-Methyl-1-phenyl-1*H*-indole (485) with Et_3SiH and Substoichiometric KO^{t}Bu

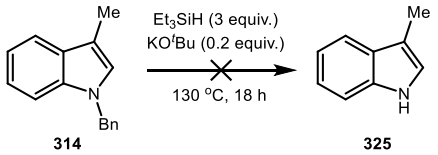


485 486

To a pressure tube, equipped with a stirrer bar in a glovebox, was added 3-methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.), Et_3SiH (0.24 mL, 1.50 mmol, 3.0 equiv.) and KO^{t}Bu (11.0 mg, 0.10 mmol, 0.2 equiv.). The tube was sealed, removed from the glovebox and heated

at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have occurred, and only starting material **485** was recovered, with data consistent with those reported previously (94 mg, 90 %).

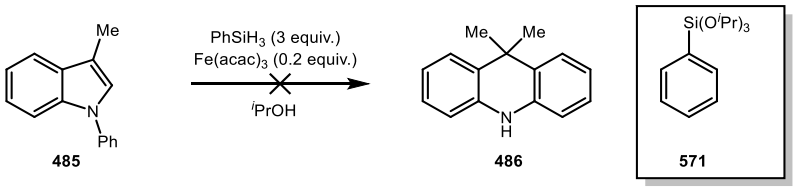
Treatment of 1-Benzyl-3-methyl-1*H*-indole (**314**) with Et_3SiH and Substoichiometric KO^tBu



314 **325**

To a pressure tube, equipped with a stirrer bar in a glovebox, was added 1-benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.), Et_3SiH (0.24 mL, 1.50 mmol, 3.0 equiv.) and KO^tBu (11 mg, 0.10 mmol, 0.2 equiv.). The tube was sealed, removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have occurred, and only starting material **314** was recovered, with data consistent with those reported previously (111 mg, 100 %).

Treatment of 3-Methyl-1-phenyl-1*H*-indole (**485**) under Iron-Catalysed Hydrogen Atom Transfer Conditions



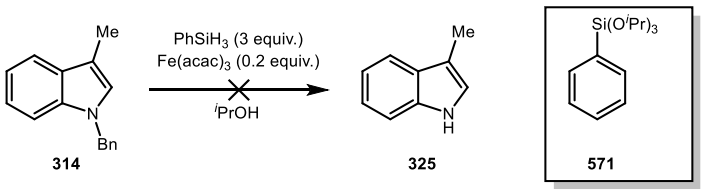
485 **486** **571**

3-Methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.) and $Fe(acac)_3$ (35.0 mg, 0.10 mmol, 0.2 equiv.) were added to a microwave vial, followed by a solution of phenylsilane (0.19 mL, 1.54 mmol, 3.1 equiv.) in isopropanol (2 mL). The mixture was stirred open to air at 50 °C for 1 h, then quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have taken place by ^1H NMR and GC-MS analysis of the crude reaction mixture. The crude sample was dissolved in $CDCl_3$ and 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 10 mol %) was added as an internal standard. The methoxy group of the internal standard (3.78 ppm) was integrated to 9 integral units, and the methyl group of **485** (2.41 ppm) was found to integrate to 22.4 integral units. Therefore, 75 % of the starting material was

remaining. No other products derived from **485** were detected by ^{1}H NMR or GC-MS of the crude mixture.

Alternatively, in a glovebox under nitrogen, 3-methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.) and $Fe(acac)_3$ (35.0 mg, 0.10 mmol, 0.2 equiv.) were added to a microwave vial, followed by a solution of phenylsilane (0.19 mL, 1.54 mmol, 3.1 equiv.) in isopropanol (2 mL). The tube was sealed, removed from the glovebox, and the mixture was stirred at 130 °C for 1 h, then quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have taken place by NMR and GC-MS analysis of the crude reaction mixture. The crude sample was dissolved in $CDCl_3$ and 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 10 mol %) was added as an internal standard. The methoxy group of the internal standard (3.78 ppm) was integrated to 9 integral units, and the methyl group of **485** (2.41 ppm) was found to integrate to 7.33 integral units. Therefore, 24 % of the starting material was remaining. No other products derived from **485** were detected by ^{1}H NMR or GC-MS of the crude reaction mixture. Also tentatively identified by ^{1}H NMR and GC-MS of the crude mixture was **571** (*m/z* = 282.0, retention time = 11.06 min). By setting the integration of the methoxy group of 1,3,5-trimethoxybenzene to 9 integral units, the integration of the septet at 4.28 ppm was found to be 16.46 integral units. This equates to a yield of 18 % based on phenylsilane. **^{1}H NMR** (400 MHz, $CDCl_3$) 1.22 (d, *J* = 6.0 Hz, 18 H, 6 x CH_3), 4.28 (spt, *J* = 6.1 Hz, 3 H, 3 x CH). The aromatic signals overlap with other signals. The visible signals for this compound are consistent with those reported in the literature.[306]

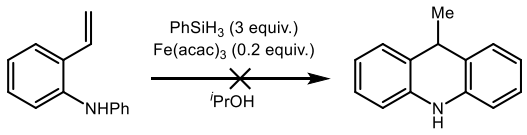
Treatment of 1-Benzyl-3-methyl-1*H*-indole (314) under Iron-Catalysed Hydrogen Atom Transfer Conditions



1-Benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.) and $Fe(acac)_3$ (35.0 mg, 0.10 mmol, 0.2 equiv.) were added to a microwave vial, followed by a solution of phenylsilane (0.19 mL, 1.54 mmol, 3.1 equiv.) in isopropanol (2 mL). The mixture was stirred open to air at 50 °C for 1 h, then quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have taken place by ^{1}H NMR and GC-MS analysis of the crude reaction mixture. The crude sample was dissolved in $CDCl_3$ and 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 10 mol %) was added as an internal standard. The methoxy group of the internal standard (3.78 ppm) was integrated to 9 integral units, and the methyl group of **314** (2.35 ppm) was found to integrate to 22.8 integral units. Therefore, 76 % of the starting material was remaining. No other products derived from **314** were detected by crude NMR or GC-MS.

Alternatively, in a glovebox under nitrogen, 1-benzyl-3-methyl-1*H*-indole **314** (111 mg, 0.50 mmol, 1.0 equiv.) and $Fe(acac)_3$ (35.0 mg, 0.10 mmol, 0.2 equiv.) were added to a microwave vial, followed by a solution of phenylsilane (0.19 mL, 1.54 mmol, 3.1 equiv.) in isopropanol (2 mL). The tube was sealed, removed from the glovebox, and the mixture was stirred at 130 °C for 1 h, then quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have taken place by ^{1}H NMR and GC-MS analysis of the crude reaction mixture. The crude sample was dissolved in $CDCl_3$ and 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 10 mol %) was added as an internal standard. The methoxy group of the internal standard (3.78 ppm) was integrated to 9 integral units, and the methyl group of **314** (2.35 ppm) was found to integrate to 16.85 integral units. Therefore, 56 % of the starting material was remaining. No other products derived from **314** were detected by ^{1}H NMR or GC-MS. Also tentatively identified by ^{1}H NMR and GC-MS of the crude reaction mixture was **571** (*m/z* = 282.1, retention time = 11.07 min). By setting the integration of the methoxy group of 1,3,5-trimethoxybenzene to 9 integral units, the integration of the septet at 4.28 ppm was found to be 34.49 integral units. This equates to a yield of 38 % based on phenylsilane. **^{1}H NMR** (400 MHz, $CDCl_3$) 1.22 (d, *J* = 6.0 Hz, 18 H, 6 x CH_3), 4.28 (spt, *J* = 6.1 Hz, 3 H, 3 x CH). The aromatic signals overlap with other signals. The visible signals for this compound are consistent with those reported in the literature.[306]

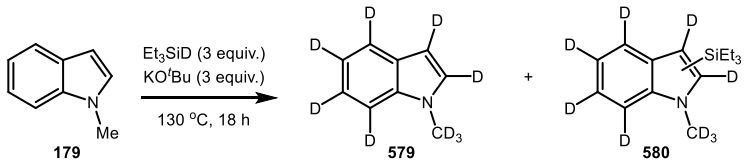
Treatment of *N*-Phenyl-2-vinylaniline (595) under Iron-Catalysed Hydrogen Atom Transfer Conditions



595 **491**

To a microwave vial containing a stirrer bar and $Fe(acac)_3$ (35.0 mg, 0.10 mmol, 0.2 equiv.) was added a solution of phenylsilane (0.19 mL, 1.54 mmol, 3.1 equiv.) in isopropanol (1 mL) at 50 °C. A solution of *N*-phenyl-2-vinylaniline **595** (98.0 mg, 0.50 mmol, 1.0 equiv.) in isopropanol (1 mL) was added dropwise over 1 h, and the mixture was then stirred for a further 1 h at room temperature. The mixture was then quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Polymerisation was found to have occurred as judged by the broad nature of the ^{1}H NMR spectrum, and no **491** was detected.

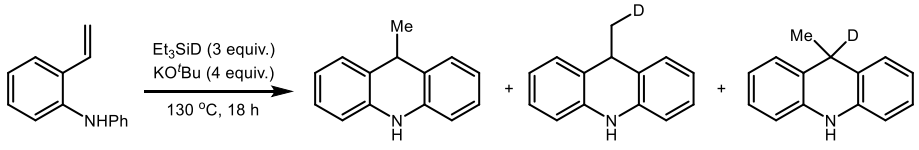
Treatment of 1-Methyl-1*H*-indole (615) with Et_3SiD/KO^tBu



179 579 580

N-methylindole **179** (0.06 mL, 0.48 mmol, 1.0 equiv.), Et_3SiD (0.24 mL, 1.50 mmol, 3.1 equiv.) and KO^tBu (168 mg, 1.50 mmol, 3.1 equiv.) were sealed in a pressure tube in a nitrogen-filled glovebox. The tube was removed and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. A complex mixture of products resulted, however, crude NMR and GC-MS analysis indicate that deuteration has taken place in all positions. GC-MS indicates the presence of a number of isomers with *m/z* ranging from 131 (no deuteration, *i.e.* **179**) to 140 (full deuteration, *i.e.* **579**). Deuterium NMR indicated the presence of deuterium atoms in all positions, with peaks appearing at the same chemical shifts as the protons in the ^{1}H NMR of **179**.

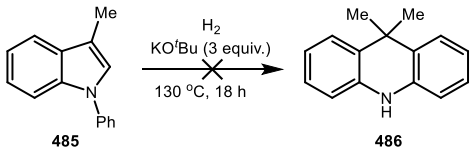
Treatment of *N*-phenyl-2-vinylaniline (595) with Et_3SiD/KO^tBu



595 491 596 597

To a microwave vial in the glovebox was added Et_3SiD (0.24 mL, 1.50 mmol, 3.0 equiv.), and KO^tBu (224 mg, 2.0 mmol, 4.0 equiv.). The vial was sealed and removed from the glovebox and heated at 130 °C behind a shield. *N*-phenyl-2-vinylaniline **595** (98.0 mg, 0.50 mmol, 1.0 equiv.) was added dropwise over 1 h, and the resulting mixture was then stirred at this temperature for 18 h. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 90:10) afforded an inseparable mixture of 9-methyl-9,10-dihydroacridine **491**, 9-(methyl-*d*)-9,10-dihydroacridine **596**, and 9-methyl-9,10-dihydroacridine-9-*d* **597** (7 mg, ~ 7 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.34 - 1.37 (m, overlapping signals for CH_3 and CH_2D), 4.12 (q, *J* = 6.8 Hz, 1 H, CH), 6.04 (br. s., 1 H, NH), 6.72 (dd, *J* = 8.1, 1.0 Hz, 2 H, 2 x ArH), 6.90 (app. td, *J* = 7.4, 1.0 Hz, 2 H, 2 x ArH), 7.11 (app. td, *J* = 7.6, 1.4 Hz, 2 H, 2 x ArH), 7.18 (d, *J* = 7.5 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 26.1 (t, *J* = 20.0 Hz), 26.4 (s), 36.6 (s), 36.7 (s), 113.4 (s), 120.8 (s), 125.7 (s), 126.8 (s), 128.1 (s), 139.0 (s). **^{2}D{^{1}H}-NMR** (61 MHz, $CHCl_3$) 1.37 (s), 4.10 (s). ***m/z* (CI)** 197.2 $[M+H]^+$ (one deuterium atom), 196.1 $[M+H]^+$ (no deuterium atoms), 195.1 $[M+H]^+$ and 194.2 $[M+H]^+$. Presumably, *m/z* = 195.1 and 194.1 arise from partial oxidation of **491** and **596**-**597**.

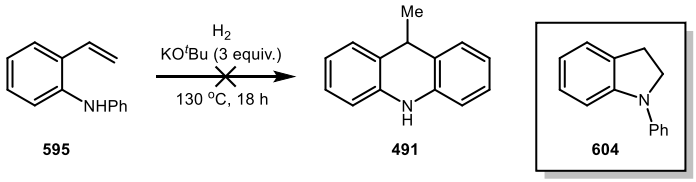
Treatment of 3-Methyl-1-Phenyl-1*H*-indole (485) with KO^{t}Bu + H_2



485 486

To a microwave vial in the glovebox was added 3-methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox, and vacuum was applied to remove the nitrogen atmosphere, which was replaced by hydrogen gas from a balloon. The mixture was stirred at 130 °C for 18 h behind a shield. After cooling to room temperature, the vial was purged with argon and then opened. The mixture was quenched with water and extracted into Et_2O, dried over Na_2SO_4, filtered and concentrated under reduced pressure. No reaction was found to have taken place, and starting material **485** was recovered with data consistent with those reported previously (104 mg, 100 %).

Treatment of *N*-Phenyl-2-vinylaniline (595) with KO^{t}Bu + H_2

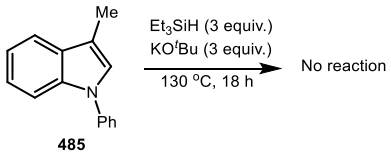


595 491 604

To a microwave vial in the glovebox was added potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox, and vacuum was applied to remove the nitrogen atmosphere, which was replaced by hydrogen gas from a balloon. The mixture was stirred at 130 °C behind a shield, and *N*-phenyl-2-vinylaniline **595** was added dropwise by needle and syringe over the course of 1 h. After cooling to room temperature, the vial was purged with argon and then opened. The mixture was quenched with water and extracted into diethyl ether, dried over Na_2SO_4, filtered and concentrated under reduced pressure. No dihydroacridines were detected, and ^{1}H NMR of the crude reaction mixture with 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.1 equiv.) added as an internal standard indicated that the yield of recovered starting material **595** was 46 %. This was determined by comparison of the integration of the aromatic protons of the internal standard (6.11 ppm, 3 integral units) to the integration one the alkene signals (5.32-5.35 ppm, 4.57 integral units). GC-MS of the crude mixture indicated that starting material was present (*m/z* = 195.1, retention time = 13.648 min) alongside a second component which could also be detected by ^{1}H NMR and GC-MS. This second component was tentatively identified as **604** by ^{1}H NMR, with key signals at 3.15 (t, *J* = 8.5 Hz, 1 H) 3.97 (t, *J* = 8.4 Hz, 1 H), which are consistent with the ^{1}H NMR signals reported in the literature.[307] However, GC-MS indicated *m/z* = 193.1 (retention time = 13.867 min), suggesting that oxidation is taking place at the high temperature of the GC-MS (300 °C). NIST searching of the mass spectroscopy library suggests with a high degree of confidence that this compound is *N*-phenyl-1*H*-indole, although no C3 proton for an indole is observed by NMR. This indole would result if **604** was oxidised in

the GC-MS. The yield of **604** was calculated to be 4 % by comparing the integration of the methoxy peak of the internal standard (9 integral units) to the relative integration of a CH_2 of **604** (0.80 integral units).

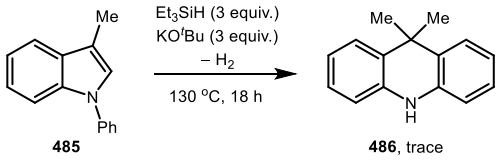
Treatment of 3-Methyl-1-phenyl-1*H*-indole (485) with Et_3SiH/KO^tBu in a Flask with a Condenser



485

This reaction was carried out according to General Procedure C from 3-methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.), but in an oven-dried flask with a condenser rather than in a pressure tube as before. No reaction was found to take place, and **485** was recovered with data consistent with those reported above.

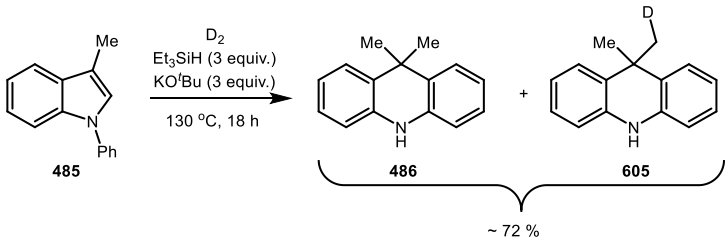
Treatment of 3-Methyl-1-phenyl-1*H*-indole (485) with Et_3SiH/KO^tBu with the Removal of H_2



485 **486**, trace

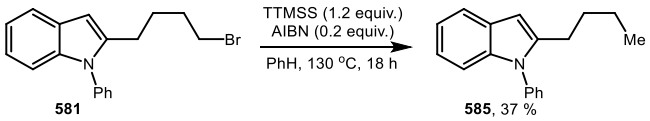
In a microwave vial in the glovebox was added triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox, and heated at 130 °C for 1 h behind a shield. After this time, the hydrogen gas generated was removed by purging the vial with argon. 3-Methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.) was then added and the mixture stirred at 130 °C for 18 h. After cooling to room temperature, the mixture was diluted with water and extracted into diethyl ether, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 90:10) afforded starting material **485**, with data consistent with those reported earlier (76 mg, 73 %) and 9,9-dimethyl-9,10-dihydroacridine **486**, which was detected by GC-MS, with data consistent with those reported earlier (<1 mg).

Treatment of 3-Methyl-1-phenyl-1*H*-indole (**485**) with Et_3SiH/KO^tBu with the Replacement of H_2 with D_2



To a microwave vial in the glovebox was added triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The vial was sealed and removed from the glovebox and stirred at 130 °C for 1 h behind a shield. After cooling to room temperature, the hydrogen gas generated was removed under vacuum and replaced with deuterium gas from a balloon. 3-Methyl-1-phenyl-1*H*-indole **485** (104 mg, 0.50 mmol, 1.0 equiv.) was then added and the mixture stirred at 130 °C for 18 h behind a shield. After cooling to room temperature, the atmosphere was removed under vacuum and replaced with argon. The tube was then opened, and the mixture was diluted with water and extracted into diethyl ether, dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 90:10) afforded starting material **485** with data consistent with those reported previously (6 mg, 6 %), and an inseparable mixture of 9,9-dimethyl-9,10-dihydroacridine **486** and 9-methyl-9-(methyl-*d*)-9,10-dihydroacridine **605** (75 mg, ~72 %). This dihydroacridine mixture was found to quickly oxidise to a radical species in air, and this was reduced by dissolving the sample in DCM and washing with saturated potassium iodide solution. The organic layer was dried over a hydrophobic frit and concentrated under reduced pressure. **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.59 - 1.64 (m, 2 x CH_3 + CH_3 and CH_2D), 6.15 (br. s., 1 H, NH), 6.72 (dd, *J* = 7.9, 1.1 Hz, 2 H, 2 x ArH), 6.96 (app. td, *J* = 7.5, 1.3 Hz, 2 H, 2 x ArH), 7.14 (app. td, *J* = 7.6, 1.4 Hz, 2 H, 2 x ArH), 7.42 (dd, *J* = 7.8, 1.0 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 30.2 (t, *J* = 19.3 Hz), 30.5, 36.1, 36.2, 113.4, 120.6, 125.5, 126.7, 129.1, 138.4. **^{2}D{^{1}H}-NMR** (61 MHz, $CHCl_3$) 1.63 (s, CH_2D), 6.77 (s, ArD). ***m/z* (EI)** 211.1 ($[M+2D]^+$, 2), 210.1 ($[M+D]^+$, 6), 209.2 (M^+, 10), 208.1 (2), 195.1 (41), 194.1 (100), 193.1 (15), 192.1 (12), 191.1 (7).

Treatment of 2-(4-Bromobutyl)-1-phenyl-1H-indole (**581**) with $(Me_3Si)_3SiH$/AIBN



2-(4-Bromobutyl)-1-phenyl-1H-indole **581** (160 mg, 0.49 mmol, 1.0 equiv.), tris(trimethylsilyl)silane (0.18 mL, 0.59 mmol, 1.2 equiv.) and AIBN (16.0 mg, 0.10 mmol, 0.2 equiv.) were dissolved in benzene (1 mL) in a glovebox under nitrogen. The tube was removed and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched by the addition of water (50 mL) and the products were extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated

under reduced pressure. Purification by column chromatography (hexane) afforded 2-butyl-1-phenyl-1*H*-indole **585** as a colourless oil (45 mg, 37 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.86 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.33 (sxt, *J* = 7.5 Hz, 2 H, CH_2), 1.58 (quin, *J* = 7.5 Hz, 2 H, CH_2), 2.64 (t, *J* = 7.5 Hz, 2 H, CH_2), 6.43 (app. br. s., 1 H, ArH), 7.04 - 7.15 (m, 3 H, 3 x ArH), 7.33 - 7.40 (m, 2 H, 2 x ArH), 7.43 - 7.50 (m, 1 H, ArH), 7.51 - 7.58 (m, 2 H, 2 x ArH), 7.58 - 7.63 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.8, 22.3, 26.7, 30.7, 100.1, 110.0, 119.6, 119.9, 121.0, 127.8, 128.1, 128.3, 129.4, 138.1, 138.3, 141.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3053, 2954, 2927, 2858, 1595, 1546, 1496, 1456, 1392, 1209, 1149, 1016, 1004, 987, 761, 744, 734. ***m/z* (EI)** 249.2 (M^+, 39), 220.2 (6), 206.2 (100), 191.1 (5), 178.1 (6), 165.1 (2), 152.1 (1), 128.1 (5), 115.1 (3), 102.2 (4), 89.1 (3), 77.1 (6), 63.1 (2), 51.1 (4). **HRMS (CI)** calcd. for $C_{18}H_{20}N^+$ ([M+H]$^+$): 250.1596, found: 250.1596.

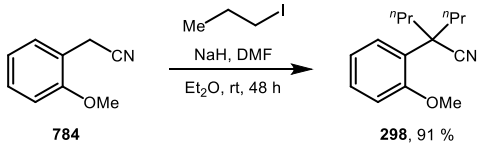
Treatment of 2-(4-Bromobutyl)-1-phenyl-1H-indole (581) with Bu_3SnH/AIBN

581 **586**, 46 %

2-(4-Bromobutyl)-1-phenyl-1H-indole **581** (160 mg, 0.49 mmol, 1.0 equiv.), tributyltin hydride (0.16 mL, 0.59 mmol, 1.2 equiv.) and AIBN (16.0 mg, 0.10 mmol, 0.2 equiv.) were dissolved in benzene (1 mL) in a glovebox under nitrogen. The tube was removed and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched by the addition of water (50 mL) and the products were extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane) afforded 9-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole **586** as a colourless oil (56 mg, 46 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.87 - 1.96 (m, 4 H, 2 x CH_2), 2.58 - 2.65 (m, 2 H, CH_2), 2.78 - 2.86 (m, 2 H, CH_2), 7.09 - 7.15 (m, 2 H, 2 x ArH), 7.20 - 7.26 (m, 1 H, ArH), 7.35 - 7.43 (m, 3 H, 3 x ArH), 7.48 - 7.56 (m, 3 H, 3 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 21.1, 23.1, 23.2, 23.4, 109.8, 110.9, 117.7, 119.5, 121.3, 127.0, 127.2, 127.7, 129.3, 135.8, 137.2, 138.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 3047, 2929, 2839, 1597, 1498, 1452, 1375, 1230, 1207, 1012, 736, 698. ***m/z* (EI)** 247.2 (M^+, 95), 230.1 (5), 218.2 (100), 204.1 (8), 191.1 (1), 178.1 (1), 167.1 (5), 152.1 (1), 140.1 (2), 128.1 (3), 108.6 (14), 89.1 (3), 77.1 (8), 63.1 (2), 51.1 (7). The data for this compound are consistent with those reported in the literature.

8.8 – Synthesis of Substrates for Chapter 5

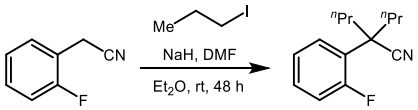
Preparation of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298)



784 **298**, 91 %

This substrate was prepared according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 8.56 g, 214 mmol, 3.15 equiv.) in dry DMF (200 mL), under nitrogen, was added a mixture of 2-(2-methoxyphenyl)acetonitrile **784** (10.0 g, 67.9 mmol, 1.00 equiv.) and 1-iodopropane (29.8 mL, 307 mmol, 4.52 equiv.) in dry diethyl ether (100 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was the dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** as a colourless oil, with data consistent to those reported above (14.38 g, 91 %).

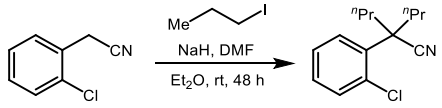
Preparation of 2-(2-Fluorophenyl)-2-propylpentanenitrile (844)



843 **844**, 79 %

This substrate was prepared according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 630 mg, 15.8 mmol, 3.15 equiv.) in dry DMF (15 mL), under nitrogen, was added a mixture of 2-(2-fluorophenyl)acetonitrile **843** (676 mg, 5.00 mmol, 1.00 equiv.) and 1-iodopropane (2.19 mL, 22.5 mmol, 4.50 equiv.) in dry diethyl ether (7.5 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature and then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-fluorophenyl)-2-propylpentanenitrile **844** as a colourless oil (866 mg, 79 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.91 (t, *J* = 7.1 Hz, 6 H, 2 x CH_3), 1.05 - 1.23 (m, 2 H, 2 x CH), 1.41 - 1.59 (m, 2 H, 2 x CH), 1.96 (td, *J* = 12.8, 4.9 Hz, 2 H, 2 x CH), 2.07 - 2.21 (m, 2 H, 2 x CH), 7.05 (ddd, *J* = 12.8, 8.4, 1.5 Hz, 1 H, ArH), 7.16 (app. td, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.27 - 7.35 (m, 1 H, ArH), 7.59 (app. td, *J* = 8.0, 1.7 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.8 (s), 19.0 (s), 40.7 (d, *J* = 3.9 Hz), 48.0 (d, *J* = 3.9 Hz), 116.6 (d, *J* = 23.1 Hz), 122.3 (s), 124.3 (d, *J* = 3.1 Hz), 125.1 (d, *J* = 10.8 Hz), 129.7 (d, *J* = 9.3 Hz), 130.0 (d, *J* = 4.6 Hz), 160.0 (d, *J* = 248.1 Hz). **ATR-IR** ν_{max} (neat)/cm^{-1} 2963, 2934, 2875, 2233, 1578, 1491, 1446, 1222, 1091, 805, 757, 545, 484. ***m/z* (EI)** 219.2 (M^+, 19), 190.1 (7), 177.1 (75), 148.1 (100), 134.1 (55), 121.1 (43), 110.0 (14), 101.1 (14), 75.1 (6). **HRMS (CI)** calcd. for $C_{14}H_{19}FN^+$ ($[M+H]^+$): 220.1502, found: 220.1507.

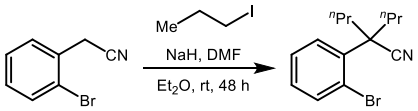
Preparation of 2-(2-Chlorophenyl)-2-propylpentanenitrile (846)



845 **846**, 100 %

This substrate was prepared according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 630 mg, 15.8 mmol, 3.15 equiv.) in dry DMF (15 mL), under nitrogen, was added a mixture of 2-(2-chlorophenyl)acetonitrile **845** (758 mg, 5.00 mmol, 1.00 equiv.) and 1-iodopropane (2.19 mL, 22.5 mmol, 4.50 equiv.) in dry diethyl ether (7.5 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature and then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-chlorophenyl)-2-propylpentanenitrile **846** as a colourless oil (1.18 g, 100 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.92 (t, *J* = 7.5 Hz, 6 H, 2 x CH_3), 1.04 - 1.24 (m, 2 H, 2 x CH), 1.37 - 1.55 (m, 2 H, 2 x CH), 1.99 (ddd, *J* = 13.9, 12.1, 4.6 Hz, 2 H, 2 x CH), 2.51 (ddd, *J* = 13.9, 12.3, 4.6 Hz, 2 H, 2 x CH), 7.23 - 7.32 (m, 2 H, 2 x ArH), 7.35 - 7.41 (m, 1 H, ArH), 7.68 - 7.73 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.9, 19.0, 39.4, 50.3, 123.0, 127.1, 129.1, 131.1, 131.8, 132.2, 134.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 2961, 2933, 2874, 22334, 1569, 1467, 1430, 1120, 1039, 758, 466. ***m/z* (EI)** 237.1 (M^+, 7), 235.1 (M^+, 21), 208.1 (3), 206.1 (9), 195.1 (22), 193.1 (69), 166.0 (38), 164.1 (100), 152.0 (17), 150.0 (48), 139.0 (13), 137.0 (36), 128.1 (21), 115.1 (12), 101.1 (16), 89.1 (6), 77.1 (9), 63.1 (4), 51.1 (6). **HRMS (CI)** calcd. for $C_{14}H_{19}ClN^+$ ($[M+H]^+$): 236.1206 and 238.1180, found: 236.1211 and 238.1184.

Preparation of 2-(2-Bromophenyl)-2-propylpentanenitrile (848)

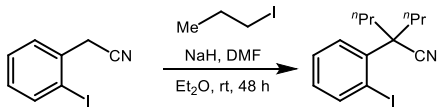


847 **848**, 100 %

This substrate was prepared according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 630 mg, 15.8 mmol, 3.15 equiv.) in dry DMF (15 mL), under nitrogen, was added a mixture of 2-(2-bromophenyl)acetonitrile **847** (0.65 mL, 5.01 mmol, 1.00 equiv.) and 1-iodopropane (2.19 mL, 22.5 mmol, 4.50 equiv.) in dry diethyl ether (7.5 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature and then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-bromophenyl)-2-propylpentanenitrile **848**

as a colourless oil (1.18 g, 100 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.92 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.04 - 1.22 (m, 2 H, 2 x CH), 1.35 - 1.54 (m, 2 H, 2 x CH) 1.97 (ddd, *J* = 14.1, 12.2, 4.6 Hz, 2 H, 2 x CH), 2.61 (ddd, *J* = 13.9, 12.3, 4.6 Hz, 2 H, 2 x CH), 7.17 (m, 1 H, ArH), 7.33 (app. td, *J* = 7.4, 1.5 Hz, 1 H, ArH), 7.61 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH), 7.72 (dd, *J* = 8.1, 1.7 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.9, 19.0, 39.3, 50.9, 120.3, 123.0, 127.6, 129.3, 131.6, 135.4, 135.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 2960, 2932, 2873, 2233, 1565, 1469, 1426, 1020, 757, 661, 532, 459. ***m/z* (EI)** 281.1 (M^+, 23), 279.1 (M^+, 23), 252.0 (9), 250.1 (10), 239.1 (70), 237.1 (74), 210.0 (98), 208.0 (100), 195.9 (45), 194.0 (47), 183.0 (30), 181.0 (31), 169.0 (8), 158.1 (12), 140.1 (9), 129.1 (33), 115.1 (37), 102.1 (32), 89.0 (13), 77.1 (20), 63.1 (9), 51.1 (15). **HRMS (CI)** calcd. for $C_{14}H_{19}BrN^+$ ([M+H]$^+$): 280.0701 and 282.0681, found: 280.0703 and 282.0684.

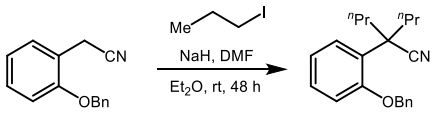
Preparation of 2-(2-Iodophenyl)-2-propylpentanenitrile (850)



849 **850**, 84 %

This substrate was prepared according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 630 mg, 15.8 mmol, 3.17 equiv.) in dry DMF (15 mL), under nitrogen, was added a mixture of 2-(2-iodophenyl)acetonitrile **849** (0.69 mL, 4.97 mmol, 1.00 equiv.) and 1-iodopropane (2.19 mL, 22.5 mmol, 4.53 equiv.) in dry diethyl ether (7.5 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature and then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-iodophenyl)-2-propylpentanenitrile **850** as a white solid (1.38 g, 84 %). **Mp** = 79-81 °C (lit. mp = 71-73 °C).[308] **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.93 (t, *J* = 7.4 Hz, 6 H, 2 x CH_3), 1.04 - 1.23 (m, 2 H, 2 x CH), 1.35 - 1.53 (m, 2 H, 2 x CH), 1.92 (ddd, *J* = 14.2, 12.2, 4.7 Hz, 2 H, 2 x CH), 2.70 (ddd, *J* = 14.0, 12.3, 4.7 Hz, 2 H, 2 x CH), 6.97 (app. td, *J* = 7.5, 1.7 Hz, 1 H, ArH), 7.36 (app. td, *J* = 7.6, 1.0 Hz, 1 H, ArH), 7.68 (dd, *J* = 8.1, 1.7 Hz, 1 H, ArH), 8.00 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.9, 18.9, 39.2, 51.3, 92.1, 123.1, 128.2, 129.3, 131.6, 137.7, 143.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 2952, 2926, 2870, 2228, 1463, 1423, 1377, 1279, 1170, 1105, 1008, 764, 731, 719, 652, 528, 454. ***m/z* (EI)** 327.1 (M^+, 48), 298.1 (8), 285.1 (64), 256.0 (100), 241.9 (42), 228.9 (31), 214.9 (5), 200.2 (4), 157.1 (20), 142.1 (13), 129.1 (39), 115.1 (42), 102.1 (25), 77.0 (16), 63.1 (8), 51.0 (11). **HRMS (CI)** calcd. for $C_{14}H_{19}IN^+$ ([M+H]$^+$): 328.0562, found: 328.0559. The data for this compound are consistent with those reported in the literature.[308]

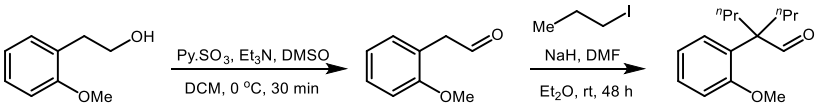
Preparation of 2-(2-(Benzyloxy)phenyl)-2-propylpentanenitrile (675)



851 **675**, 64 %

This substrate was prepared according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 630 mg, 15.8 mmol, 3.15 equiv.) in dry DMF (15 mL), under nitrogen, was added a mixture of 2-(2-)benzyloxy)phenyl)acetonitrile **851** (1.12 g, 5.02 mmol, 1.00 equiv.) and 1-iodopropane (2.19 mL, 22.5 mmol, 4.48 equiv.) in dry diethyl ether (7.5 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature and then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 9:1) afforded 2-(2-(benzyloxy)phenyl)-2-propylpentanenitrile **675** as a white solid (979 mg, 64 %). **Mp** = 94-97 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.90 (t, *J* = 7.4 Hz, 6 H, 2 x CH_3), 1.11 - 1.26 (m, 2 H, 2 x CH), 1.40 - 1.57 (m, 2 H, 2 x CH), 1.93 (ddd, *J* = 12.3, 4.4, 1.0 Hz, 2 H, 2 x CH), 2.36 (ddd, *J* = 12.3, 5.0, 1.0 Hz, 2 H, 2 x CH), 5.14 (s, 2 H, CH_2), 6.96 - 7.06 (m, 2 H, 2 x ArH), 7.27 - 7.34 (m, 1 H, ArH), 7.37 - 7.43 (m, 1 H, ArH), 7.43 - 7.48 (m, 4 H, 4 x ArH), 7.61 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.9, 19.0, 39.7, 48.6, 70.4, 112.6, 120.8, 123.6, 125.5, 127.5, 128.1, 128.6, 128.9, 129.8, 136.5, 156.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 2956, 2870, 2233, 1596, 1489, 1445, 1268, 1220, 1097, 1019, 787, 756, 737, 491. **HRMS (CI)** calcd. for $C_{21}H_{26}NO^+$ ([M+H]$^+$): 308.2014, found: 308.2014.

Preparation of 2-(2-Methoxyphenyl)-2-propylpentanal (698)



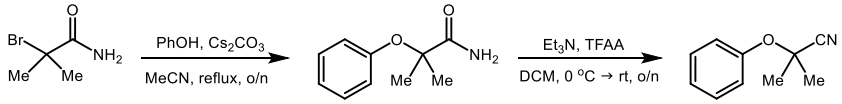
852 **853**, 47 % **698**, 35 %

The first step was carried out according to a literature procedure.[309] To a solution of 2-(2-methoxyphenyl)ethan-1-ol **852** (1.52 g, 9.99 mmol, 1.00 equiv.) and triethylamine (4.22 mL, 30.3 mmol, 3.03 equiv.) in DCM (18 mL) at 0 °C was added a solution of pyridin-1-ium-1-sulfonate (4.78 g, 30.0 mmol, 3.00 equiv.) in DMSO (5.5 mL). The resulting mixture was stirred at 0 °C for 30 min then poured into brine. The organic layer was separated and washed with 2 M HCl, then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-methyoxyphenyl)acetaldehyde **853** as a colourless oil (700 mg, 47 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 3.65 (s, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 6.88 - 7.00 (m, 2 H, 2 x ArH), 7.16 (d, *J* = 7.4 Hz, 1 H, ArH), 7.31 (app. t, *J* = 7.9 Hz, 1 H, ArH), 9.64 - 9.75 (m, 1 H, CHO). **^{13}C-NMR** (101 MHz, $CDCl_3$) 45.4, 55.4, 110.5, 120.8, 121.2, 128.9, 131.2, 157.6, 200.2. **ATR-IR** ν_{max} (neat)/cm^{-1} 3009, 2939, 2836, 1717, 1602, 1494, 1463, 1288, 1244, 1050, 1028, 752. ***m/z* (EI)** 150.1 (M$^+$, 38), 121.1

(72), 107.1 (11), 91.1 (100), 77.1 (22), 65.1 (21), 51.1 (14). The data for this compound are consistent with those reported in the literature.[310]

The second step was carried out according to a modified literature procedure.[233] To a solution of sodium hydride (60 % dispersion in mineral oil, 587 mg, 14.7 mmol, 3.15 equiv.) in dry DMF (14 mL), under nitrogen, was added a mixture of 2-(2-methoxyphenyl)acetaldehyde **853** (700 mg, 4.66 mmol, 1.00 equiv.) and 1-iodopropane (2.05 mL, 21.0 mmol, 4.51 equiv.) in dry diethyl ether (7 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature and then quenched by slow addition of methanol. The resulting mixture was concentrated under reduced pressure, redissolved in diethyl ether and washed with water, sodium bisulfite solution, and sodium carbonate solution. The organic layer was then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-(2-methoxyphenyl)-2-propylpentanal **698** as a colourless oil (382 mg, 35 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.88 (t, *J* = 7.4 Hz, 6 H, 2 x CH_3), 1.02 - 1.27 (m, 4 H, 2 x CH_2), 1.77 - 1.95 (m, 4 H, 2 x CH_2), 3.76 (s, 3 H, OCH_3), 6.91 (d, *J* = 7.9 Hz, 1 H, ArH), 7.02 (app. td, *J* = 7.5, 1.2 Hz, 1 H, ArH), 7.24 - 7.33 (m, 2 H, 2 x ArH), 9.55 (s, 1 H, CHO). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.7, 16.8, 34.4, 55.0, 55.3, 111.4, 120.8, 128.3 (2 signals), 129.9, 156.9, 204.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 2957, 2872, 2704, 1723, 1598, 1582, 1488, 1460, 1238, 1103, 1020, 791, 750, 644, 584, 511. **HRMS (CI)** calcd. for $C_{15}H_{23}O_2^+$ ([M+H]$^+$): 235.1698, found: 235.1700.

Preparation of 2-Methyl-2-phenoxypropanenitrile (**701**)



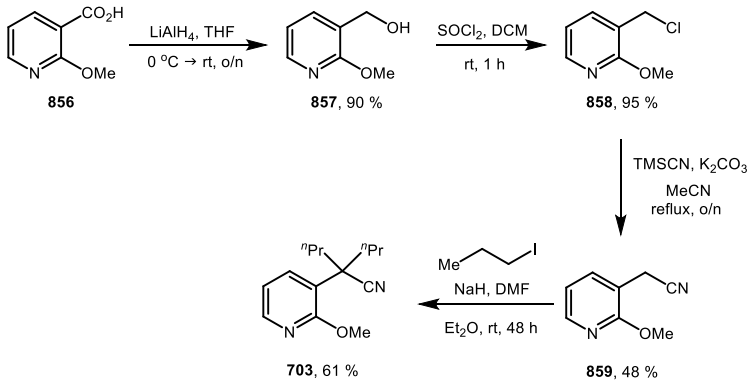
854 **855**, 24 % **701**, 67 %

This compound was prepared according to a modified literature procedure.[311] To a mixture of phenol (941 mg, 10 mmol, 1 equiv.) and 2-bromo-2-methylpropanamide **854** (1.66 g, 10.0 mmol, 1.0 equiv.) in acetonitrile (35 ml) was added cesium carbonate (4.89 g, 15 mmol, 1.5 equiv.), and the reaction mixture was refluxed overnight. After removal of the solvent, the residue was partitioned between ethyl acetate and water, and the organic layer was washed with a 1 M solution of NaOH, water and brine, then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 35:65) afforded 2-methyl-2-phenoxypropanamide **855** as a white solid (423 mg, 24 %). **Mp** = 109-112 °C (lit. Mp = 110-111 °C).[312] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.55 (s, 6 H, 2 x CH_3), 5.38 (br s, 1 H, NH), 6.65 (br s, 1 H, NH), 6.93 - 6.99 (m, 2 H, 2 x ArH), 7.09 (app. t, *J* = 7.1 Hz, 1 H, ArH), 7.30 (app. t, *J* = 7.1 Hz, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 25.0, 81.3, 121.3, 123.3, 129.3, 154.3, 177.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3451, 3298, 3237, 2993, 1659, 1585, 1483, 1401, 1366, 1294, 1223, 1149, 1026, 969, 904, 753, 698, 534. ***m/z* (EI)** 179.1 (M$^+$, 12), 135.1 (100), 107.1 (19), 94.0

(81), 86.1 (43), 77.0 (44), 65.0 (34), 58.1 (47), 51.0 (17). **HRMS (CI)** calcd. for $C_{10}H_{14}NO_2^+$ ($[M+H]^+$): 180.1025, found: 180.1027.

To a solution of 2-methyl-2-phenoxypropanamide **855** (423 mg, 2.36 mmol, 1.0 equiv.) in dry DCM (11 mL) and triethylamine (0.99 mL, 7.08 mmol, 3.0 equiv.) at 0 °C was added trifluoroacetic anhydride (0.50 mL, 3.54 mmol, 1.5 equiv.). After complete addition, the solution was allowed to warm to room temperature and stirred overnight. After this time, the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was diluted with DCM and washed with saturated $NaHCO_3$, water and brine, dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 9:1) afforded 2-methyl-2-phenoxypropanenitrile **701** as a colourless oil (255 mg, 67 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.73 (s, 6 H, 2 x CH_3), 7.14 - 7.23 (m, 3 H, 3 x ArH), 7.32 - 7.40 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 27.5, 72.0, 120.9, 121.8, 124.7, 129.5, 154.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 2995, 2965, 2932, 2238, 1591, 1490, 1369, 1220, 1149, 1072, 957, 808, 755, 696, 496. ***m/z* (EI)** 161.1 (M^+, 14), 94.1 (100), 77.1 (5), 66.1 (17), 65.1 (18), 51.1 (5). **HRMS (CI)** calcd. for $C_{12}H_{10}NO^+$ ($[M+H]^+$): 162.0919, found: 162.1911.

Preparation of 2-(2-Methoxypyridin-3-yl)-2-propylpentanenitrile (703)



This substrate was prepared according to a modified literature procedure.[313] To a solution of $LiAlH_4$ (2 M in THF, 5.50 mL, 11.0 mmol, 1.1 equiv.) at 0 °C under nitrogen was added a solution of 2-methoxynicotinic acid **856** (1.53 g, 9.99 mmol, 1 equiv.) in dry THF (21 mL). The resulting mixture was stirred overnight at room temperature, and then cooled in an ice bath. The reaction was quenched by the dropwise addition of a THF:water (4:1) solution, until bubbling ceased. 2 M NaOH solution was then added, and the reaction mixture was extracted into diethyl ether. The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure to afford (2-methoxypyridin-3-yl)methanol **857** as a yellow oil, which required no further purification (1.26 g, 90 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.00 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2), 6.89 (dd, *J* = 5.1, 7.1 Hz, 1H, ArH), 7.65 - 7.54 (m, 1H, ArH), 8.10 (dd, *J* = 5.4, 2.0 Hz, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 53.3, 61.0, 116.9, 123.3, 136.5, 145.8, 161.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3326, 2950, 1588, 1462, 1410, 1362, 1307, 1110, 1019, 782. ***m/z* (CI)** 140.1 ($[M+H]^+$). The data for this compound are consistent with those reported in the literature.[314]

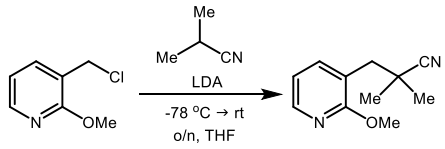
To a solution of (2-methoxypyridin-3-yl)methanol **857** (1.26 g, 9.03 mmol, 1.0 equiv) in dry DCM (43 mL) was added $SOCl_2$ (1.65 mL, 22.6 mmol, 2.5 equiv.) dropwise. The mixture was stirred for 1 h at room temperature. The mixture was then quenched by the addition of a sodium acetate/ice solution, and the mixture was stirred for 10 min. The resulting solution was neutralized with $NaHCO_3$ solution, and the organic phase was separated and dried over a hydrophobic frit. Removal of the solvent under reduced pressure afforded 3-(chloromethyl)-2-methoxypyridine **858** as a colourless oil (1.35 g, 95 %), which was used crude without any further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.02 (s, 3H, OCH_3), 4.61 (s, 2H, CH_2), 6.91 (dd, *J* = 7.3, 5.4 Hz, 1H, ArH), 7.68 (dd, *J* = 7.1, 1.7 Hz, 1H, ArH), 8.10 (dd, *J* = 5.4, 2.0 Hz, 1H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 40.9, 53.6, 116.8, 120.2, 138.5, 147.0, 161.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 2954, 2854, 1585, 1466, 1409, 1307, 1253, 1199, 1017, 856, 776, 582, 497. **HRMS (CI)** calcd. for C_7H_9NOCl ($[M+H]^+$): 158.0373, found: 158.0371.

To a mixture of 3-(chloromethyl)-2-methoxypyridine **858** (473 mg, 3.01 mmol, 1.0 equiv.) and potassium carbonate (498 mg, 3.60 mmol, 1.2 equiv.) in acetonitrile (30 ml) was added trimethylsilyl cyanide (0.40 ml, 3.20 mmol, 1.1 equiv.). The reaction mixture was refluxed overnight, then cooled to room temperature and diluted with 2 M NaOH solution to pH 14. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic phases were washed with 2 M NaOH and brine, dried over a hydrophobic frit, and the solvent was removed under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 4:1) afforded 2-(2-methoxypyridin-3-yl)acetonitrile **859** as a colourless oil (212 mg, 48 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 3.67 (s, 2 H, CH_2), 4.00 (s, 3 H, OCH_3), 6.93 (dd, *J* = 7.4, 4.9 Hz, 1 H, ArH), 7.68 (d, *J* = 7.2 Hz, 1 H, ArH), 8.15 (dd, *J* = 4.9, 2.0 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 18.5, 53.7, 113.3, 116.9, 117.0, 137.4, 146.7, 161.1. **ATR-IR** ν_{max} (neat)/cm^{-1} 2987, 2953, 2856, 2252, 1589, 1465, 1411, 1313, 1257, 1161, 1105, 1016, 779, 754. **HRMS (CI)** calcd. for $C_8H_9N_2O^+$ ($[M+H]^+$): 149.0715, found: 149.0717.

To a suspension of sodium hydride (108 mg, 4.50 mmol, 3.15 equiv.) in DMF (4 mL) under nitrogen was added a solution of 2-(2-methoxypyridin-3-yl)acetonitrile **859** (212 mg, 1.43 mmol, 1.00 equiv.) and 1-iodopropane (0.63 mL, 6.44 mmol, 4.50 equiv.) in diethyl ether (2 mL). The resulting mixture was stirred for 48 h at room temperature, and then quenched by addition of methanol. The crude residue was redissolved in diethyl ether and washed with water, saturated sodium sulfite solution, and saturated sodium carbonate solution, and then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 4:1) afforded 2-(2-methoxypyridin-3-yl)-2-propylpentanenitrile **703** as a colourless oil (202 mg, 61 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.89 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.00 - 1.14 (m, 2 H, 2 x CH), 1.43 (tdd, *J* = 12.5, 7.4, 4.8 Hz, 2 H, 2 x CH), 1.90 (td, *J* = 12.9, 4.7 Hz, 2 H, 2 x CH), 2.27 (td, *J* = 12.9, 4.7 Hz, 2 H, 2 x CH), 3.98 (s, 3 H, OCH_3), 6.91 (dd, *J* = 7.4, 5.0 Hz, 1 H, ArH), 7.83 (dd, *J* = 7.4, 1.6 Hz, 1 H, ArH), 8.13 (dd, *J* = 5.0,

1.6 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.0, 19.0, 39.1, 47.9, 53.3, 116.8, 120.4, 122.8, 138.3, 146.0, 160.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 2958, 2931, 2873, 2233, 1581, 1462, 1406, 1099, 1014, 800, 777, 711. ***m/z* (EI)** 232.2 (M^+, 16), 203.1 (6), 189.1 (100), 173.1 (3), 162.1 (30), 147.1 (27), 130.1 (7), 117.0 (6), 104.1 (5), 92.0 (4), 77.0 (4), 65.0 (2), 51.0 (2). **HRMS (CI)** calcd. for $C_{14}H_{21}N_2O^+$ ($[M+H]^+$): 233.1648, found: 233.1650.

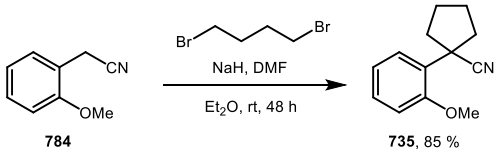
Preparation of 3-(2-Methoxypyridin-3-yl)-2,2-dimethylpropanenitrile (708)



859 **708**, 76 %

To a solution of diisopropylamine (1.15 mL, 8.22 mmol, 1.3 equiv.) in dry THF (23 mL) at -78 °C was added *n*-butyllithium (1.4 M in toluene, 5.42 mL, 7.58 mmol, 1.2 equiv.) and the mixture stirred for 1 min. Isobutyronitrile (0.68 mL, 7.58 mmol, 1.2 equiv.) in THF (12 mL) was added and the mixture stirred at this temperature for 20 min. Finally, a solution of 3-(chloromethyl)-2-methoxypyridine **859** (996 mg, 6.32 mmol, 1.0 equiv.) in THF (11 mL) was added, and the mixture stirred for 20 min at -78 °C then warmed to room temperature and stirred overnight. The reaction was quenched by addition of saturated ammonium chloride solution then water, and extracted into diethyl ether. The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 4:1) afforded 3-(2-methoxypyridin-3-yl)-2,2-dimethylpropanenitrile **708** as a yellow oil (918 mg, 76 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.37 (s, 6 H, 2 x CH_3), 2.86 (s, 2 H, CH_2), 3.95 (s, 3 H, OCH_3), 6.90 (dd, *J* = 7.1, 5.1 Hz, 1 H, ArH), 7.59 (dd, *J* = 7.3, 2.0 Hz, 1 H, ArH), 8.12 (dd, *J* = 4.9, 2.0 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 26.4, 33.9, 39.1, 53.3, 116.8, 118.7, 124.7, 140.0, 146.0, 162.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 2979, 2954, 2233, 1585, 1465, 1411, 1309, 1262, 1190, 1131, 1097, 1020, 782, 606, 500. **HRMS (CI)** calcd. for $C_{11}H_{15}N_2O^+$ ($[M+H]^+$): 191.1184, found: 191.1189.

Preparation of 1-(2-Methoxyphenyl)cyclopentane-1-carbonitrile (735)

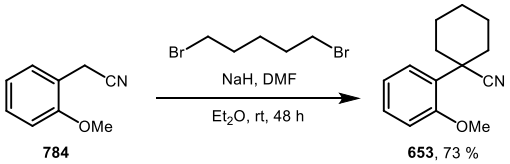


784 **735**, 85 %

To a suspension of oil-free sodium hydride (378 mg, 15.8 mmol, 3.15 equiv.) in DMF (18 mL) under nitrogen was added a solution of 2-methoxyphenylacetonitrile **784** (736 mg, 5.00 mmol, 1.00 equiv.) and 1,4-dibromobutane (2.69 mL, 22.5 mmol, 4.50 equiv.) in diethyl ether (9 mL) at room temperature. The resulting mixture was stirred at room temperature for 48 h, then quenched by addition of methanol. The resulting mixture was concentrated under reduced pressure and redissolved in diethyl ether. The solution was washed with water, sodium bisulfite and saturated

sodium carbonate solution, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 95:5) afforded 1-(2-methoxyphenyl)cyclopentane-1-carbonitrile **735** as a white solid (854 mg, 85 %). **Mp** = 71 - 73 °C (lit. mp = 67-68 °C).[196] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.80 - 1.94 (m, 2 H, 2 x CH), 1.94 - 2.07 (m, 2 H, 2 x CH), 2.07 - 2.18 (m, 2 H, 2 x CH), 2.48 - 2.61 (m, 2 H, 2 x CH), 3.93 (s, 3 H, OCH_3), 6.90 - 7.00 (m, 2 H, 2 x ArH), 7.28 - 7.36 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 23.8, 37.7, 44.7, 55.5, 111.7, 120.4, 124.5, 126.5, 127.5, 129.3, 157.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 2962, 2916, 2223, 1597, 1490, 1462, 1435, 1294, 1253, 1126, 1056, 1024, 952, 943, 898, 786, 653. ***m/z* (EI)** 201.1 (M^+, 59), 186.1 (18), 172.1 (18), 159.1 (51), 144.1 (100), 131.1 (22), 116.1 (27), 103.1 (15), 89.0 (19), 77.0 (16), 63.0 (11), 51.0 (9). The data for this compound are consistent with those reported in the literature.[196]

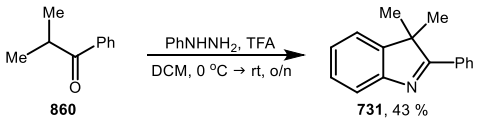
Preparation of 1-(2-Methoxyphenyl)cyclohexane-1-carbonitrile (653)



784 **653**, 73 %

To a suspension of oil-free sodium hydride (378 mg, 15.8 mmol, 3.15 equiv.) in DMF (18 mL) under nitrogen was added a solution of 2-methoxyphenylacetonitrile **784** (736 mg, 5.00 mmol, 1.00 equiv.) and 1,5-dibromopentane (3.06 mL, 22.5 mmol, 4.50 equiv.) in diethyl ether (9 mL) at room temperature. The resulting mixture was stirred at room temperature for 48 h, then quenched by addition of methanol. The resulting mixture was concentrated under reduced pressure and redissolved in diethyl ether. The solution was washed with water, sodium bisulfite and saturated sodium carbonate solution, then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1), followed by recrystallisation from hexane, afforded 1-(2-methoxyphenyl)cyclohexane-1-carbonitrile **653** as a white solid (796 mg, 73 %). **Mp** = 101 – 103 °C (lit. m.p. = 102-103 °C).[196] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.17 - 1.34 (m, 1 H, CH), 1.78 (td, *J* = 13.0, 3.5 Hz, 2 H, 2 x CH), 1.81 - 1.97 (m, 5 H, 5 x CH), 2.38 (app. d, *J* = 12.1 Hz, 2 H, 2 x CH), 3.93 (s, 3 H, OCH_3), 6.95 - 7.00 (m, 2 H, 2 x ArH), 7.29 - 7.36 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 23.3, 25.3, 34.5, 40.8, 55.5, 112.2, 120.8, 122.5, 125.9, 129.1, 129.1, 157.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 2931, 2860, 2229, 1597, 1581, 1489, 1456, 1436, 1292, 1249, 1122, 1012, 904, 785, 731. ***m/z* (EI)** 215.2 (M^+, 78), 200.1 (4), 186.1 (18), 172.1 (21), 159.1 (68), 144.1 (100), 131.1 (22), 116.1 (30), 103.1 (14), 89.0 (19), 77.0 (16), 63.0 (8), 51.0 (8). The data for this compound are consistent with those reported in the literature.[196]

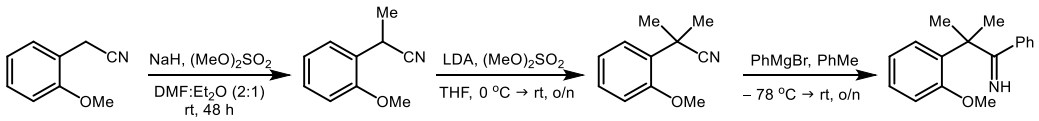
Preparation of 3,3-Dimethyl-2-phenyl-3*H*-indole (**731**)



860 **731**, 43 %

This substrate was prepared according to a modified literature procedure.[315] To an ice-cooled solution of isobutyrophenone **860** (1.50 mL, 10.0 mmol, 1.0 equiv.) in DCM (100 mL) was added phenylhydrazine **88** (0.98 mL, 9.99 mmol, 1.0 equiv.). After stirring for 10 min, trifluoroacetic acid (2.30 mL, 30.1 mmol, 3.0 equiv.) was added dropwise and the mixture was then warmed to room temperature and stirred overnight. The mixture was then diluted with water and extracted into DCM. The organic layer was washed with water, saturated sodium carbonate solution and brine, and then dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 97:3) afforded 3,3-dimethyl-2-phenyl-3*H*-indole **731** as an orange oil (953 mg, 43 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.62 (s, 6 H, 2 x CH_3), 7.30 (d, *J* = 7.3 Hz, 1 H, ArH), 7.34 - 7.41 (m, 2 H, 2 x ArH), 7.48 - 7.54 (m, 3 H, 3 x ArH), 7.73 (d, *J* = 7.1 Hz, 1 H, ArH), 8.13 - 8.23 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 24.8, 53.6, 120.8, 120.9, 125.9, 127.8, 128.4, 128.6, 130.6, 133.1, 147.5, 152.8, 183.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3057, 2964, 2926, 2864, 1519, 1490, 1452, 1440, 1384, 1336, 1265, 1220, 1209, 1168, 1109, 1074, 1002, 987, 935, 862, 771, 750, 694. ***m/z* (EI)** 221.2 (M^+, 100), 220.2 (69), 506.1 (59), 178.1 (5), 165.1 (9), 144.1 (13), 128.1 (6), 117.1 (26), 103.1 (26), 91.1 (14), 77.1 (29), 63.0 (6), 51.0 (8). The data for this compound are consistent with those reported in the literature.[196]

Preparation of 2-(2-Methoxyphenyl)-2-methyl-1-phenylpropan-1-imine (**745**)



784 **861** **744**, 72 % (2 steps) **745**, 29 %

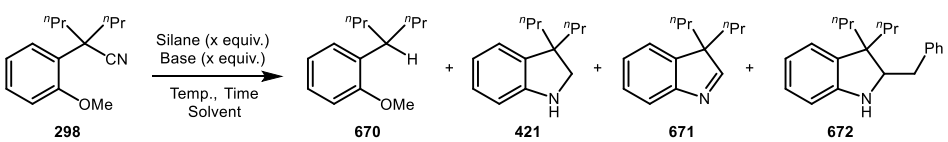
To a suspension of sodium hydride (756 mg, 31.5 mmol, 3.15 equiv.) in DMF (36 mL) under argon was added a solution of 2-methoxyphenylacetonitrile **784** (1.47 g, 10.0 mmol, 1.00 equiv.) and dimethyl sulfate (4.26 mL, 44.9 mmol, 4.49 equiv.) in diethyl ether (18 mL). The resulting mixture was stirred at room temperature for 48 h. After this time, all of the sodium hydride was consumed, and mainly mono-alkylated product **861** was detected by GC-MS. A further portion of sodium hydride (378 mg, 15.8 mmol, 1.58 equiv.) was added under positive argon pressure, followed by dimethyl sulfate (2.13 mL, 22.5 mmol, 2.25 equiv.). The resulting mixture was again stirred at room temperature overnight. Crude GC-MS indicated that still mono-alkylated product **861** was the major product (*m/z* = 161.1). The reaction was quenched by addition of methanol and concentrated under reduced pressure. The residue was redissolved in diethyl ether and washed with water, sodium bisulfite solution and saturated sodium carbonate solution, and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude sample (1.37 g, ~8.50 mmol, 1.0 equiv.) was dissolved in THF (10 mL) under argon, and cooled to 0 °C. A solution of LDA (1.00 g, 9.35 mmol, 1.1 equiv.) in THF (10 mL) was added dropwise at this temperature.

The solution was stirred at this temperature for 10 min, and then dimethyl sulfate was added (0.97 mL, 10.2 mmol, 1.2 equiv.). The resulting mixture was warmed to room temperature and stirring overnight. The mixture was then quenched with water (50 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 97:3) afforded 2-(2-methoxyphenyl)-2-methylpropanenitrile **744** as a colourless oil (1.262 g, 72 % across two steps). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.78 (s, 6 H, 2 x CH_3), 3.94 (s, 3 H, OCH_3), 6.92 - 7.00 (m, 2 H, 2 x ArH), 7.29 - 7.38 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 27.0, 34.5, 55.5, 112.0, 120.7, 124.8, 125.9, 128.7, 129.3, 157.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 2978, 2939, 2233, 1598, 1583, 1490, 1458, 1435, 1386, 1363, 1290, 1249, 1180, 1147, 1089, 1051, 1024, 758, 752, 677. ***m/z* (EI)** 175.1 (57, $[M]^+$), 160.1(100), 143.9 (5), 133.0 (53), 116.0 (9), 105.1 (60), 91.0 (16), 77.0 (20), 63.0 (9), 51.0 (8). The data for this compound are consistent with those reported in the literature.

2-(2-Methoxyphenyl)-2-methylpropanenitrile **744** (1.26 g, 7.20 mmol, 1.0 equiv.) was dissolved in dry toluene (36 mL) and cooled to -78 °C. A solution of phenylmagnesium bromide (1 M in THF, 10.8 mL, 10.8 mmol, 1.5 equiv.) was added and the resulting mixture was stirred at room temperature overnight. The mixture was then diluted with brine (50 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 1:1) afforded, in order of elution, starting material **915**, with data consistent with those reported above (993 mg, 79 %), and 2-(2-methoxyphenyl)-2-methyl-1-phenylpropan-1-imine **745** as a colourless oil (529 mg, 29 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.66 (s, 6 H, 2 x CH_3), 3.66 (s, 3 H, OCH_3), 6.77 (d, *J* = 8.3 Hz, 1 H, ArH), 6.98 (app. td, *J* = 7.5, 1.0 Hz, 1 H, ArH), 7.14 - 7.27 (m, 3 H, 3 x ArH), 7.27 - 7.35 (m, 3 H, 3 x ArH), 7.39 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 27.7, 46.5, 54.8, 111.2, 120.7, 126.5, 127.2, 127.5, 128.2, 128.6, 134.6, 140.4, 157.1, 187.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3057, 2966, 1664, 1608, 1489, 1462, 1338, 1290, 1244, 1180, 1161, 1087, 1026, 952, 891, 752, 700. ***m/z* (EI)** 253.1 (5, $[M]^+$), 238.1 (3), 222.1 (85), 207.1 (13), 150.1 (35), 135.1 (100), 119.1 (25), 104.1 (61), 91.0 (42), 77.0 (44), 65.0 (7), 51.0 (15). The data for this compound are consistent with those reported in the literature.[196]

8.9 – Treatment of Substrates with Et_3SiH/KO^tBu from Chapter 5

Optimisation of the Cyclisation of 298 to Produce 421



Entry	*T/°C*	*t/h*	*Silane*	*Base*	*x*	*Solvent*	***421***	***670***	***671***	***298***

1	130	18	Et_3SiH	KO^{t}Bu	3	None				
2	90	18	Et_3SiH	KO^{t}Bu	3	None	59 %	20 %	-	-
3	rt	18	Et_3SiH	KO^{t}Bu	3	None	5 %	-	2 %	[a]
4	60	18	Et_3SiH	KO^{t}Bu	3	None	60 %	1 %	-	Trace
5	40	18	Et_3SiH	KO^{t}Bu	3	None	36 %	15 %	Trace	18 %
6	70	18	Et_3SiH	KO^{t}Bu	3	None	72 %	11 %	-	Trace
7	80	18	Et_3SiH	KO^{t}Bu	3	None	66 %	12 %	-	Trace
8	70	6	Et_3SiH	KO^{t}Bu	3	None	38 %	8 %	-	10 %
9	70	18	Et_3SiH	LiO^{t}Bu	3	None	-	-	-	95 %
10	70	18	Et_3SiH	NaO^{t}Bu	3	None	-	-	-	93 %
11	70	18	Et_3SiH	KHMDS	3	None	-	-	-	81 %
12	70	18	Et_3SiH	KOH	3	None	-	-	-	85 %
13	70	18	Et_3SiH	KOEt	3	None	-	-	-	68 %
14	70	18	Et_3SiH	Et_3N	3	None	-	-	-	66 %
15	70	18	Et_3SiH	NaH	3	None	-	-	-	97 %
16	70	18	Et_3SiH	KH	3	None	12 %	-	-	63 %
17	70	18	Et_3SiH	KO^{t}Bu	3	THF	42 %	34 %	1 %	-
18	70	18	Et_3SiH	KO^{t}Bu	3	dioxane	63 %	6 %	6 %	Trace
19	70	18	Et_3SiH	KO^{t}Bu	3	Toluene	53 %	25 %	-	Trace
20	70	18	Et_3SiH	KO^{t}Bu	3	Hexane	44 %	Trace	-	13 %
21	70	18	Et_3SiH	KO^{t}Bu	4	None	69 %	16 %	-	Trace
22	70	18	Et_3SiH	KO^{t}Bu	2	None	56 %	20 %	-	[b]

[a] contains an inseparable mixture of **298** and an aldehyde by-product (total mass = 66 mg, 0.16:1 aldehyde:**298**). The mass of **298** at the start of the reaction was 116 mg.

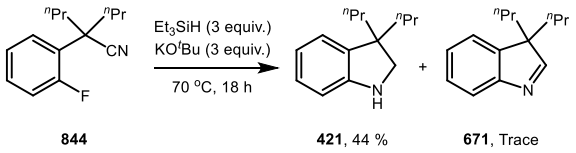
[b] contains an inseparable mixture of **298** and an aldehyde by-product (total mass = 24 mg, 0.12:1 aldehyde:**298**). The mass of **298** at the start of the reaction was 116 mg.

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.), triethylsilane [(0.16 mL, 1.00 mmol, 2.0 equiv.) or (0.24 mL, 1.50 mmol, 3.0 equiv.) or (0.32 mL, 2.00 mmol, 4.0 equiv.)], and the appropriate base {[potassium *tert*-butoxide (112 mg, 1.00 mmol, 2.0 equiv.) or (168 mg, 1.50 mmol, 3.0 equiv.) or (224 mg, 2.00 mmol, 4.0 equiv.)], or lithium *tert*-butoxide (120 mg, 1.50 mmol, 3.0 equiv.), or sodium *tert*-butoxide (144 mg, 1.50 mmol, 3.0 equiv.), or KHMDS (299 mg, 1.50 mmol, 3.0 equiv.), or potassium hydroxide (84.0 mg, 1.50 mmol, 3.0 equiv.), or potassium ethoxide (126 mg, 1.50 mmol, 3.0 equiv.), or triethylamine (0.21 mL, 1.51 mmol, 3.0 equiv.) or sodium hydride (36.0 mg, 1.50 mmol, 3.0 equiv.) or potassium hydride (60.0 mg, 1.50 mmol, 3.0 equiv.)]} with the appropriate solvent [no solvent, or THF (1 mL), 1,4-dioxane (1 mL), toluene (1 mL) or hexane (1 mL)]. The tube was sealed, removed from the glovebox and stirred at the appropriate temperature [room temperature, 40 °C, 60 °C, 70 °C, 80 °C, 90 °C or 130 °C) for the appropriate time [6 h or 18 h]. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl

ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Column chromatography (cyclohexane:ethyl acetate, 100:0 → 4:1) afforded 1-(heptan-4-yl)-2-methoxybenzene **670** as a colourless oil in the yields shown above. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.85 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.08 - 1.30 (m, 4 H, 2 x CH_2), 1.50 - 1.63 (m, 4 H, 2 x CH_2), 3.07 - 3.20 (m, 1 H, CH), 3.81 (s, 3 H, OCH_3), 6.86 (d, *J* = 8.3 Hz, 1 H, ArH), 6.92 (app. td, *J* = 7.3, 1.0 Hz, 1 H, ArH), 7.11 - 7.18 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.2, 20.6, 36.8, 38.2, 55.5, 110.6, 120.5, 126.3, 127.5, 134.7, 157.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 2953, 2854, 1598, 1500, 1462, 1375, 1236, 1049, 881, 738. ***m/z* (EI)** 206.2 (M^+, 59), 163.2 (60), 147.2 (6), 134.1 (10), 121.2 (100), 103.1 (13), 91.1 (93), 77.1 (26), 65.1 (24), 51.1 (7). **HRMS (CI)** calcd. for $C_{14}H_{23}O^+$ ([M+H]$^+$): 207.1749, found: 207.1745. Also isolated was recovered starting material **298**, with data consistent with those reported above. Also isolated was 3,3-dipropylindoline **421** as a colourless oil, with data consistent with those reported above. Also isolated was 3,3-dipropyl-3*H*-indole **671** as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.78 (t, *J* = 6.9 Hz, 6 H, 2 x CH_3), 0.83 - 0.92 (m, 2 H, 2 x CH), 0.98 - 1.12 (m, 2 H, 2 x CH), 1.70 - 1.92 (m, 4 H, 2 x CH_2), 7.22 - 7.27 (m, 2 H, 2 x ArH), 7.30 - 7.37 (m, 1 H, ArH), 7.62 (d, *J* = 7.3 Hz, 1 H, ArH), 8.03 (s, 1 H, CHN). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.5, 17.7, 37.6, 62.4, 121.0, 121.8, 125.9, 127.5, 142.5, 155.8, 179.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 2957, 2931, 2871, 1556, 1455, 1378, 1295, 1201, 1014, 937, 773, 753. **HRMS (CI)** calcd. for $C_{14}H_{20}N^+$ ([M+H]$^+$): 202.1596, found: 202.1601.

When toluene was used as the solvent, 2-benzyl-3,3-dipropylindoline **672** was also isolated as a white solid (17 mg, 12 %); m.p. = 85-86 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.90 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.94 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.22 - 1.49 (m, 5 H, 2 x CH_2 + CH), 1.65 - 1.84 (m, 3 H, CH + CH_2), 2.76 (dd, *J* = 13.2, 11.3 Hz, 1 H, CH), 2.92 (dd, *J* = 13.2, 3.0 Hz, 1 H, CH), 3.78 (dd, *J* = 11.3, 2.5 Hz, 1 H, CH), 6.54 (d, *J* = 7.8 Hz, 1 H, ArH), 6.71 (app. td, *J* = 7.3, 1.0 Hz, 1 H, ArH), 6.91 - 7.08 (m, 2 H, 2 x ArH), 7.22 - 7.30 (m, 3 H, 3 x ArH), 7.30 - 7.38 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.8, 15.0, 17.5, 17.9, 35.8, 36.5, 38.7, 49.9, 69.2, 109.3, 118.1, 124.0, 126.4, 127.1, 1287, 129.1, 135.6, 140.2, 149.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3370, 3026, 2958, 2927, 1604, 1462, 1452, 1356, 1237, 1073, 847, 764, 740, 694, 591. **HRMS (CI)** calcd. for $C_{21}H_{28}N^+$ ([M+H]$^+$): 294.2222, found: 294.2230.

Treatment of 2-(2-Fluorophenyl)-2-propylpentanenitrile (**844**) with Et_3SiH/KO^tBu

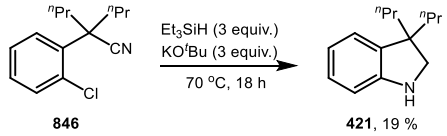


844 **421**, 44 % **671**, Trace

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-fluorophenyl)-2-propylpentanenitrile **844** (110 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed,

removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 4:1) afforded, in order of elution, 3,3-dipropylindoline **436** as a colourless oil, with data consistent with those reported above (45 mg, 44 %), and 3,3-dipropyl-3H-indole **731** as a colourless oil, with data consistent with those reported above (<1 mg).

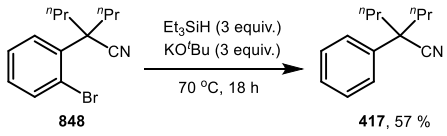
Treatment of 2-(2-Chlorophenyl)-2-propylpentanenitrile (846) with Et_3SiH/KO^tBu



846 **421**, 19 %

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-chlorophenyl)-2-propylpentanenitrile **846** (118 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 4:1) afforded 3,3-dipropylindoline **421** as a colourless oil, with data consistent with those reported above (19 mg, 19 %).

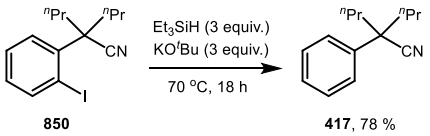
Treatment of 2-(2-Bromophenyl)-2-propylpentanenitrile (848) with Et_3SiH/KO^tBu



848 **417**, 57 %

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-bromophenyl)-2-propylpentanenitrile **848** (140 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane) afforded an inseparable mixture of compounds from which **417** could be identified as the major component, with data consistent with those reported above. The addition of 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol, 0.1 equiv.) allowed for calculation of the yield (57 %) by comparison of the integration of the methoxy groups of the internal standard (9 integral units) to the signal at 1.92 – 2.00 ppm, corresponding to 2 x CH (11.3 integral units).

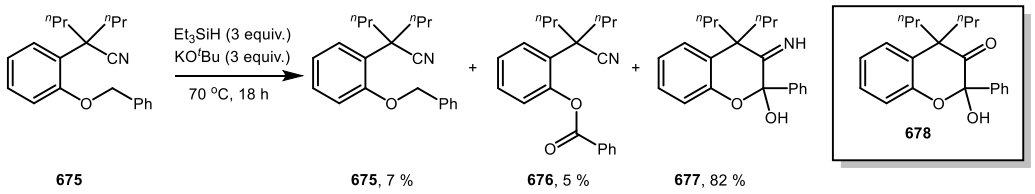
Treatment of 2-(2-Iodophenyl)-2-propylpentanenitrile (**850**) with Et_3SiH/KO^tBu



850 **417**, 78 %

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-iodophenyl)-2-propylpentanenitrile **850** (164 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded 2-phenyl-2-propylpentanenitrile **417** (79 mg, 78 %) as a colourless oil, with data consistent with those reported above.

Treatment of 2-(2-(Benzyloxy)phenyl)-2-propylpentanenitrile (**675**) with Et_3SiH/KO^tBu



675 **675**, 7 % **676**, 5 % **677**, 82 % **678**

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-(benzyloxy)phenyl)-2-propylpentanenitrile **675** (154 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 9:1) afforded recovered starting material **675** with data consistent with those reported above (10 mg, 7 %), and 2-(4-cyanoheptan-4-yl)phenyl benzoate **676** as a colourless oil (8 mg, 5 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.88 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 1.17 - 1.31 (m, 2 H, CH_2), 1.43 - 1.52 (m, 2 H, CH_2), 1.93 (ddd, *J* = 13.7, 12.2, 4.4 Hz, 2 H, CH_2), 2.08 (ddd, *J* = 13.7, 12.7, 4.9 Hz, 2 H, CH_2), 7.18 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.30 (app. td, *J* = 7.2, 1.5 Hz, 1 H, ArH), 7.37 - 7.44 (m, 1 H, ArH), 7.57 (app. t, *J* = 7.5 Hz, 2 H, 2 x ArH), 7.64 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.67 - 7.73 (m, 1 H, ArH), 8.19 - 8.23 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 13.9, 18.8, 41.1, 47.7, 122.8, 124.7, 126.2, 128.9, 129.0, 129.2, 129.4, 129.7, 130.2, 134.0, 148.2, 164.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 2961, 2933, 2873, 2233, 1740, 1606, 1489, 1447, 1257, 1206, 1089, 1057, 1023, 756, 706, 494. **HRMS (CI)** calcd. for $C_{21}H_{24}NO_2^+$ ($[M+H]^+$): 322.1807, found: 322.1806. Also isolated was 3-imino-2-phenylchroman-2-ol **677** (133 mg, 82 %) as a white solid. **Mp** = 83-85 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.68 (t, *J* = 7.1 Hz, 3 H, CH_3), 0.99

(t, *J* = 7.3 Hz, 3 H, CH_3), 1.05 - 1.20 (m, 2 H, CH_2), 1.49 - 1.70 (m, 4 H, 2 x CH_2), 1.79 - 1.98 (m, 2 H, CH_2), 2.43 (br s, 2 H, NH + OH), 6.87 (d, *J* = 7.8 Hz, 1 H, ArH), 6.92 (app. td, *J* = 7.3, 1.0 Hz, 1 H, ArH), 7.09 (dd, *J* = 7.3, 1.0 Hz, 1 H, ArH), 7.17 (app. td, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.39 - 7.46 (m, 2 H, 2 x ArH), 7.53 (app. tt, *J* = 7.3, 1.5 Hz, 1 H, ArH), 8.11 - 8.17 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.4, 15.0, 17.1, 17.7, 35.2, 37.5, 55.2, 105.8, 110.4, 120.9, 124.5, 128.1, 128.2, 130.0, 132.4, 133.7, 137.4, 156.0, 199.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3070, 3028, 2958, 2931, 2871, 1695, 1648, 1595, 1477, 1456, 1225, 1102, 1010, 906, 729, 699, 463. **HRMS (CI)** calcd. for $C_{21}H_{26}NO_2^+$ ($[M+H]^+$): 324.1958, found: 324.1966. This compound was recrystallised from hexane and analysed by x-ray crystallography and was found to be 2-hydroxy-2-phenylchroman-3-one **678** (Figure 25).

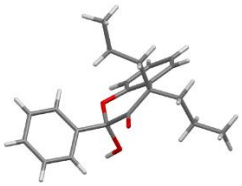


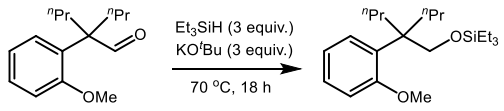
*Figure 25 - X-ray Structure of **678***

Crystal data and structure refinement for jam2019jan.

Identification code:	jam2019jan	
Empirical formula:	C_{21} H_{24} N_0 O_3	
Formula weight:	324.40	
Temperature:	566(2) K	
Wavelength:	0.71073 Å	
Crystal system:	Monoclinic	
Space group:	P $2_{1/c}$	
Unit cell dimensions:	a = 18.880(5) Å	a= 90°.
	b = 9.799(2) Å	b= 98.61(2)°.
	c = 9.6731(17) Å	g = 90°.
Volume:	1769.4(7) $Å^3$	
Z:	4	
Density (calculated):	1.218 Mg/m^3	
Absorption coefficient:	0.080 mm^{-1}	
F(000):	696	

Crystal size:	0.35 x 0.25 x 0.05 mm^3
Theta range for data collection:	2.976 to 24.999°.
Index ranges:	−21<=h<=22, −11<=k<=11, −11<=l<=11
Reflections collected:	9495
Independent reflections:	3119 [R(int) = 0.0829]
Completeness to theta = 24.999°:	99.8 %
Absorption correction:	Semi-empirical from equivalents
Max. and min. transmission:	1.00000 and 0.42838
Refinement method:	Full-matrix least-squares on F2
Data / restraints / parameters:	3119 / 1 / 222
Goodness-of-fit on F^2:	1.048
Final R indices [I>2sigma(I)]:	R1 = 0.0884, wR2 = 0.2322
R indices (all data):	R1 = 0.1497, wR2 = 0.2834
Extinction coefficient:	n/a
Largest diff. peak and hole:	0.335 and -0.266 e.Å-3

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanal (698) with Et_3SiH/KO^tBu

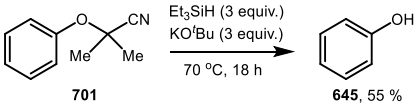


698 **699**, 68 %

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanal **698** (117 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium tert-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 95:5) afforded triethyl((2-(2-methoxyphenyl)-2-propylpentyl)oxy)silane **699** as a colourless oil (119 mg, 68 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.58 (q, *J* = 7.9 Hz, 6 H, 3 x CH_2), 0.84 (t, *J* = 6.9 Hz, 6 H, 2 x CH_3), 0.90 - 1.02 (m, 11 H, 3 x CH_3 + 2 x CH), 1.04 - 1.19 (m, 2 H, 2 x CH), 1.71 - 1.92 (m, 4 H, 2 x CH_2), 3.81 (s, 3 H, OCH_3), 3.92 (s, 2 H, OCH_2), 6.80 - 6.93 (m, 2 H, 2 x ArH), 7.11 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH), 7.18 (app. td, *J* = 7.4, 1.5 Hz, 1 H, ArH). **^{13}C NMR** (101 MHz, $CDCl_3$) 4.5, 6.8, 15.0, 17.6, 36.5, 46.3, 55.0, 65.1, 111.4, 120.1, 126.7, 128.8, 133.4, 158.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 2954, 2873, 1606, 1578, 1490,

1457, 1236, 1180, 1089, 1031, 1005, 819, 741. ***m/z* (EI)** 350.3 (M^+, 0.5), 321.3 (12), 263.1 (3), 205.2 (39), 191.1 (6), 163.1 (18), 149.1 (22), 135.1 (10), 121.1 (100), 105.1 (5), 91.1 (20), 75.0 (9), 59.0 (10). **HRMS (CI)** calcd. for $C_{21}H_{39}O_2Si^+$ ([M+H]$^+$): 351.2719, found: 351.2709.

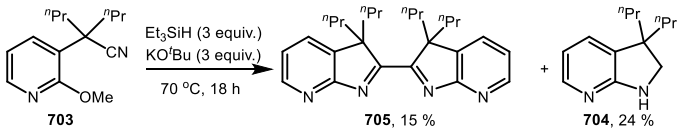
Treatment of 2-Methyl-2-phenoxypropanenitrile (701) with Et_3SiH/KO^tBu



701 **645**, 55 %

To a pressure tube in the glovebox, under nitrogen, was added 2-methyl-2-phenoxypropanenitrile **701** (81 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography eluting with hexane:ethyl acetate (100:0 → 4:1) afforded phenol **645** as an off-white solid (26 mg, 55 %). **Mp** = 37-38 °C (lit. mp = 39-41 °C).[264] **^{1}H-NMR** (400 MHz, $CDCl_3$) 4.71 (br. s., 1 H, OH), 6.85 (dd, *J* = 8.5, 0.8 Hz, 2 H, 2 x ArH), 6.95 (app. t, *J* = 7.4 Hz, 1 H, ArH), 7.26 (app. t, *J* = 8.3 Hz, 2 H, 2 x ArH). **^{13}C NMR** (101 MHz, $CDCl_3$) 115.3, 120.8, 129.7, 155.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3315, 1593, 1496, 1469, 1363, 1219, 1070, 1024, 999, 885, 808, 748, 666. ***m/z* (EI)** 94.0 (100, $[M]^+$), 66.0 (55), 65.1 (39), 64.0 (15), 55.0 (11), 51.0 (9). The data for this compound are consistent with those reported in the literature.[264]

Treatment of 2-(2-Methoxypyridin-3-yl)-2-propylpentanenitrile (703) with Et_3SiH/KO^tBu

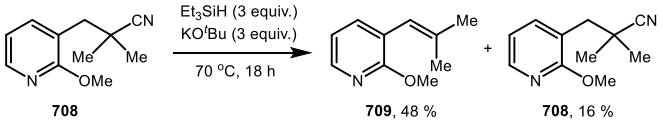


703 **705**, 15 % **704**, 24 %

To a pressure tube in a glovebox under nitrogen was added 2-(2-methoxypyridin-3-yl)-2-propylpentanenitrile **703** (116 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 70 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 7:3) afforded starting material **703** as a colourless oil, with data consistent with those reported above (23 mg, 20 %); and 3,3,3',3'-tetrapropyl-3H,3'H-2,2'-bipyrrolo[2,3-b]pyridine **705** as a yellow solid (31 mg, 15 %). **Mp** = 192 °C (decomposition). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.58 - 0.80 (m, 20 H, 4 x CH_3 + 4 x CH_2), 2.04 - 2.18 (m, 4 H, 4 x CH), 2.59 - 2.75 (m, 4 H, 4 x CH), 7.25 - 7.30 (m, 2 H, 2 x ArH), 7.71 (dd, *J* = 7.4, 1.6 Hz, 2 H, 2 x ArH), 8.59 (dd, *J* = 4.9, 1.6 Hz, 2 H, 2 x ArH). **^{13}C-NMR**

(101 MHz, $CDCl_3$) 14.1, 17.6, 39.5, 64.2, 121.9, 130.5, 138.2, 148.7, 168.0, 181.0. **ATR-IR** ν_{max} (neat)/cm^{-1} 2958, 2927, 2870, 2285, 1581, 1462, 1392, 1226, 1134, 1054, 1029, 1014, 902, 800, 729, 623. ***m/z* (EI)** 402.4 (M^+, 2), 373.4 (100), 360.3 (65), 331.3 (75), 317.3 (98), 301.2 (12), 287.2 (23), 271.2 (30), 259.2 (44), 201.2 (52), 173.1 (35), 159.1 (13), 144.1 (10), 130.1 (14), 117.1 (19), 104.1 (4), 92.1 (4), 77.1 (5), 65.1 (2), 51.1 (1). **HRMS (CI)** calcd. for $C_{26}H_{35}N_4^+$ ($[M+H]^+$): 403.2856, found: 403.2854 Also isolated was 3,3-dipropyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine **704** as a yellow semi-solid (24 mg, 24 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.90 (t, *J* = 7.5 Hz, 6 H, 2 x CH_3), 1.12 - 1.24 (m, 2 H, 2 x CH), 1.30 - 1.40 (m, 2 H, 2 x CH), 1.51 - 1.61 (m, 2 H, 2 x CH), 1.61 - 1.71 (m, 2 H, 2 x CH), 3.40 (s, 2 H, CH_2N), 4.50 (br. s., 1 H, NH), 6.53 (dd, *J* = 7.0, 5.3 Hz, 1 H, ArH), 7.14 (dd, *J* = 7.0, 1.5 Hz, 1 H, ArH), 7.79 - 7.91 (m, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.6, 17.4, 41.4, 47.4, 54.8, 113.0, 128.7, 130.4, 145.7, 163.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3224, 2956, 2927, 2870, 1654, 1608, 1463, 1421, 1249, 767, 734. ***m/z* (EI)** 204.2 (M^+, 12), 173.1 (7), 161.1 (100), 145.1 (5), 131.1 (31), 119.1 (26), 104.1 (5), 92.0 (4), 77.0 (4), 65.0 (2), 51.0 (2). **HRMS (CI)** calcd. for $C_{13}H_{21}N_2^+$ ($[M+H]^+$): 205.1705, found: 205.1701.

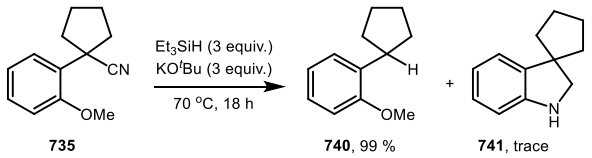
Treatment of 3-(2-Methoxypyridin-3-yl)-2,2-dimethylpropanenitrile (708) with Et_3SiH/KO^tBu



708 **709**, 48 % **708**, 16 %

To a pressure tube in the glovebox, under nitrogen, was added 3-(2-methoxypyridin-3-yl)-2,2-dimethylpropanenitrile **708** (95 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 4:1) afforded 2-methoxy-3-(2-methylprop-1-en-1-yl)pyridine **709** as a colourless oil (39 mg, 48 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.81 (d, *J* = 1.5 Hz, 3 H, CH_3), 1.95 (d, *J* = 1.5 Hz, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 6.22 (s, 1 H, CH), 6.86 (dd, *J* = 7.1, 5.2 Hz, 1 H, ArH), 7.39 - 7.50 (m, 1 H, ArH), 8.03 (dd, *J* = 5.0, 2.0 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 19.5, 26.7, 53.4, 116.3, 119.1, 121.6, 137.3, 138.0, 144.3, 161.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 2965, 2925, 2854, 1737, 1456, 1262, 1021, 802. **HRMS (CI)** calcd. for $C_{10}H_{14}NO^+$ ($[M+H]^+$): 164.1075, found: 164.1074. Also isolated was starting material **708**, with data consistent with those reported above (15 mg, 16 %).

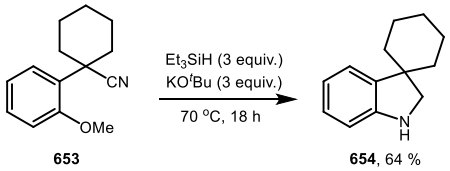
Treatment of 1-(2-Methoxyphenyl)cyclopentane-1-carbonitrile (735) with Et_3SiH/KO^tBu



735 **740**, 99 % **741**, trace

To a pressure tube in the glovebox, under nitrogen, was added 1-(2-methoxyphenyl)cyclopentane-1-carbonitrile **735** (101 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded 1-cyclopentyl-2-methoxybenzene **740** as a colourless oil (89 mg, 99 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.51 - 1.64 (m, 2 H, 2 x CH), 1.64 - 1.75 (m, 2 H, 2 x CH), 1.76 - 1.86 (m, 2 H, 2 x CH), 1.95 - 2.10 (m, 2 H, 2 x CH), 3.26 - 3.45 (m, 1 H, CH), 3.84 (s, 3 H, OCH_3), 6.86 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 6.92 (app. td, *J* = 7.5, 1.1 Hz, 1 H, ArH), 7.17 (app. td, *J* = 7.7, 1.6 Hz, 1 H, ArH), 7.23 (dd, *J* = 7.5, 1.8 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 25.4, 33.0, 39.0, 55.4, 110.4, 120.4, 126.5, 126.7, 134.6, 157.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 2949, 2866, 1598, 1583, 1490, 1462, 1436, 1359, 1313, 1288, 1238, 1174, 1111, 1053, 1029, 923, 748. ***m/z* (EI)** 176.2 (M^+, 84), 161.1 (17), 147.1 (100), 134.1 (27), 121.1 (35), 105.1 (18), 91.1 (87), 77.1 (23), 65.1 (19), 51.1 (12). The data for this compound are consistent with those reported in the literature.[316] Also tentatively identified was a trace amount of impure spiro[cyclopentane-1,3'-indoline] **741** (<1 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.66 - 1.78 (m, 2 H, 2 x CH), 1.78 - 1.93 (m, 6 H, 6 x CH), 3.39 (s, 2 H, NCH_2), 6.68 (d, *J* = 7.8 Hz, 1 H, ArH), 6.77 (app. td, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.03 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.06 - 7.12 (m, 1 H, ArH). The ^{1}H NMR spectrum for this compound is consistent with that reported in the literature.[317]

Treatment of 1-(2-Methoxyphenyl)cyclohexane-1-carbonitrile (653) with Et_3SiH/KO^tBu

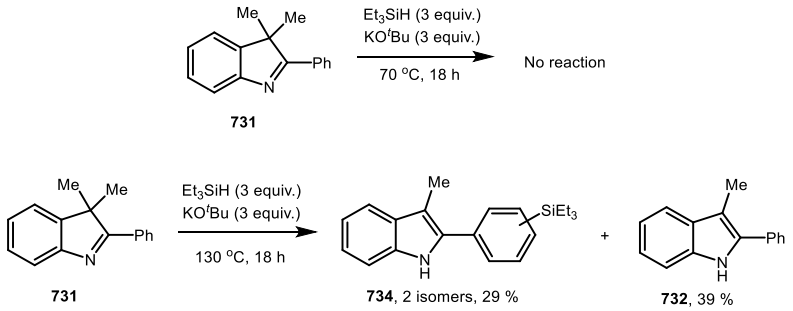


653 **654**, 64 %

To a pressure tube in a glovebox under nitrogen was added 1-(2-methoxyphenyl)cyclohexane-1-carbonitrile **653** (108 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 70 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1)

spiro[cyclohexane-1,3'-indoline] **654** as an orange solid (60 mg, 64 %). **Mp** = 69-70 °C (lit. mp = 76-77 °C).[318] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.23 - 1.47 (m, 3 H, 3 x CH), 1.54 - 1.67 (m, 2 H, 2 x CH), 1.67 - 1.82 (m, 5 H, 5 x CH), 3.44 (s, 2 H, NCH_2), 6.65 (d, *J* = 7.6 Hz, 1 H, ArH), 6.75 (app. t, *J* = 7.3 Hz, 1 H, ArH), 7.04 (app. td, *J* = 7.6, 1.1 Hz, 1 H, ArH), 7.07 (d, *J* = 7.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 23.2, 25.8, 36.4, 46.1, 56.7, 109.6, 118.6, 122.5, 127.4, 138.4, 150.4. **ATR-IR** ν_{max} (neat)/cm^{-1} 3201, 2920, 2850, 1602, 1485, 1448, 1325, 1247, 1190, 1022, 933, 964, 871, 839, 825, 740. ***m/z* (EI)** 187.1 (M^+, 22), 144.1 (19), 130.1 (100), 117.1 (14), 103.1 (4), 90.0 (4), 77.0 (5), 63.0 (1), 56.1 (1), 51.0 (1). The data for this compound are consistent to those reported in the literature.[317]

Treatment of 3,3-Dimethyl-2-phenyl-3*H*-indole (731) with Et_3SiH/KO^tBu



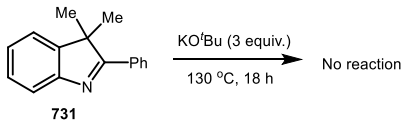
To a pressure tube in the glovebox under nitrogen was added 3,3-dimethyl-2-phenyl-3*H*-indole **731** (111 mg, 0.50 mmol, 1.0 equiv.), triethylsilane (0.24 mL, 1.50 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed and removed from the glovebox, and then heated at the specified temperature (70 or 130 °C) for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. At 70 °C, no reaction was found to occur, and starting material **731** was recovered, with data consistent with those reported above (111 mg, 100 %). At 130 °C, no starting material remained. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 95:5) afforded an inseparable mixture of two isomers of silylated indole **734** (46 mg, 29 %). This was detected by ^{1}H NMR and by GC-MS. The key signals are **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.76 - 0.92 (m, 6 H, 3 x CH_2), 0.95 - 1.09 (m, 9 H, 3 x CH_3), and multiple signals at 2.40 - 2.54 (m, 3 H, CH_3). GC-MS (*m/z* = 321.2, retention times = 18.021 and 18.191 min). Also isolated was 3-methyl-2-phenyl-1*H*-indole **732** as a white solid (40 mg, 39 %). M.p. = 87-89 °C (lit. m.p. = 93-94 °C).[250] **^{1}H-NMR** (400 MHz, $CDCl_3$) 2.48 (s, 3 H, CH_3), 7.16 (ddd, *J* = 8.0, 7.3, 1.3 Hz, 1 H, ArH), 7.19 - 7.25 (m, 1 H, ArH), 7.33 - 7.41 (m, 2 H, 2 x ArH), 7.45 - 7.53 (m, 2 H, 2 x ArH), 7.57 - 7.64 (m, 3 H, 3 x ArH), 8.03 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 9.6, 108.7, 110.6, 119.0, 119.5, 122.3, 127.3, 127.7, 128.8, 130.0, 133.3, 134.0, 135.8. **ATR-IR** ν_{max} (neat)/cm^{-1} 3410, 3053, 2916, 2860, 1602, 1485, 1458, 1332, 1303, 1242, 1153, 1118, 1072, 1031, 1002, 914, 765, 738, 696. ***m/z* (EI)** 207.1 (M^+, 100), 206.1 (96), 178.1 (12), 130.1 (29),

102.2 (15), 89.0 (4), 77.0 (14), 63.0 (4), 51.0 (5). The data for this compound are consistent with those reported in the literature.[319]

The silylated compounds **734** were dissolved in diethyl ether (1 mL) and conc. HCl (1 mL) was added. The mixture was stirred at room temperature overnight. The mixture was quenched by careful addition of an aqueous solution of $NaHCO_3$ and the products were extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. No isolable products were detected.

The reaction of **731** was repeated as above, and the crude reaction mixture was dissolved in THF (1 mL) and TBAF (1 M in THF, 0.65 mL, 0.65 mmol, 3.0 equiv.) was added. The mixture was refluxed overnight. After cooling to room temperature, the mixture was quenched with water and extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. No isolable products were detected.

Treatment of 3,3-Dimethyl-2-phenyl-3*H*-indole (731) with KO^{t}Bu Alone

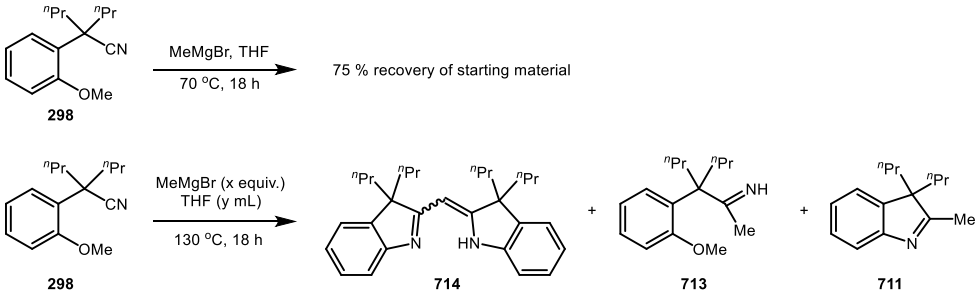


731

To a pressure tube in the glovebox under nitrogen was added 3,3-dimethyl-2-phenyl-3*H*-indole **731** (111 mg, 0.50 mmol, 1.0 equiv.) and potassium *tert*-butoxide (168 mg, 1.50 mmol, 3.0 equiv.). The tube was sealed and removed from the glovebox, and then heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to occur, and starting material **731** was recovered, with data consistent with those reported above (111 mg, 100 %).

5.10 – Treatment of Substrates with Organometallic Reagents from Chapter 5

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with MeMgBr



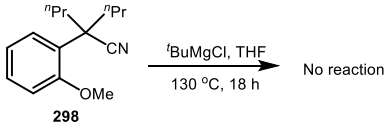
To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and methylmagnesium bromide (3.6 M in 2-methylTHF, 0.44 mL, 1.58 mmol, 3.2 equiv.) and THF (0.56 mL). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 9:1) afforded starting material **298** only (87 mg, 75 %).

Entry	x	**713**	**711**	**714**
1	3	40 %	-	9 %
2	2	24 %	-	4 %
3	4	37 %	28 %	14 %
4	10	15 %	40 %	Trace

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and methylmagnesium bromide [3.6 M in 2-methylTHF, (0.28 mL, 1.01 mmol, 2.0 equiv., or 0.42 mL, 1.51 mmol, 3.0 equiv., or 0.56 mL, 2.02 mmol, 4.0 equiv.) or (1.39 mL, 5.00 mmol, 10 equiv.)] and THF (0.72 mL, 0.58 mL or 0.44 mL or 0 mL respectively). The tube was sealed, removed from the glovebox and stirred at 130 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 0:100) afforded 2-((3,3-dipropylindolin-2-ylidene)methyl)-3,3-dipropyl-3*H*-indole **714** as a yellow solid; **Mp** = 155-158 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.65 - 0.80 (m, 16 H, 4 x CH_3 + 2 x CH_2), 0.89 - 1.02 (m, 4 H, 2 x CH_2), 1.65 - 1.76 (m, 4 H, 2 x CH_2), 1.85 - 1.96 (m, 4 H, 2 x CH_2), 5.08 (s, 1 H, CH), 7.01 (app. td, *J* = 7.1, 1.5 Hz, 2 H, 2 x ArH), 7.16 (d, *J* = 6.9 Hz, 2 H, 2 x ArH), 7.18 - 7.21 (m, 2 H,

2 x ArH), 7.21 - 7.26 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.3, 17.4, 42.5, 58.2, 82.6, 113.4, 121.7, 121.9, 127.5, 137.8, 150.9, 174.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3063, 2952, 2927, 2903, 2871, 2844, 1599, 1492, 1448, 1426, 1332, 1227, 1180, 1097, 1013, 772, 745, 677. ***m/z* (EI)** 414.4 (M^+, 85), 385.3 (81), 371.3 (100), 342.3 (8), 329.2 (15), 313.2 (8), 299.2 (26), 285.1 (36), 269.1 (71), 256.1 (62), 241.1 (1), 228.1 (1), 214.2 (48), 200.2 (36), 185.2 (5), 170.1 (55), 158.1 (14), 144.1 (11), 130.1 (12), 115.5 (4), 103.1 (1), 91.1 (1), 77.1 (1), 65.1 (1), 51.1 (1). **HRMS (CI)** calcd. for $C_{29}H_{39}N_2^+$ ($[M+H]^+$): 415.3113, found: 415.3112. Also isolated was 2-methyl-3,3-dipropyl-3*H*-indole **711** as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.57 - 0.67 (m, 2 H) 0.70 - 0.83 (m, 8 H) 1.64 - 1.78 (m, 2 H) 1.81 - 1.95 (m, 2 H) 2.26 (s, 3 H) 7.18 - 7.24 (m, 2 H) 7.29 - 7.35 (m, 1 H) 7.54 (d, *J* = 7.5 Hz, 1 H). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.2, 16.0, 17.0, 39.2, 62.8, 119.5, 121.6, 124.8, 127.4, 142.3, 155.0, 186.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 2956, 2872, 2846, 1575, 1456, 1377, 756. ***m/z* (EI)** 215.2 (M^+, 39), 200.5 (5), 186.2 (68), 172.2 (38), 157.1 (28), 144.1 (100), 128.1 (12), 115.1 (20), 102.1 (9), 91.1 (9), 77.1 (9), 63.1 (3), 51.1 (3). **HRMS (CI)** calcd. for $C_{15}H_{22}N^+$ ($[M+H]^+$): 216.1752, found: 216.1755. Also isolated was 3-(2-methoxyphenyl)-3-propylhexan-2-imine **713** as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.82 - 0.98 (m, 8 H, 2 x CH_3 + 2 x CH), 1.04 - 1.19 (m, 2 H, 2 x CH), 1.63 - 1.79 (m, 2 H, 2 x CH), 1.82 (s, 3 H, CH_3), 1.94 - 2.09 (m, 2 H, 2 x CH), 3.72 (s, 3 H, OCH_3), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1 H, ArH), 6.95 (app. td, *J* = 7.6, 1.1 Hz, 1 H, ArH), 7.21 - 7.27 (m, 1 H, ArH), 7.29 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.8, 17.4, 23.8, 34.7, 53.0, 55.0, 111.3, 120.3, 127.8, 128.0, 133.0, 157.4, 185.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 2956, 2870, 1633, 1489, 1435, 1373, 1321, 1290, 1238, 1153, 1099, 1028, 902, 877, 846, 746. ***m/z* (EI)** 247.2 (M^+, 1), 216.2 (81), 206.1 (8), 174.1 (15), 163.1 (25), 144.1 (11), 131.1 (14), 121.1 (100), 115.1 (14), 105.1 (14), 91.1 (45), 77.0 (11), 65.0 (5), 55.0 (4). **HRMS (CI)** calcd. for $C_{16}H_{26}NO^+$ ($[M+H]^+$): 248.2014, found: 248.2017.

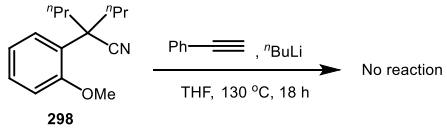
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with ^{t}BuMgCl



298

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and *tert*-butylmagnesium chloride (3.6 M in 2-methylTHF, 0.44 mL, 1.58 mmol, 3.2 equiv.) and THF (0.56 mL). The tube was sealed, removed from the glovebox and stirred at 130 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. No reaction was found to have occurred, and starting material **298** was recovered (116 mg, 100 %).

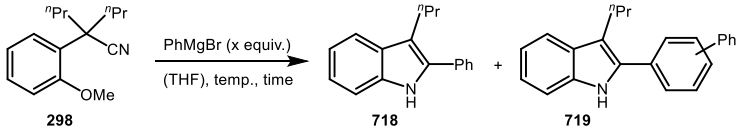
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with Phenylacetylene and ^{n}BuLi



298

Phenylacetylene (0.17 mL, 1.55 mmol, 3.0 equiv.) and ^{n}BuLi (2.5 M in hexane, 0.60 mL, 1.5 mmol, 3.0 equiv.) were stirred together in a pressure tube in a glovebox under nitrogen for 30 min. After this time, a solution of 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) in THF (0.4 mL) was added and the tube was sealed. The tube was removed from the glovebox and stirred at 130 °C for 18 h behind a shield. After cooling to room temperature, the reaction was quenched with water (50 mL) and the products were extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Although the crude NMR indicated the presence of a small amount of a second unidentified component, this could not be isolated. Purification by column chromatography afforded clean starting material **298** (100 mg, 86 %).

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with PhMgBr



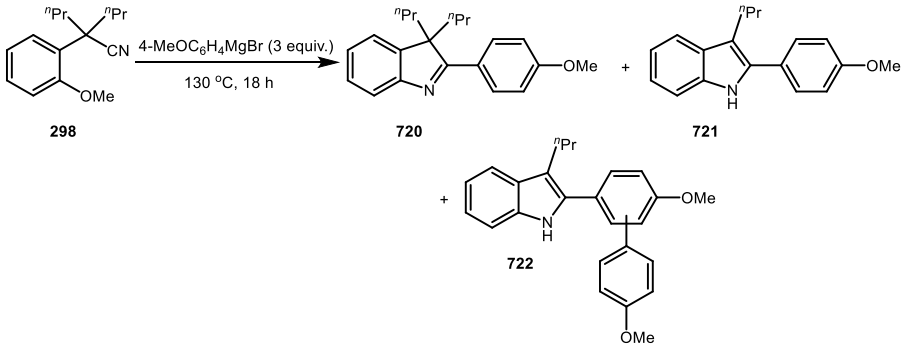
298 718 719

Entry	x	Temp.	Time	**718**	**719**	**298**
1	3	130 °C	18 h	30 %	30 %	2 %
2	2	130 °C	18 h	28 %	22 %	5 %
3	1	130 °C	18 h	7 %	5 %	52 %
4	2	130 °C	6 h	6 %	3 %	78 %
5	2	100 °C	18 h	3 %	3 %	87 %

To a pressure tube in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and phenylmagnesium bromide [1 M in THF, (1.50 mL, 1.50 mmol, 3.0 equiv.) or (1.00 mL, 1.00 mmol, 2.0 equiv.) or (0.50 mL, 0.50 mmol, 1.0 equiv.)] and THF (0 mL, 0.5 mL or 1 mL respectively). The tube was removed and stirred at the appropriate temperature (100 °C or 130 °C) for the appropriate time (6 h or 18 h) behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. 1,3,5-Trimethoxybenzene (8.4 mg, 0.05 mmol, 0.1 equiv.) was added as an internal standard to determine the yield of both compounds **718** and **719** by comparison of the integration of the methoxy group of the internal standard (3.80 ppm, 9 integral units) to the CH_2 of **718** and **719** [2.91 ppm (5.99 integral units) and 2.62 ppm (5.98 integral units) respectively]. From one experiment (3.0 equiv. of PhMgBr,

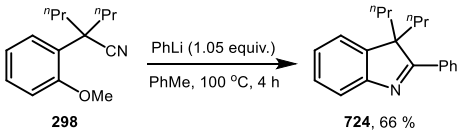
130 °C, 18 h), compounds **718** and **719** were purified by preparative HPLC to afford 2-phenyl-3-propyl-1*H*-indole **718** as a white solid (33 mg, 28 %). M.p. = 77-79 °C (lit. m.p. = 78-79 °C).[320] **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.01 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.78 (sxt, *J* = 7.8 Hz, 2 H, CH_2), 2.82 - 2.94 (m, 2 H, CH_2), 7.10 - 7.18 (m, 1 H, ArH), 7.22 (app. td, *J* = 7.5, 1.3 Hz, 1 H, ArH), 7.34 - 7.42 (m, 2 H, ArH), 7.45 - 7.52 (m, 2 H, 2 x ArH), 7.54 - 7.61 (m, 2 H, 2 x ArH), 7.66 (dd, *J* = 7.8, 0.8 Hz, 1 H, ArH), 7.99 (br. s., 1 H, NH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.4, 24.2, 26.7, 110.7, 114.0, 119.4, 119.4, 122.2, 127.5, 127.9, 128.8, 129.4, 133.5, 134.1, 135.9. **ATR-IR** ν_{max} (neat)/cm^{-1} 3400, 3055, 2956, 2868, 1604, 1537, 1487, 1446, 1340, 1305, 1072, 906, 738, 696. ***m/z* (EI)** 235.1 (M^+, 28), 206.1 (100), 178.1 (15), 165.0 (3), 152.1 (3), 128.0 (4), 115.0 (3), 102.1 (7), 89.0 (3), 77.0 (8), 63.0 (3), 51.0 (4); and 2-(biphenyl)-3-propyl-1*H*-indole **719** as a white solid (41 mg, 26 %). M.p. = 90-92 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.54 (sxt, *J* = 7.5 Hz, 2 H, CH_2), 2.56 - 2.65 (m, 2 H, CH_2), 7.03 - 7.18 (m, 3 H, 3 x ArH), 7.19 - 7.25 (m, 5 H, 5 x ArH), 7.41 - 7.56 (m, 5 H, 4 x ArH + NH), 7.58 (d, *J* = 7.3 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.5, 23.5, 26.8, 110.5, 114.5, 119.0, 119.3, 121.6, 127.0, 127.3, 128.3, 128.4, 128.5, 128.8, 130.6, 131.4, 131.6, 133.6, 135.7, 140.9, 141.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3402, 2954, 2927, 1479, 1456, 1425, 1305, 1008, 738, 700. ***m/z* (EI)** 311.2 (M^+, 42), 282.1 (100), 267.1 (19), 254.1 (5), 239.1 (3), 204.1 (7), 165.1 (7), 152.1 (3), 139.2 (3), 77.1 (4), 63.0 (1), 51.1 (1). **HRMS (CI)** calcd. for $C_{23}H_{21}N^+$ ([M+H]$^+$): 312.1747, found: 312.1748.

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with 4-$MeOC_6H_4MgBr$



To a pressure tube in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 3.00 mL, 1.50 mmol, 3.0 equiv.). The tube was removed and stirred at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. From the GC-MS of the crude reaction, compounds **298**, and **720**-**722** were tentatively identified (*m/z* = 231.2, retention time = 12.80 min, *m/z* = 307.1, retention time = 16.14 min, *m/z* = 265.1, retention time = 16.67 min, and *m/z* = 371.2, retention time = 18.993 min respectively).

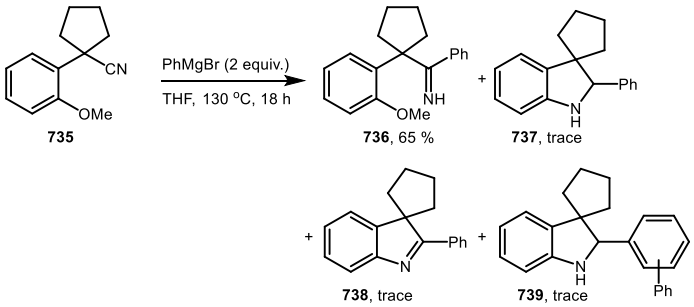
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with PhLi



298 **724**, 66 %

To a microwave vial in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.00 equiv.) and toluene (5 mL). The vial was sealed and removed from the glovebox, and the mixture was cooled to −78 °C. A solution of phenyllithium (1.56 M in dibutyl ether, 0.34 mL, 0.53 mmol, 1.05 equiv.) was added dropwise and the mixture was stirred for 1 h at −78 °C, then 1 h at room temperature, followed by 2 h at 100 °C. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded 2-phenyl-3,3-dipropyl-3*H*-indole **724** as a colourless oil (92 mg, 66 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.51 - 0.64 (m, 2 H, 2 x CH), 0.66 (t, *J* = 7.3 Hz, 6 H, 2 x CH_3), 0.75 - 0.93 (m, 2 H, 2 x CH), 2.05 (td, *J* = 12.8, 4.3 Hz, 2 H, 2 x CH), 2.13 - 2.27 (m, 2 H, 2 x CH), 7.27 - 7.30 (m, 2 H, 2 x ArH), 7.33 - 7.41 (m, 1 H, ArH), 7.45 - 7.54 (m, 3 H, 3 x ArH), 7.68 (d, *J* = 7.3 Hz, 1 H, ArH), 8.12 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.2, 17.1, 41.1, 63.3, 120.5, 120.9, 125.6, 127.6, 127.7, 128.6, 130.5, 134.2, 144.5, 154.7, 181.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3057, 2954, 2929, 2870, 1608, 1593, 1519, 1492, 1456, 1442, 1377, 1340, 1261, 1222, 1180, 1155, 1101, 1074, 1010, 920, 879, 856, 773, 732, 690, 578. ***m/z* (EI)** 277.2 ([M]$^+$, 75), 262.1 (3), 248.1 (100), 234.1 (44), 219.1 (27), 206.1 (77), 193.1 (7), 178.1 (7), 165.1 (5), 144.1 (2), 128.0 (16), 115.0 (14), 103.0 (7), 91.0 (14), 77.0 (12), 63.0 (2), 51.0 (3). **HRMS (CI)** calcd. for $C_{20}H_{24}N^+$ ([M+H]$^+$): 278.1909, found: 278.1909.

Treatment of 1-(2-Methoxyphenyl)cyclopentane-1-carbonitrile (735) with PhMgBr

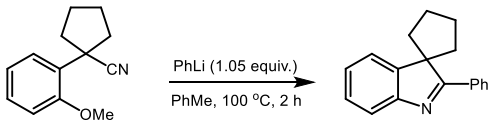


735 **736**, 65 % **737**, trace **738**, trace **739**, trace

To a pressure tube in a glovebox under nitrogen was added 1-(2-methoxyphenyl)-cyclopentane-1-carbonitrile **735** (101 mg, 0.50 mmol, 1.0 equiv.), phenylmagnesium bromide (1 M in THF, 1.00 mL, 1.00 mmol, 2.0 equiv.) and THF (0.5 mL). The tube was sealed and removed and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 50:50) afforded

(1-(2-methoxyphenyl)cyclopentyl)(phenyl)methanimine **736** as a yellow oil (91 mg, 65 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.64 - 1.74 (m, 2 H, 2 x CH), 1.75 - 1.85 (m, 2 H, 2 x CH), 2.14 - 2.27 (m, 2 H, 2 x CH), 2.30 - 2.45 (m, 2 H, 2 x CH), 3.71 (s, 3 H, OCH_3), 6.77 (dd, *J* = 8.3, 0.8 Hz, 1 H, ArH), 6.92 (app. td, *J* = 7.5, 1.0 Hz, 1 H, ArH), 7.16 - 7.26 (m, 6 H, 6 x ArH), 7.29 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 23.8, 36.8, 54.9, 58.4, 111.2, 120.3, 127.3, 127.5, 127.5, 128.2, 128.9, 132.7, 139.9, 157.2, 186.7. **ATR-IR** ν_{max} (neat)/cm^{-1} 3055, 2953, 2872, 1608, 1575, 1489, 1462, 1435, 1344, 1244, 1180, 1118, 1055, 1028, 906, 752, 698. ***m/z* (EI)** 279.2 (M^+, 10), 248.2 (100), 206.1 (7), 176.2 (60), 161.1 (7), 147.1 (30), 121.1 (40), 104.1 (63), 91.1 (45), 77.1 (48), 65.0 (8), 51.0 (17). **HRMS (CI)** calcd. for $C_{19}H_{22}NO^+$ ($[M+H]^+$): 280.1696, found: 280.1697. Also collected was a complex fraction in which compounds **737**-**739** were tentatively identified, in low yield. Compound **737** (*m/z* = 249.2, retention time = 16.220 min), compound **738** (*m/z* = 247.2, retention time = 15.984 min) and compound **739** (*m/z* = 325.3, retention time = 17.761 and 17.839 min).

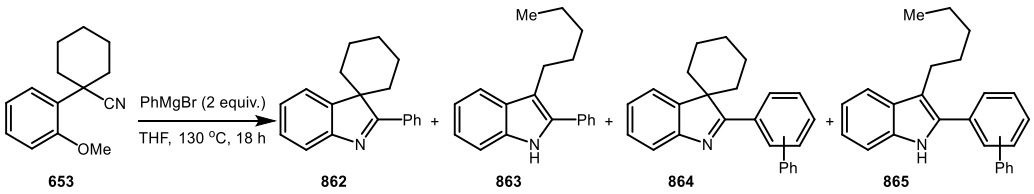
Treatment of 1-(2-Methoxyphenyl)cyclopentane-1-carbonitrile (735) with PhLi



735 **738**, 41 %

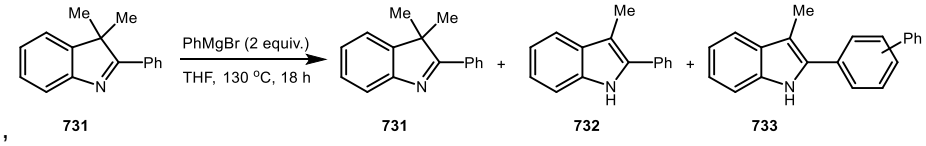
To a microwave vial in the glovebox under nitrogen was added 1-(2-methoxyphenyl)cyclopentane-1-carbonitrile **735** (101 mg, 0.50 mmol, 1.00 equiv.) and toluene (5 mL). The vial was sealed and removed from the glovebox, and the mixture was cooled to −78 °C. A solution of phenyllithium (1.56 M in dibutyl ether, 0.34 mL, 0.53 mmol, 1.05 equiv.) was added dropwise and the mixture was stirred for 1 h at −78 °C, then 1 h at room temperature, followed by 2 h at 100 °C. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 9:1) afforded 2'-phenylspiro[cyclopentane-1,3'-indole] **738** as a colourless oil (51 mg, 41 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 1.88 - 2.03 (m, 2 H, 2 x CH), 2.16 - 2.31 (m, 4 H, 4 x CH), 2.38 - 2.53 (m, 2 H, 2 x CH), 7.22 - 7.26 (m, 1 H, ArH), 7.36 (app. td, *J* = 7.6, 1.1 Hz, 1 H, ArH), 7.41 (d, *J* = 7.5 Hz, 1 H, ArH), 7.46 - 7.55 (m, 3 H, 3 x ArH), 7.71 (d, *J* = 7.5 Hz, 1 H, ArH), 8.05 - 8.16 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 27.5, 36.8, 63.2, 120.6, 120.9, 125.8, 127.3, 128.2, 128.5, 130.4, 132.8, 150.1, 152.9, 182.6. **ATR-IR** ν_{max} (neat)/cm^{-1} 3057, 2953, 2872, 1519, 1454, 1440, 1342, 1265, 1220, 1207, 1180, 1157, 1109, 1074, 1018, 947, 927, 862, 769, 748, 694. ***m/z* (EI)** 247.1 (100, $[M]^+$), 230.1 (3), 218.1 (77), 204.1 (27), 189.1 (2), 170.1 (20), 156.1 (4), 143.1 (9), 128.0 (24), 115.0 (31), 102.0 (14), 89.0 (9), 77.0 (16), 63.0 (7), 51.0 (9). The data for this compound are consistent with those reported in the literature.[196]

Treatment of 1-(2-Methoxyphenyl)cyclohexane-1-carbonitrile (653) with PhMgBr



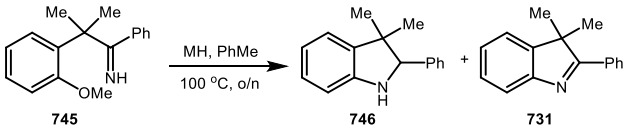
To a pressure tube in a glovebox under nitrogen was added 1-(2-methoxyphenyl)-cyclohexane-1-carbonitrile **653** (108 mg, 0.50 mmol, 1.0 equiv.), phenylmagnesium bromide (1 M in THF, 1.00 mL, 1.00 mmol, 2.0 equiv.) and THF (0.5 mL). The tube was sealed, removed from the glovebox, and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. A complex mixture of products was observed, from which nothing could be isolated as pure. GC-MS of the crude reaction mixture indicated compounds **862**-**865** may be present, but this is inconclusive. Compound **862**, (*m/z* = 261.1, retention time = 16.122 and 16.691 min), compound **863** (*m/z* = 263.1, retention time = 15.807 and 16.211 min), compound **864** (*m/z* = 337.2, retention times = 17.338 and 18.005 min), compound **865** (*m/z* = 339.2, retention times = 17.761 and 17.957 min).

Treatment of 3,3-Dimethyl-2-phenyl-3*H*-indole (731) with PhMgBr



To a pressure tube in the glovebox under nitrogen was added 3,3-dimethyl-2-phenyl-3*H*-indole **731** (111 mg, 0.50 mmol, 1.0 equiv.) and phenylmagnesium bromide (1 M in THF, 1.00 mL, 1.00 mmol, 2.0 equiv.) and THF (0.5 mL). The tube was sealed and removed from the glovebox, and then stirred at 130 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Column chromatography (ethyl acetate:hexane, 0:100 → 10:90) failed to separate out any compounds, and the ^{1}H NMR was very complex, preventing determination of yields by internal standard. However, compounds **731**, **732** and **733** were tentatively identified by GC-MS [*m/z* = 221.1, retention time = 13.930 min, *m/z* = 207.1, retention time = 14.983 min, and *m/z* = 283.1, retention time = 16.710 min, respectively).

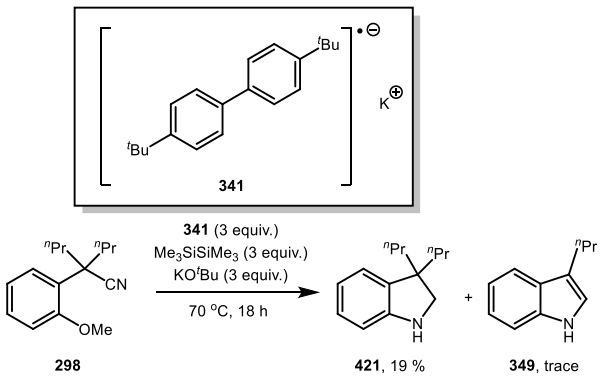
Treatment of 2-(2-Methoxyphenyl)-2-methyl-1-phenylpropan-1-imine (745) with Metal Hydrides



2-(2-Methoxyphenyl)-2-methyl-1-phenylpropan-1-imine **745** (127 mg, 0.50 mmol, 1.0 equiv.) was dissolved in dry toluene (1 mL) in a pressure tube in the glovebox under nitrogen and appropriate metal hydride [LiH (7.0 mg, 0.9 mmol, 1.8 equiv.) or NaH (22.0 mg, 0.92 mmol, 1.8 equiv.) or KH (36.0 mg, 0.90 mmol, 1.8 equiv.)] was added. The tube was sealed and removed from the glovebox and heated at 100 °C overnight. After cooling to room temperature, the mixture was quenched with *iso*propanol then water, and extracted into DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. With LiH and NaH, no reaction was found to have taken place and starting material **745** (101 mg, 80 % and 113 mg, 89 % respectively) was recovered, with data consistent with those reported above. From KH, no starting material remained. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 4:1) afforded 3,3-dimethyl-2-phenylindoline **746** as a pink solid (25 mg, 22 %). M.p. = 92-94 °C (lit. m.p. = 89-91 °C).[321] **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.76 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 4.62 (s, 1 H, CH), 6.77 (d, *J* = 7.6 Hz, 1 H, ArH), 6.83 (app. t, *J* = 7.4 Hz, 1 H, ArH), 7.04 - 7.13 (m, 2 H, 2 x ArH), 7.30 - 7.40 (m, 3 H, 3 x ArH), 7.43 - 7.51 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 24.5, 26.5, 45.3, 75.5, 109.1, 118.9, 122.4, 127.4, 127.4, 127.5, 128.1, 138.0, 139.9, 149.3. **ATR-IR** ν_{max} (neat)/cm^{-1} 3365, 2958, 1608, 1519, 1483, 1458, 1361, 1240, 744, 702. ***m/z* (EI)** 223.1 (M^+, 51), 208.1 (100), 193.1 (39), 180.1 (4), 165.1 (7), 146.1 (10), 130.1 (19), 115.1 (10), 103.1 (10), 91.1 (17), 77.1 (21), 65.1 (5), 51.1 (8). Also isolated was 3,3-dimethyl-2-phenyl-3H-indole **731** as a yellow oil, with data consistent with those reported above (18 mg, 16 %).

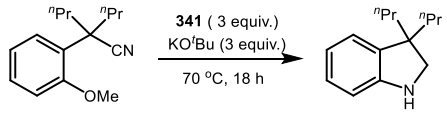
5.11 – Mechanistic Study from Chapter 5

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with 341, $Me_3SiSiMe_3$ and KO^{t}Bu



Compound **341** was prepared as reported on page 167. To a pressure tube in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.), potassium di-*tert*-butylbiphenylide **341** (458 mg, 1.50 mmol, 3.0 equiv.), hexamethyldisilane (0.31 mL, 1.51 mmol, 3.0 equiv.) and potassium *tert*-butoxide (168 mg. 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 70 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluting with hexane:ethyl acetate (100:0 → 9:1) to afford starting material **298** as a colourless oil (55 mg, 47 %), with data consistent with those reported above, 3,3-dipropylindoline **421** as a colourless oil (19 mg, 19 %), with data consistent with those reported above, and 3-propyl-1*H*-indole **349** (<1 mg), with data consistent with those reported above.

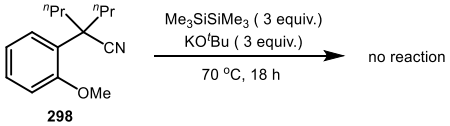
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with 341 and KO^{t}Bu



298 **421**, trace

To a pressure tube in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.), **341** (458 mg, 1.50 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg. 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 70 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluting with hexane:ethyl acetate (100:0 → 9:1) to afford starting material **298** as a colourless oil (61 mg, 53 %), with data consistent with those reported above, and 3,3-dipropylindoline **421** as a colourless oil (<1 mg), with data consistent with those reported above.

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with $Me_3SiSiMe_3$ and KO^{t}Bu

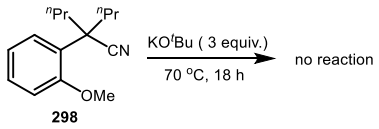


298

To a pressure tube in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.), hexamethyldisilane (0.31 mL, 1.51 mmol, 3.0 equiv.), and potassium *tert*-butoxide (168 mg. 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 70 °C for 18 h behind a shield. After cooling

to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. No reaction was found to have taken place, and 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** was recovered with data consistent with those reported above (116 mg, 100 %).

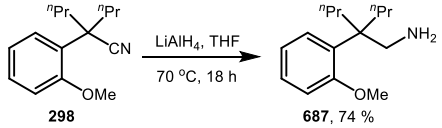
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with KO^{t}Bu Alone



298

To a pressure tube in the glovebox under nitrogen was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.), and potassium *tert*-butoxide (168 mg. 1.50 mmol, 3.0 equiv.). The tube was sealed, removed from the glovebox and heated at 70 °C for 18 h behind a shield. After cooling to room temperature, the mixture was diluted with water (50 mL) and extracted into diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. No reaction was found to have taken place, and 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** was recovered with data consistent with those reported above (104 mg, 90 %).

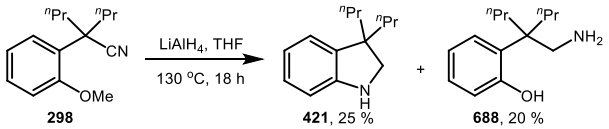
Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with $LiAlH_4$ at 70 °C



298 **687**, 74 %

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and lithium aluminium hydride (2 M in THF, 0.75 mL, 1.50 mmol, 3.0 equiv.) and THF (0.25 mL). The tube was sealed, removed from the glovebox and stirred at 70 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water:THF (1:4, 50 mL) then 2 M NaOH (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (cyclohexane:ethyl acetate, 100:0 → 9:1) afforded 2-(2-methoxyphenyl)-2-propylpentan-1-amine **687** as a colourless oil (87 mg, 74 %). **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.88 (t, *J* = 6.9 Hz, 6 H, 2 x CH_3), 1.01 - 1.20 (br. m, 6 H, 2 x CH_2 + NH_2), 1.69 (ddd, *J* = 13.8, 11.8, 5.4 Hz, 2 H, CH_2), 1.82 (ddd, *J* = 13.8, 11.8, 4.9 Hz, 2 H, CH_2), 3.05 (s, 2 H, CH_2N), 3.82 (s, 3 H, OCH_3), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 6.92 (app. td, *J* = 7.4, 1.0 Hz, 1 H, ArH), 7.15 - 7.24 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 15.0, 17.3, 36.1, 46.5, 46.6, 55.1, 111.6, 120.3, 127.2, 129.4, 133.0, 158.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 2954, 2869, 1578, 1488, 1455, 1289, 1236, 1180, 1095, 1027, 746, 470. **HRMS (CI)** calcd. for $C_{15}H_{26}NO^+$ ($[M+H]^+$): 236.2014, found: 236.2016.

Treatment of 2-(2-Methoxyphenyl)-2-propylpentanenitrile (298) with $LiAlH_4$ at 130 °C



298 **421**, 25 % **688**, 20 %

To a pressure tube in the glovebox, under nitrogen, was added 2-(2-methoxyphenyl)-2-propylpentanenitrile **298** (116 mg, 0.50 mmol, 1.0 equiv.) and lithium aluminium hydride (28.0 mg, 1.50 mmol, 3.0 equiv.) and THF (1 mL). The tube was sealed, removed from the glovebox and stirred at 130 °C for 18 h. After cooling to room temperature, the reaction mixture was quenched by addition of water (50 mL) then 2 M NaOH (50 mL). The products were extracted into diethyl ether (3 x 50 mL) and the combined organic layers were dried over a hydrophobic frit and concentrated under reduced pressure. Purification by column chromatography (hexane:ethyl acetate, 100:0 → 1:9) afforded 3,3-dipropylindoline **421** as a yellow oil (25 mg, 25 %), with data consistent with those reported above, and 2-(4-(aminomethyl)heptan-4-yl)phenol **688** as a white solid (22 mg, 20 %). **Mp** = 90 – 91 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$) 0.92 (t, *J* = 7.4 Hz, 6 H, 2 x CH_3), 1.06 - 1.21 (m, 2 H, 2 x CH), 1.24 - 1.38 (m, 2 H, 2 x CH), 1.62 - 1.73 (m, 2 H, 2 x CH), 1.81 (ddd, *J* = 13.6, 12.4, 4.8 Hz, 2 H, 2 x CH), 3.05 (s, 2 H, NCH_2), 6.72 - 6.80 (m, 1 H, ArH), 6.87 (dd, *J* = 7.9, 1.3 Hz, 1 H, ArH), 7.04 - 7.13 (m, 2 H, 2 x ArH). **^{13}C-NMR** (101 MHz, $CDCl_3$) 14.8, 17.1, 38.5, 45.3, 49.1, 118.2, 119.1, 127.6, 128.5, 130.6, 157.5. **ATR-IR** ν_{max} (neat)/cm^{-1} 3371, 2954, 2868, 1620, 1581, 1463, 1440, 1425, 1280, 1224, 904, 839, 748. **HRMS (CI)** calcd. for $C_{14}H_{24}NO^+$ ($[M+H]^+$): 222.1852, found: 222.1853.