Asymmetric synthesis of novel bioactive pyrrolidines for use in drug discovery

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1. List of Abbreviations

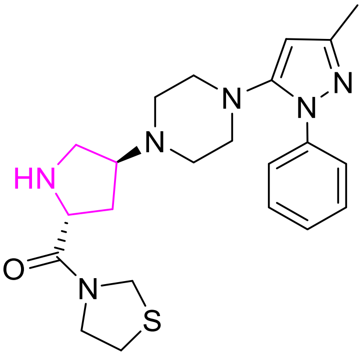
acac	Acetylacetone
Ar	Aryl
atm	Atmosphere
AQ	Aminoquinoline
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Boc	tert-butyloxycarbonyl
coe	cyclooctene
DABCO	(1,4-diazabicyclo[2.2.2]octane)
dba	dibenzylideneacetone
DG	Directing group
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMPip	1,4-dimethylpiperazine
DOS	Diversity-orientated synthesis
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
dppp	1,3-Bis(diphenylphosphino)propane
Hünigs base	N,N-Diisopropylethylamine
MH	Mizoroki-Heck
NHC	N-heterocyclic carbene
NMP	N-Methyl-2-pyrrolidone

NTf_2	Triflimide
OTf	Trifluoromethanesulfonate
***o*-Tol**	*ortho*-Toluene
PHOX	Phosphinooxazoline
PivOH	Pivalic acid
PMB	*para*-methoxy benzyl
PMHS	Polymethylhydrosiloxane
SEGPHOS	Bis(diphenylphosphino)-4,4’-bi-1,3-benzodioxole
TMA	Trimethylamine
THF	Tetrahydrofuran

2. Introduction

Saturated cyclic amines are important structural motifs in natural products, with the most prominent being 5- and 6-membered systems.[1] Saturated heterocycles; nitrogen containing rings are crucial components across a range of biologically active compounds featuring greatly in pharmaceuticals.[2] Pyrrolidines in particular have inspired extensive studies as an important template in drug discovery.[3]

More recently, the use of pyrrolidines in medicinal chemistry has led to calls for increased saturation and more 3-dimensional characteristics in drug-like compounds.[4] These chiral pyrrolidines are playing a crucial role as both building blocks for auxiliaries as well as key structures in biologically active substances and it is proposed that the increased fraction of sp[3] centres will afford more successful drug candidates.[5] Therefore, reliable asymmetric synthetic methods that can provide the pyrrolidine motif with control over the 3-dimensional arrangement of substituents are highly valuable. For example, the diabetes drug, pyrrolidine **1** (Figure 1) is the 199th bestselling in all small molecule pharmaceuticals for 2018 with $347 million in retail sales.[6]



1
Tenelia
(Teneligliptin)

Figure 1. Chemical Structure of **1** with chiral pyrrolidine at the centre.[6]

3. Diversity-Orientated Synthesis

In pharmaceutical chemistry research, there is often major inspiration for the design and synthesis of compound libraries and their underlying motif/scaffold from natural products.[7] These natural products are often used as drug leads because they are often already biologically active. Diversity-orientated synthesis (DOS) aims to generate the structural diversity required for effective screening in an efficient manner especially within small molecule research. There are multiple ways that this diversity can be achieved in compound libraries, which include appendage diversity, functional group diversity, stereochemical diversity and skeletal diversity. DOS is, therefore, a tool for the discovery of novel and biologically active small molecules. With the demand for niche chemically diverse compound libraries so high, DOS will be a key factor to utilise for this project to deliver a library of novel heteroaryl-pyrrolidine compounds.[8]

4. Targets and Key Disconnections

The pyrrolidine motif has uses as pharmaceutical drug candidates,[9] building blocks in organic synthesis, ligands and as organocatalysts.[10] With such lucrative and versatile uses, there is therefore, a great amount of interest in the asymmetric synthetic approaches to pyrrolidines. As a result, there is already a vast amount of research into the asymmetric synthesis of 3-substituted pyrrolidines (Figure 2).

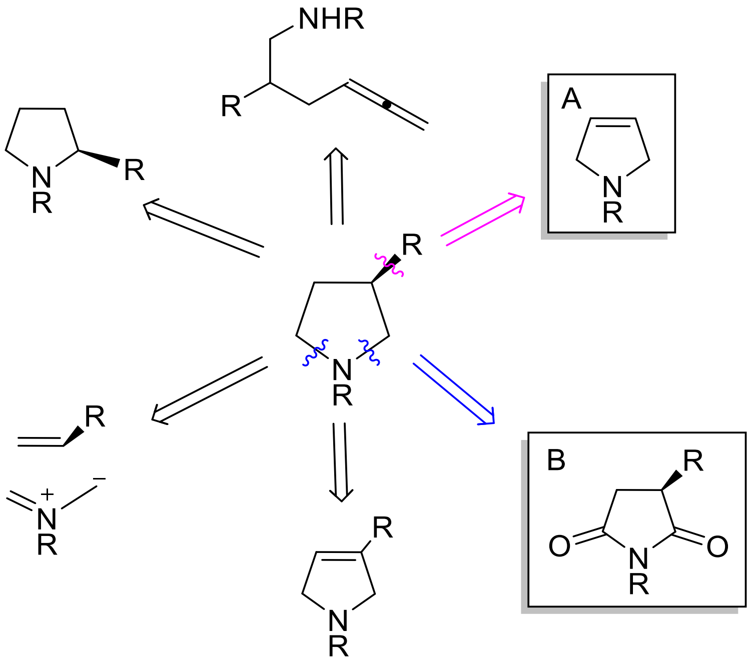


Figure 2. The key disconnections relevant to the proposed body of work.

As part of this research project a small pharmaceutical contract research company, Apex Molecular, have some novel target templates in order to define the scope of the research. All the compounds are 3-subsituted chiral pyrrolidines (Figure 3). Despite these target compounds, the general goal is to develop synthetic methods and approaches and to expand the scope of molecular diversity around these novel small molecule templates. As a result, the key disconnections this project discusses on are A: Reductive Heck/Arylation and B: via the Reduction of Chiral Succinimides (Figure 2). Considering the previous work and expertise in the Sweeney group, these key synthetic approaches yield the best chance of synthesising the target compounds and creating a possible library with scope for molecular diversity.

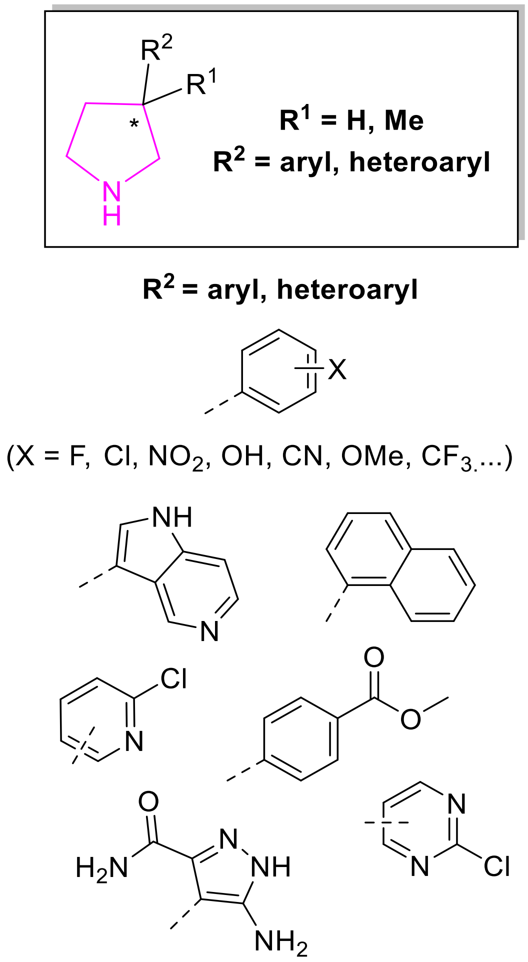
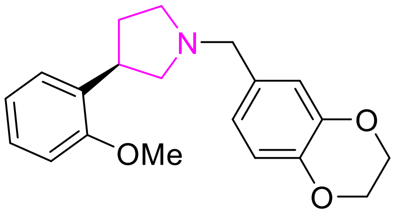


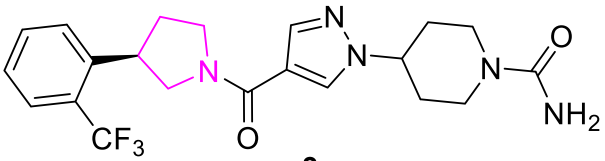
Figure 3. General Structure of Novel Target Compounds with some specific Target Compounds to be incorporated into the library.

The majority of functionalised pyrrolidine synthesis involves ring construction rather than modification of an already formed pyrrolidine ring. There are examples of work developing techniques that convert unsubstituted pyrrolidines, to their 2-substituted derivatives [11,12] however, this project will focus on the synthesis of 3-substituted pyrrolidines. Examples of a couple of biologically active compounds which are attainable through this project are the potent α-2-adrenoceptor antagonist (**2**)[13,14] developed by Novartis[15] and a HSD-1 inhibitor (**3**)[16] (Figure 4).



2

α-2-adrenoceptor antagonist



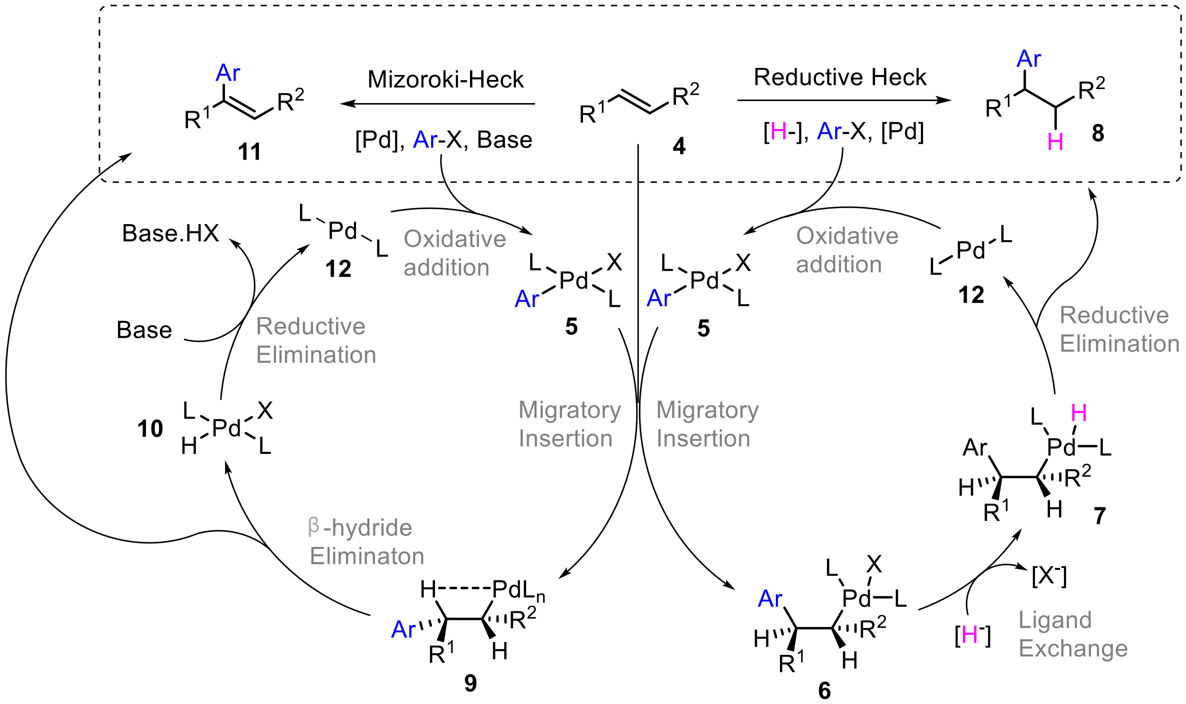
3

HSD-1 inhibitor

Figure 4. Biologically active compounds which are synthetically attainable through this project.[13,14,15,16]

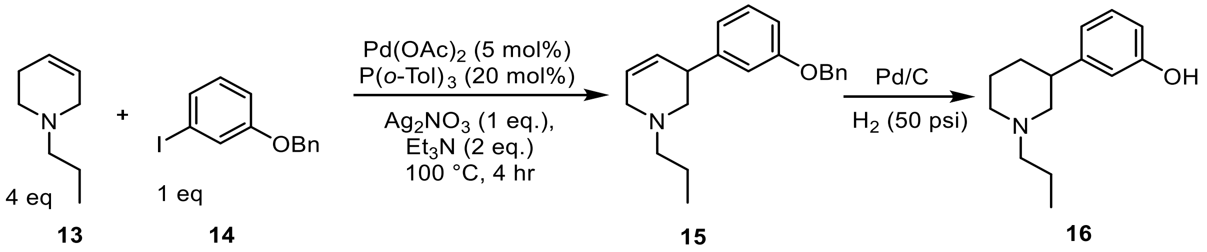
5. The Heck reaction

The Mizoroki-Heck (MH) reaction is amongst the most extensively researched metal catalysed cross-coupling reactions, which involves a coupling between aryl (pseudo)halides and alkenes in the presence of a base and palladium catalyst to form a new C-C bond. In contrast its counterpart the palladium catalysed reductive Heck reaction is significantly less researched. Mechanistically, the Heck reactions are very similar (Scheme 1). The MH reaction catalytic cycle starts with the oxidative addition of an aryl (pseudo)halide to a palladium (0) catalyst followed by 1,2-migratory insertion forming the aryl palladium (II) species **9**. At this point the mechanisms differ, the MH reaction undergoes β-hydride elimination to yield the newly substituted alkene product **11**, followed by regeneration of the palladium (0) catalyst (**12**) using the base present. Alternatively, the reductive Heck mechanism following 1,2-migratory insertion, undergoes ligand exchange with a hydride source. The resulting intermediate (**7**) can undergo reductive elimination to form the new C-H bond and yield the substituted product (**8**) with the new C-C bond.[17] Generally, the MH reaction also does not yield a chiral centre, this only happens in cyclic olefins[18] and intramolecular reactions[19], as β-hydride elimination is hampered by C-C bond rotation therefore, one advantage of the reductive Heck reaction, is the formation of chiral centres, which as discussed are highly valuable in medicinal chemistry.



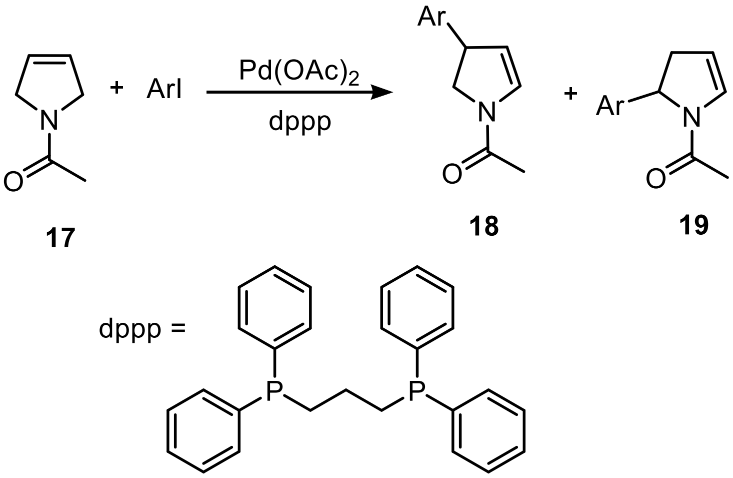
Scheme 1. Reductive vs Mizoroki Heck mechanisms.[17]

Notwithstanding the proven synthetic power of the MH reaction, there are some weaknesses to the synthetic technique, namely that certain alkene classes are unreliable substrates. Cyclic allylamines (such as tetrahydropyridines and pyrrolines) fall into this category of substrate that require high substrate/catalyst loading or electron withdrawing N-protecting groups for the nitrogen lone pair to delocalise into, in order to perform well. The interest for using the MH reaction on cyclic allylamines started in the 1990s when Hallberg synthesised the dopamine agonist Preclamol (**16**), which was isolated in 40% yield with respect to the aryl iodide starting material (Scheme 2).[20] In his work on 6-membered tetrahydropyridines, Hallberg proposed that Pd-N chelation was responsible for the observed regioselectivity, with a preference for the 3-arylation vs. 4-arylation of greater than 14:1 ratio. This is due to the favoured formation of a 5-membered palladium adduct when arylation occurs at the 3-position. Hallberg also suggested that the silver additives are crucial as they form silver salts, which limit double bond migration and consequently stop the formation of reactive enamines. As shown, in the absences of silver additives, the yield of the desired 3-arylated product is low with high molecular weight compounds being formed.[20]



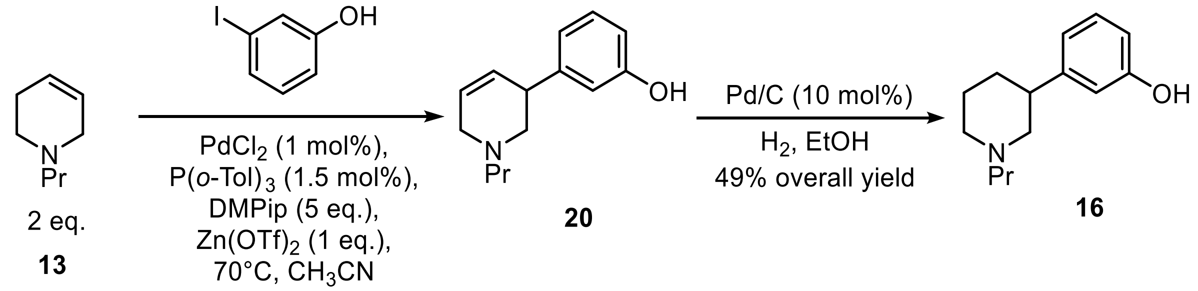
Scheme 2. 2-step synthesis of **16** (Preclamol) by Hallberg.[20]

In 1996 Hallberg *et* al. expanded the SAR (structure-activity relationship) to produce a procedure for the regioselective palladium-catalysed arylation of N-substituted 2,5-dihydropyrroles to produce 2-/3- aryl-(heteroaryl)pyrrolines which following hydrogenation can yield 3-aryl-(heteroaryl)pyrrolidines with potential as dopamine receptor antagonists.[21] They proposed that the allyl amide undergo two types of Pd-catalysed reaction: 1) arylation to produce the desired product **18** and 2) double bond isomerisation, which leads to product **19** (Scheme 3). Again silver additives, some influence of which was observed by Overman's group[22–24], were used to stop double bond isomerisation and 0.7 equivalents of silver carbonate suppressed the formation of **19** completely.



Scheme 3. The two regioisomer outcomes following palladium catalysed arylation in the absence of silver additives.[21]

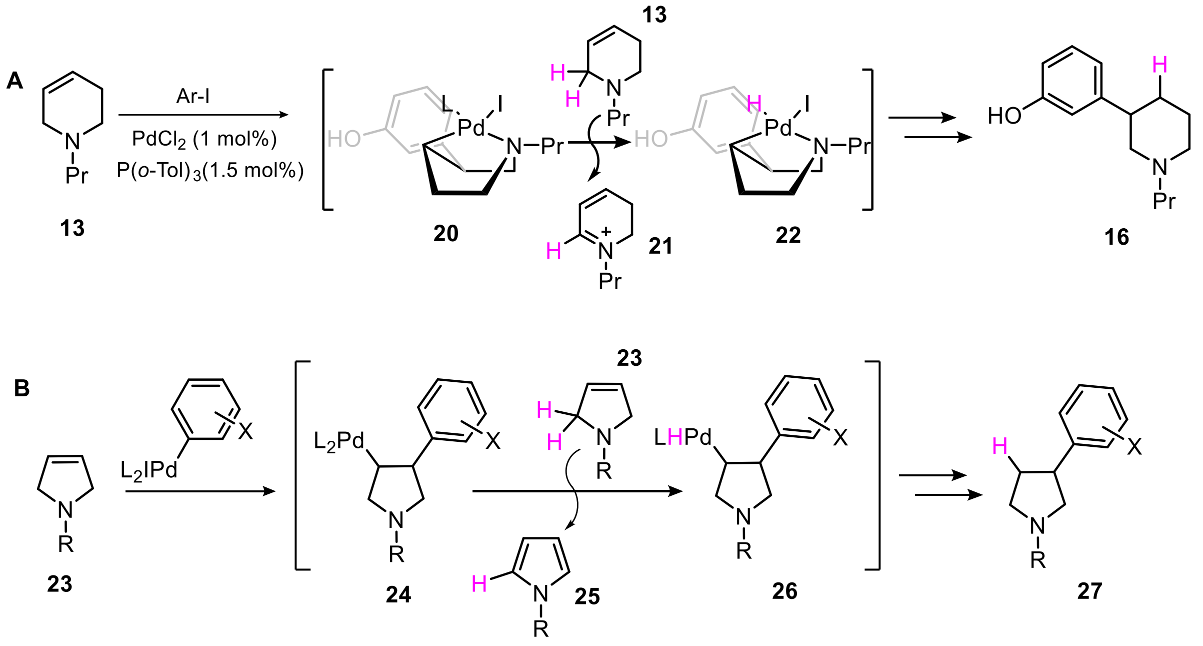
This work inspired the Sweeney group to also work on the Preclamol (**16**) synthesis in 2018. The aim, whilst optimising the MH reaction with tetrahydropyridines, was to reduce the catalyst loading to ≤1 mol% and avoid the use of silver additives. As shown in Scheme 4 the improved synthetic conditions used an alternative additive ($Zn(OTf)_2$) and required only 1 mol% catalyst loading to synthesise **16** in good overall yield.[25]



Scheme 4. Improved synthesis of **16** (Preclamol).[26]

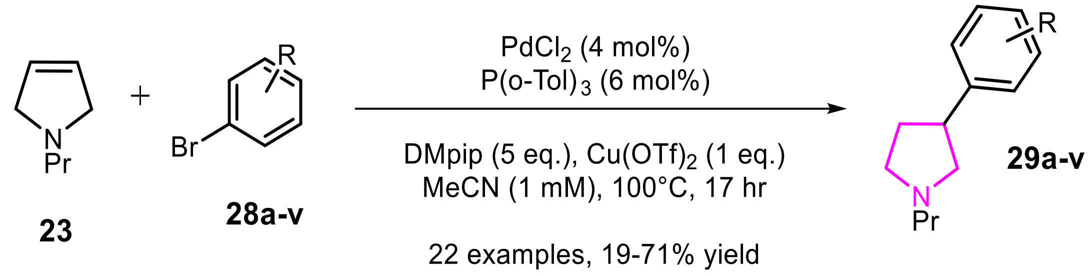
5.1 Hydride Source for the Reductive Heck reaction

In a following paper, also from 2018, the Sweeney group proposed that interception of the chelated Pd-complex intermediate by a hydride source could lead to saturated products, rather than alkenes, via a reductive Heck reaction.[27] This was proposed during the course of the optimisation of the Preclamol synthesis route when it became clear that there were competing redox side reactions to the desired arylation/Heck reaction.[26] This was evident as the monoarylated (MH) product was obtained with approximately 3% of the hydroarylated (Reductive Heck) product (**16**). They proposed that the hydride required for the reductive Heck to proceed, was being supplied by the tetrahydropyridine substrate, **13** (present in excess), which resulted in dihydropyridiniums (**21**) being produced as by-products (Scheme 5A). Dihydropyridiniums are extremely reactive and are expected to be undergoing their own side reactions such as dimerization. Based on this analysis, they hypothesised that reaction with pyrrolines instead of tetrahydropyridines, would therefore, lead to the hydroarylated product more efficiently as the analogous oxidised by-product **25** (pyrrole) would be stable and, as a result, does not undergo further side reactions (Scheme 5B). They were, therefore extremely pleased when, under the same conditions used on the tetrahydropyridine, the pyrroline **23** gave only the 3-arlyated pyrrolidine product, **27**, in approximately equal yield. This confirmed the hydride source to the be the substrate, which again was used in excess (3 eq.).[27]

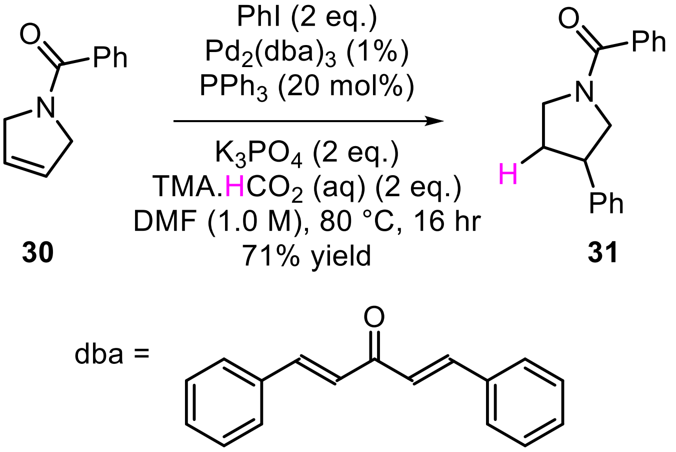


Scheme 5. Redox side reactions occurring in palladium-catalysed reductive Heck reaction of aryl halides with cyclic allylamines: A) tetrahydropyridines and B) pyrrolines.[27]

The Sweeney group took this finding and developed the palladium-catalysed hydroarylation of pyrrolines to synthesise 3-aryl substituted pyrrolidines **29a-v**. The optimised conditions were determined for broad scope arylation to deliver 22 examples of chiral pyrrolidines in varying yields from (19-71%, Figure 26). Interestingly during the optimisation traditional silver (I) additives gave low yields, with $Zn(OTf)_2$ giving good yield but $Cu(OTf)_2$ gave better yields still. When no additive was used, only protodehalogentation occurred with 97% yield, which could indicate that the additive is acting as a Lewis acid to abstract the halide from the palladium complex. The process, which was optimised for N-propylpyrroline, was importantly also applicable to N-benzylpyrroline. This is a main focus for this project as, although depropylation is possible, it is not as efficiently carried out as debenzylation. An optimised system to produce N-benzyl pyrrolidines should allow for the more efficient tractable synthesis of bioactive pyrrolidines that can undergo further functionalisation for drug target compounds.[27] Sweeney and co-workers' development of this system is a valuable development in the synthesis of 3-aryl substituted pyrrolidines, as it can be achieved in one step. Only one other example can be found where a reductive Heck system has been applied to the 1 step synthesis of such compounds. This work, performed by Gurak and Engle, to synthesise compound **31** was achieved in 71% yield, whilst exploring the alkene scope of their reductive Heck system (Scheme 7).[28]



Scheme 6. Broad scoped palladium-catalysed hydroarylation of pyrrolines to synthesise their 3-aryl substituted pyrrolidines.[27]

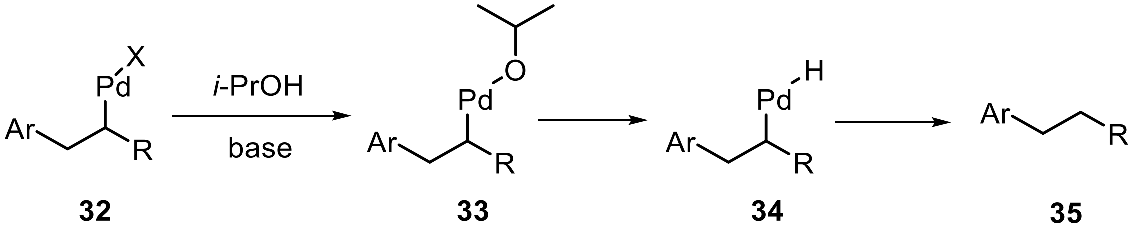


Scheme 7. Reductive Heck system to produce 3-arylated pyrrolidines in 1 step.[28]

The Sweeney group's findings were also an important development in the study of the reductive Heck reaction because of the use of the substrate as the hydride source. Although an interesting insight into the reaction, in practice, using the substrate as a hydride source is not necessarily always practical. This is especially true if the substrate is expensive or made by a long stepwise synthetic scheme, using 3 equivalents of these substrates is therefore not practical for industrial scale up. As a result, research into efficient, cheap and readily available hydride sources is extremely valuable for the reductive Heck reaction to reach its full potential in industry. Existing work on the reductive Heck reaction usually used formates as the hydride source (often sodium formate or formic acid).[29–32]

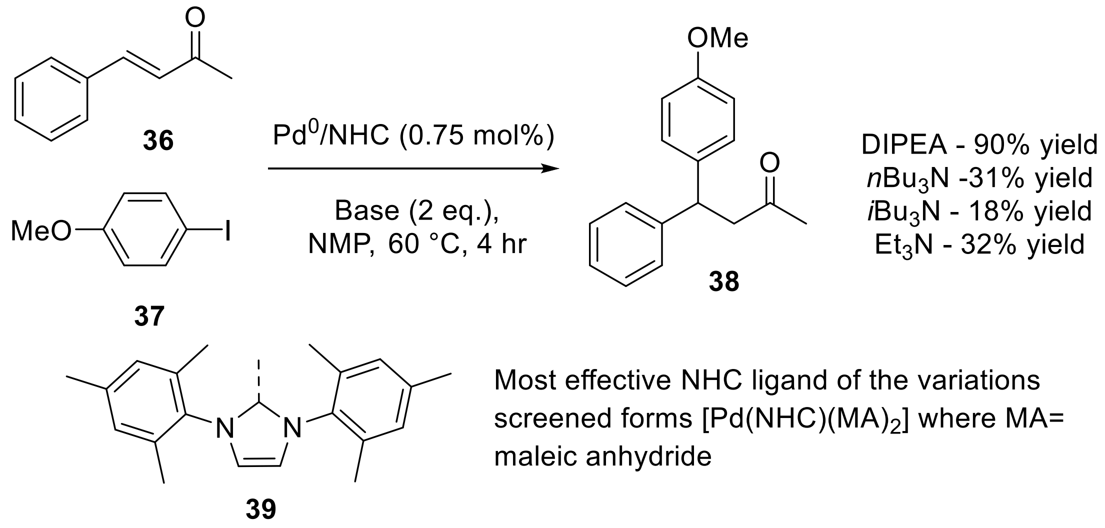
In more recent year's developments have been made to identify alternative hydride sources. These alternative hydride sources have been studied mechanistically as well, often by following deuterium labelling experiments in order to propose the most realistic path for the hydride transfer. In 2018 Jin and co-workers developed a reductive Heck reaction between a range of olefins and aryl bromides using *i*-PrOH as the hydride source. By performing deuterium labelling experiments, the optimised reaction conditions were carried out using

$(CD_3)_2CDOD$, providing the desired product in 63% yield with 98% deuterium incorporation. When *t*-BuOH was used as a solvent, no reaction occurred but most interestingly when the reaction was performed using $(CH_3)_2CHOD$ the product was obtained with 67% yield but without deuterium incorporation. Jin *et* al. therefore, proposed that the most plausible mechanistic pathway for this reaction, was when *i*-PrO$^-$ binds to the palladium (**33**) and supplies the hydride through β-hydride elimination (**34**), followed by reductive elimination to yield the hydroarylated product, **35** (Scheme 7).[33]



Scheme 7. Plausible mechanistic pathway for Pd-catalysed reductive Heck reaction using *i*-PrOH as the hydride source.[33]

Similar to the Sweeney group's use of pyrrolines as the hydride source, using amines as the hydride source in reductive Heck reactions is well established. Raoufmoghaddam and co-workers, from 2011-2018, developed a Palladium/N-heterocyclic carbene (NHC) ligand catalysed reductive Heck system for the reaction of enone **36** with aryl iodide **37**. Their work was to progress the first reported hydride source combination of formates[34] and trialkylamine bases. Raoufmoghaddam *et* al. proposed that using their Palladium/NHC complex, trialkylamines such as *N*,*N*-diisopropylethylamine (DIPEA), *N*-methyl-2-pyrrolidone (NMP) and both tributyl-/triethylamine could be used as hydride sources in the reductive Heck reaction without the requirement for formates.[35,36,37]

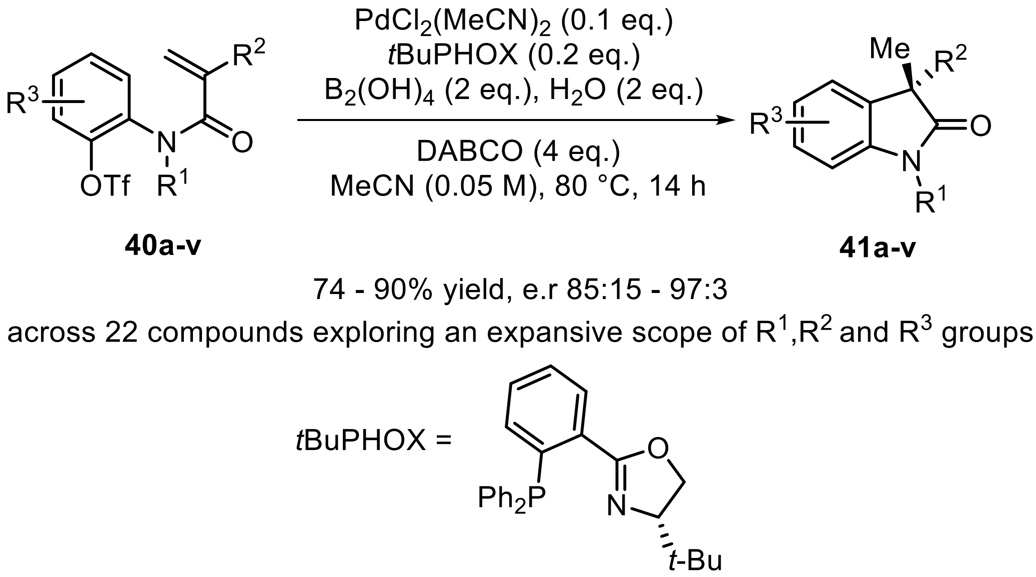


DIPEA - 90% yield
$n\mathrm{Bu}_3\mathrm{N}$ -31% yield
$i\mathrm{Bu}_3\mathrm{N}$ - 18% yield
$\mathrm{Et}_3\mathrm{N}$ - 32% yield

Most effective NHC ligand of the variations screened forms [Pd(NHC)(MA)$_2$] where MA= maleic anhydride

Scheme 8. Palladium/N-heterocyclic carbene (NHC) ligand catalysed reductive Heck system tested using various base and solvent combinations, with the most effective using DIPEA and NMP.[35,36,37]

In 2017, Kong and co-workers developed an extremely interesting enantioselective intramolecular reductive Heck system. By 2017, tertiary amines (proton sponge, *N*-methyl dicyclohexylamine)[38], formates[29–32], *i*-PrOH[33], *i*Pr$_2$NEt[35] and others have been used as hydride donors in combination with the palladium catalyst and often chiral ligands. However, as water is the most cost-efficient and environmentally benign hydride source available for the reductive Heck reaction, Kong *et* al. decided to develop a reductive Heck system using $B_2(OH)_4$ /H_2O as a hydride source. Kong *et* al. proposed that through transmetallation an alkyl-Pd^{II}-boron complex could be formed, which upon reaction with a water molecule could form a coordinated complex, liable to undergo β-hydride elimination furnishing the alkyl-Pd^{II}-H species. Using this system utilising diboron/H_2O as a hydride source, Kong and co-workers synthesised a series of enantioenriched oxindoles, **41a-v**, bearing a C-3 quaternary stereocentre in excellent yields (74-90%) with high enantioselectivities (e.r. 85:15 - e.r. 97:3).[39]

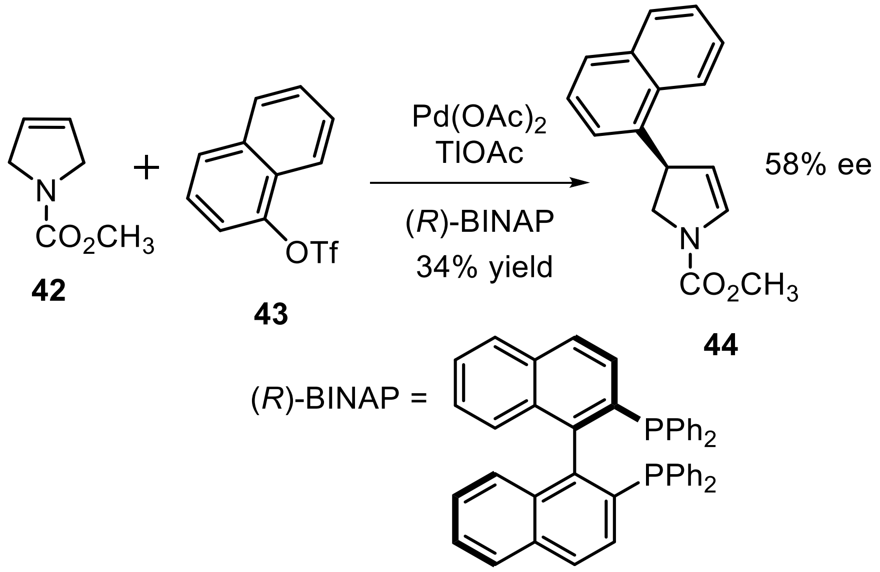


Scheme 9. Kong and co-workers reductive Heck system using $B_2(OH)_4$/H_2O as a hydride source.[39]

As this project will involve exploring and optimising the use of an effective hydride source for our own reductive Heck system, it is important to use this previous research to aid our decisions on which hydride sources to include. Of particular interest are hydride sources that are effective in similar systems and especially selective in their role as a reductant.

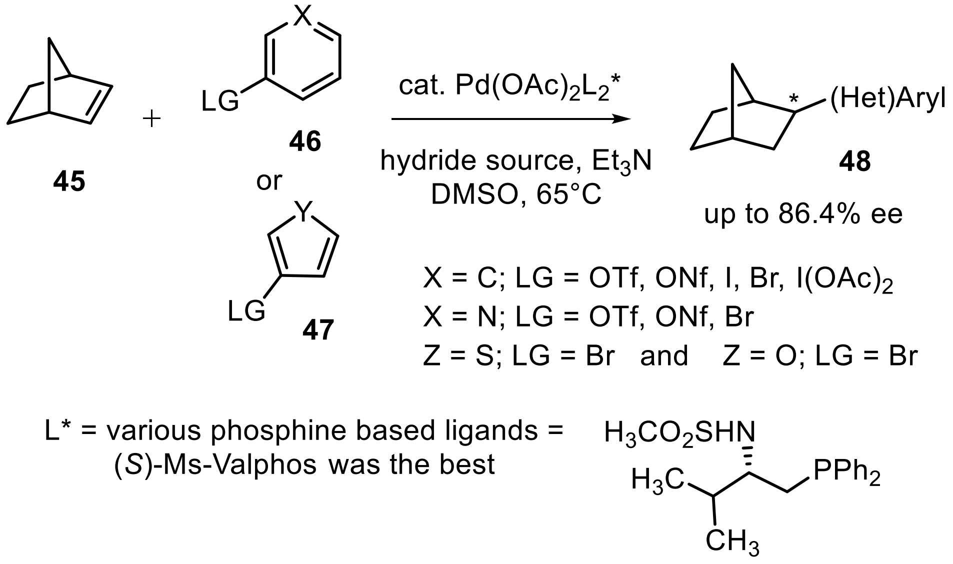
5.2 Asymmetric Reductive Heck potential

The first examples of intramolecular asymmetric MH reactions were developed in 1989 by Shibasaki[40] and Overman[41], whilst the first intermolecular Heck reactions were not reported upon until 1991 by Hayashi, who performed arylations on *N*-substitued-2,3-dihydropyrroles with aryl and alkenyl triflates, whilst achieving high enantiomeric excess.[21,42–44] This work encouraged Hallberg's 1996 attempts to study the potential asymmetric arylation of 1-(methoxycarbonyl)-2,5-dihydropyrrole (**42**) using 1-naphthyl triflate (**43**) as an arylating agent. Hallberg and co-workers performed the reactions using catalyst generated *in situ* from $Pd(OAc)_2$ and (*R*)-BINAP and upon addition of one equivalent of thallium acetate instead of acetic acid allowed the synthesis of isomerically pure C-3 arylated dihydropyrrole (**44**) in 58% ee and 34% isolated yield (Scheme 10). The arylated cyclic enamides had the potential for further regiocontrolled functionalisation or could undergo subsequent hydrogenation to yield 3-aryl pyrrolidines. Hallberg and co-workers attributed the poor yield to an inefficient insertion step and not to the oxidative addition, which was proven to be efficient by the large amounts of naphthalene formed. Unfortunately, adequate chiral induction was not achieved using phenyl or 2-napthyl triflate and, similar to previous work by Hayashi, 1-iodonaphthalene also proved ineffective to achieve enantiomeric excess.[21,44] Although these reported examples highlight asymmetric arylation using the MH reaction instead of the reductive Heck, they have relevance to this body of work as proven interception of the Pd-complex intermediate, mid reaction, with a hydride source could yield the asymmetrically hydroarylated product. These studies are the foundation for the early attempts to achieve enantioselectivity in both synthetic Heck techniques.



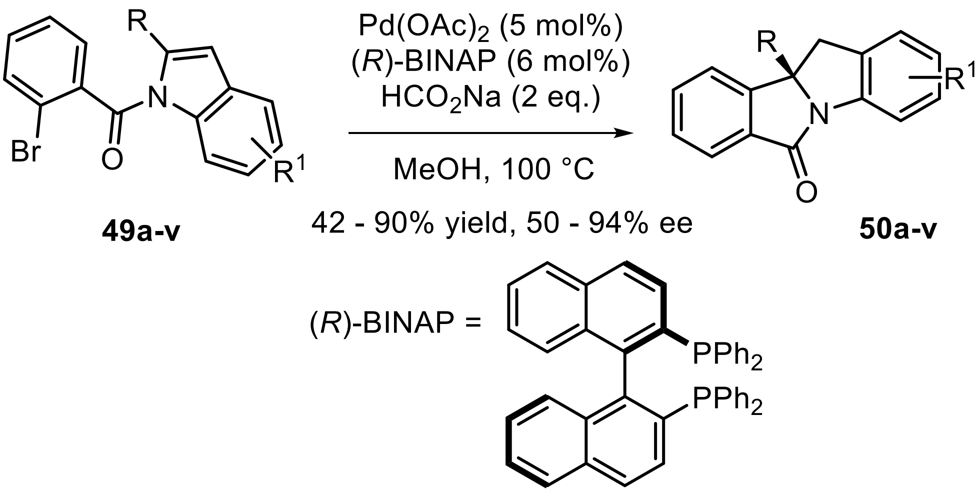
Scheme 10. Asymmetric Heck reaction of 1-(methoxycarbonyl)-2,5-dihydropyrrole (**42**) with 1-naphthyl triflate (**43**).[21]

Studies have since progressed into asymmetric reductive Heck techniques, which are much more relevant to this project. To achieve this many research groups have taken advantage of strained alkenes such as norbornene substrates where they have utilised the diasterospecificity of migratory insertion and β-hydride elimination of norbornene.[32,45,46] Major investigations were carried out by Kaufmann and co-workers in 1997 using a range of phosphane based ligands to obtain (het)aryl norbornanes in an enantioselective manner from the hydroarylation of norbornene using a range of hydride sources, including formic acid, potassium formate, PMHS and THF (Scheme 11). Asymmetric inductions of up to 86.4% ee were achieved and the most interesting enantiomeric yield improvement (42.6% to 82.4%) was achieved changing the leaving group from iodide to triflate. The best enantioselectivities were achieved using sulfonates (pseudo halides) and therefore acting as the leaving group during the starting material oxidative addition to the palladium. Interestingly, the highest chemical yield obtained was with phenyliodium diacetate, however, yields were usually in the range 30-60%, with complete consumption of the starting material. This was attributed to protodehalogenation of aryl halides, as discussed previously, and Kaufmann *et* al. decided that to overcome this problem they would require a more selective hydride source than formic acid or potassium formate.[21,32]



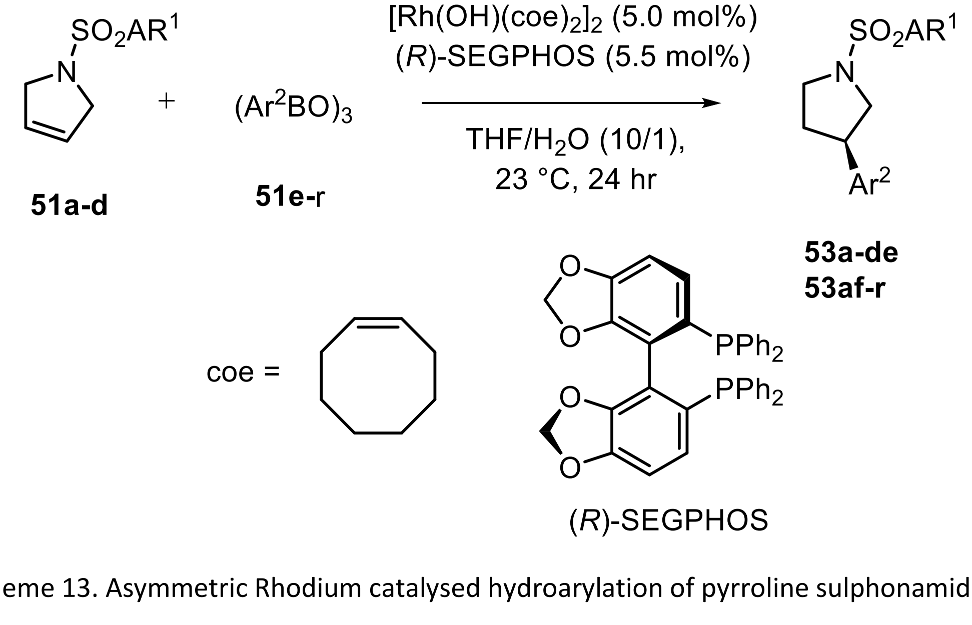
Scheme 11. Pd-catalysed enantioselective hydro(het)arylation of norbornene using chiral ligands.[32]

A large majority of research completed on the reductive Heck reaction has been taking advantage of tethered alkenes to access highly functionalised heterocyclic motifs, which are of particular interest in the pharmaceutical industry, especially when performed enantioselectively if paired with chiral ligands. Since the first asymmetric reductive Heck coupling of a tethered alkene in 1998[47], other notable asymmetric intramolecular examples have been developed to produce chiral substituted hetercycles.[38,48] Notably Buchwald and co-workers in 2007 to asymmetrically synthesise 3-substituted indanones (**50a-v**) with generally good yields (42- 90%) and moderate to excellent enantioselectivity (50-94% ee) using a chiral ligand and HCO_2Na as the hydride source (Scheme 12).[38] Overall, throughout asymmetric reductive Heck literature, pseudo halides substrates consistently provide better enantioselectivity than arylhalides.[21,32,38,42–44] Generally, it is the case that triflate, and other pseudo halides, is a noncoordinating anion and as a result does not compete with the chiral ligand for coordination to the palladium[49] therefore, one would expect this is why pseudo halides provide improved enantioselectivity .



Scheme 12. Optimised reaction conditions for Buchwald and co-workers' asymmetric reductive Heck reaction.

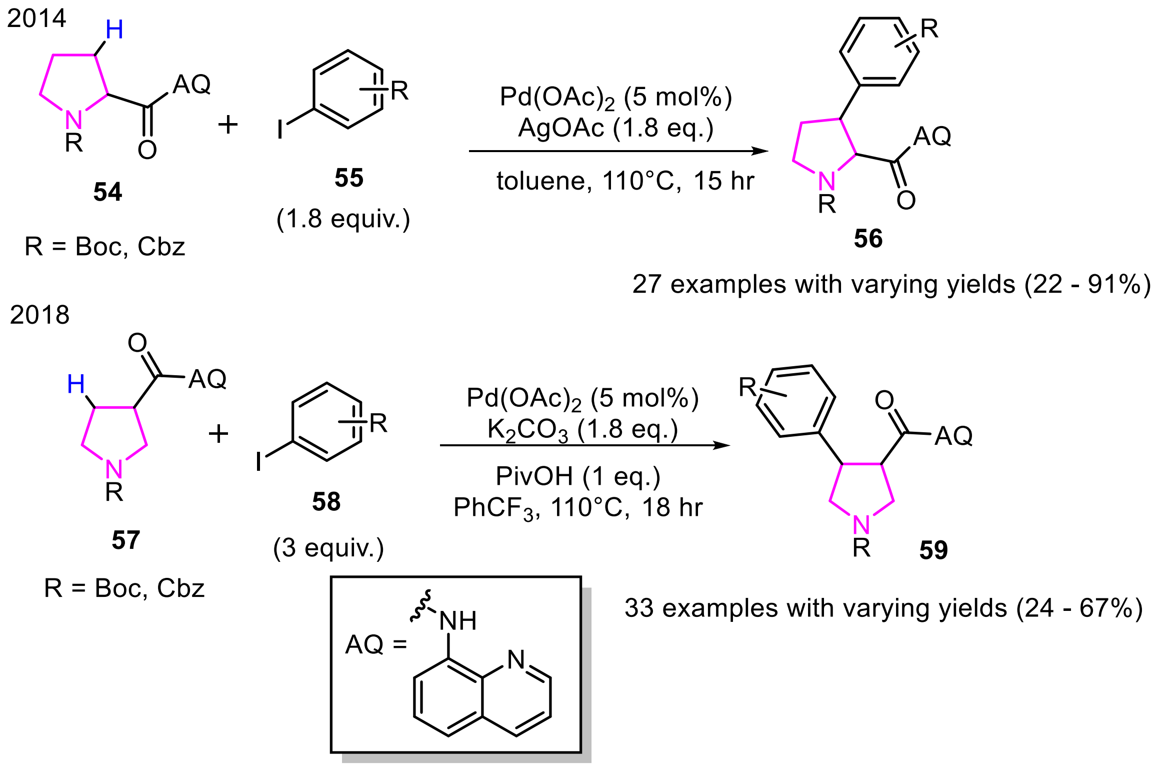
Ultimately, only one asymmetric 'reductive Heck' technique has been published to synthesise to enantioselective 3-substituted pyrrolidines, which uses a Rhodium/(*R*)-SEGPHOS ligand system to produce 18 different 3-aryl pyrrolidines in high ee (89 – 96%) and excellent yields (80 – 99%) from **51a-d** (Scheme 13).[50] Therefore, in order to attempt to develop a novel reaction with the potential for similar enantioselectivity, the discussed papers must provide key inspiration and a starting point to optimise a set of conditions.



Scheme 13. Asymmetric Rhodium catalysed hydroarylation of pyrroline sulphonamides.[50]

6. Directed Arylation

Alternatively, recent work in 3-substituted pyrrolidine synthesis via a similar synthetic approach has been achieved by Affron and co-workers. As part of a programme of fragment orientated synthesis, iterative functionalisation of C-3 position on pyrrolidine rings has been achieved via directed C(sp^3)-H arylation. Since 2014, Affron and co-workers have been developing transition metal catalysed C-H arylation using the 8-aminoquinoline (AQ) directing group (DG) to locate the transition metal species and stabilise any intermediates.[51] The amide linked DG makes arylation possible but importantly allows removal of the DG post arylation.[4,51] Affron and co-workers have optimised reaction conditions for a broad scope of aryl iodides for both C-4 and C-3 arylation using a C-3 and C-2 linked AQ DGs respectively (Scheme 14). Both palladium catalysed reactions required a base and or pivalic acid to improve selectivity. Yields achieved varied as the scope of the aryl iodides was so large.[4,52]



Scheme 14. Palladium catalysed C-H arylation using the 8-aminoquinoline (AQ) directing group.[4,51,22]

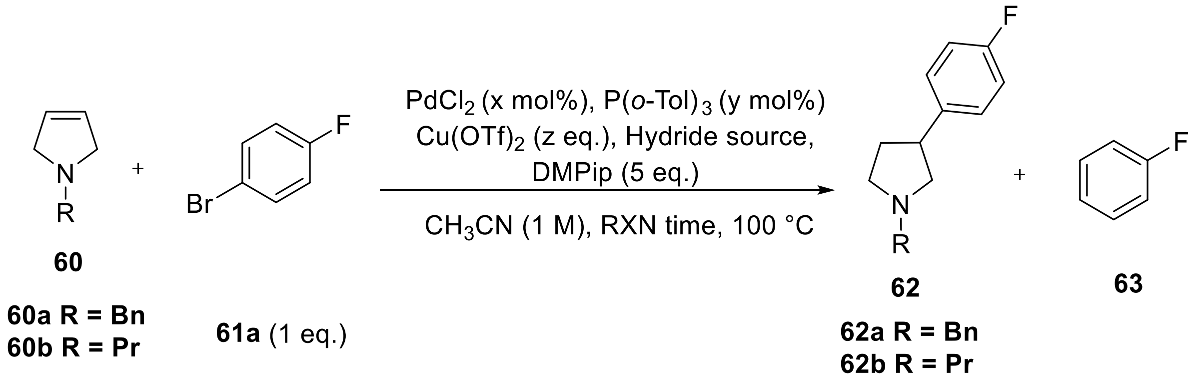
7. Results and Discussion

7.1 Reductive Heck

Following the Sweeney group's success adapting their MH to a reductive Heck system, they were able to create a set of optimised conditions to produce a range of 3-arylated N-propyl pyrrolidines and importantly this method was shown to be applicable to N-benzyl pyrrolines.[27] Work continued in the group to optimise conditions for this system using N-benzyl pyrroline following the publication (Table 1). Unfortunately, under the same conditions used on N-Propyl pyrroline, only 31% yield was obtained with poor conversion and 49% starting material still present (Table 1, entry 1). Increasing the amount of pyrroline to 6 equivalents was proposed to improve the yield (Table 1, entry 3), however, although the product **57** was obtained in a higher 60% yield, there was still 22% unreacted aryl bromide. Based on the effect of the copper additive on the rate of reaction observed in their previous work, the Sweeney group proposed modifying the amount of $Cu(OTf)_2$ used. Using 2 equivalents allowed the reaction to go to completion and with 3 equivalents of N-benzyl pyrroline, the product was obtained in 72% yield (Table 1, entry 6). Using these optimised conditions, compound **59** was isolated in 64% yield, which compares well to the previous work, as the product was isolated in 69% yield using N-propyl analogues.[27]

As discussed, this work used large excess of the N-propyl/N-benzyl pyrroline starting materials to act as a sacrificial hydride source. The Sweeney group then proposed that the use of an external hydride source, as previously mentioned, should allow for the reduction of excess 3-pyrroline and could provide significant improvement of the reaction. Upon screening a select number of known reductive Heck hydride sources (Table 1, entries 7-10), it was determined that the most successful hydride source was the Hantzsch ester (Table 1, entry 10), however, as full conversion of the 4-Fluoro bromobenzene was never achieved, further optimisations were required. As a result of the findings in this unpublished work, the first goal for this project was therefore, to further optimise the reductive Heck system established by the Sweeney group, for N-benzyl pyrroline and adapt the previous conditions to include the Hantzsch ester hydride source as a crucial component.

Table 1. Previous work carried out by the Sweeney group to optimise their reductive Heck system for N-benzyl pyrrolines and to test a select range of hydride sources.



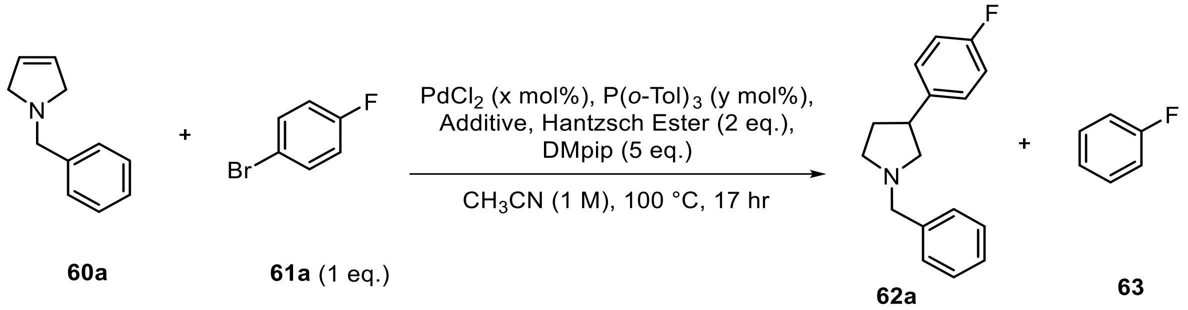
Entry	**60a** (eq.)	**60b** (eq.)	PdCl$_2$ (mol %)	P(o-Tol)$_3$ (mol%)	RXN Time (hr)	Additive	Hydride Source	**62a/b** yield (%)*	**61a** yield (%)*	**63** yield (%)*
1	3	-	4	6	17	Cu(OTf)$_2$ 1 eq.	-	31	49	10
2	3	-	4	6	40	Cu(OTf)$_2$ 1 eq.	-	31	48	10
3	6	-	4	6	17	Cu(OTf)$_2$ 1 eq.	-	60	22	2
4	6	-	4	6	40	Cu(OTf)$_2$ 1 eq.	-	60	19	3
5	6	-	4	6	17	Cu(OTf)$_2$ 2 eq	-	76	0	5
6	**3**	**-**	**4**	**6**	**17**	**Cu(OTf)$_2$ 2 eq.**	**-**	**72**	**3**	**3**
7	-	1	5	7.5	17	Cu(OTf)$_2$ 1 eq.	HCO$_2$Na 2 eq.	47	26	10
8	-	1	5	7.5	17	Cu(OTf)$_2$ 1 eq.	HCO$_2$H 2 eq.	0	63	20
9	-	1	5	7.5	17	Cu(OTf)$_2$ 1 eq.	HCO$_2$NH$_4$ 2 eq.	0	73	26
10	**-**	**1**	**5**	**7.5**	**17**	**Cu(OTf)$_2$ 1 eq.**	**Hantzsch ester 2 eq.**	**63**	**13**	**4**

*yields determined by ^{19}F NMR

7.1.1 Optimisation of reaction

During the optimisation of this reaction the yields were determined, in the same way as the previous Sweeney group work[27], following reactions performed on a 1 mmol scale using ^{19}F NMR (by taking the integration of all signals, then calculating the yield based on the ratio of integration of product/overall integration or using 1,3-difluorobenzene as an internal standard. Both showed similar results.). The first round of background reactions performed confirmed the requirement of all components in the system (Table 2, entries 1-8) and established the standard starting reaction conditions (Table 2, entry 1). This first round of background reactions confirmed the necessity of PdCl$_2$, Cu(OTf)$_2$ (Cu additive) and DMpip (base) to the success of the reaction as without them no product was obtained (Table 2, entries 3, 5 and 8). Similarly, crucial to the efficiency of the reaction is the phosphine ligand (P(*o*-Tol)$_3$) where the yield dropped from 85% yield (Table 2, entry 1) to 6% yield without its presence. Entries 6 and 7 show how important Hantzsch ester as a hydride source is to the efficiency of this reductive Heck system. With no Hantzsch ester and 1.2 equivalents of N-benzyl pyrroline (**60a**) (Table 2, entry 6) only 21% yield could be obtained, whereas when 3 equivalents of **60a** was used, the increased yield (53%) (Table 2, entry 7) confirmed the ability of N-benzyl pyrroline to act as a hydride source. As shown in entry 2, increased palladium did not improve the reaction. The amount of Cu(OTf)$_2$ used in the reaction was studied (entries 9 & 10) showing that 1 equivalent of copper additive was sufficient to achieve full conversion and obtain 82% yield (Table 2, entry 10). This was an interesting observation as previously 2 equivalents of Cu(OTf)$_2$ were required to obtain sufficient yield/conversion when no Hantzsch ester was used in the reaction (Table 1, entry 6)[27]. Therefore, use of Hantzsch ester somehow allows the amount of copper additive to be reduced. The poor yield, 19%, obtained when using Zn(OTf)$_2$ (Table 2, entry 11), as a result of high protodehalogenation and confirmed that the Sweeney group's transition from Zn(OTf)$_2$[25] to Cu(OTf)$_2$[27] was essential to maximise yields in this reductive Heck system.

Table 2. First round of optimisations: background reactions and Cu additive reductions.



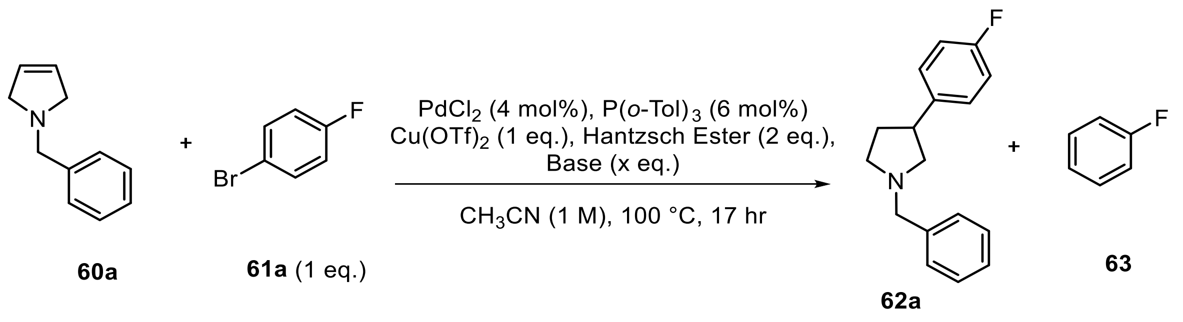
Entry	**60a** (eq.)	PdCl$_2$ (mol%)	P(*o*-Tol)$_3$ (mol%)	Additive	Hydride source	Base	**62a** yield (%)*	**61a** yield (%)*	**63** yield (%)*
1	1.2	4	6	Cu(OTf)$_2$ 2 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	85	2	3
2	1.2	6	9	Cu(OTf)$_2$ 2 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	79	3	3
3	1.2	-	6	Cu(OTf)$_2$ 2 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	-	95	-
4	1.2	4	-	Cu(OTf)$_2$ 2 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	6	76	10
5	1.2	4	6	-	Hantzsch Ester 2 eq.	DMPip 5 eq.	-	3	40

6	1.2	4	6	Cu(OTf)₂ 2 eq.	-	DMPip 5 eq.	21	44	2
7	3	4	6	Cu(OTf)₂ 2 eq.	-	DMPip 5 eq.	53	18	6
8	1.2	4	6	Cu(OTf)₂ 2 eq.	Hantzsch Ester 2 eq.	-	-	80	-
9	1.2	4	6	Cu(OTf)₂ 1.5 eq	Hantzsch Ester 2 eq.	DMPip 5 eq	80	-	2
10	**1.2**	**4**	**6**	**Cu(OTf)₂ 1 eq.**	**Hantzsch Ester 2 eq.**	**DMPip 5 eq.**	**82**	**-**	**3**
11	1.2	4	6	Zn(OTf)₂ 2 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	17	-	49

*yields determined by ^{19}F NMR

For the second round of optimisation (Table 3), the equivalents of DMpip (base) were lowered (Table 3, entries 12-15). Gratifyingly, lowering the amount of DMpip to 1 equivalent (Table 3, entry 15), had no negative impact on the yield of the reaction, even with only 1 equivalent of $Cu(OTf)_2$. The Sweeney group had previously established that DMpip was the optimal base for both MH and reductive Heck systems using cyclic allylamine olefins.[25,27] However, as discussed previously, tertiary amines are established bases that can also, in some reductive Heck systems, perform as hydride sources.[35,36,38] Based on this logic, triethylamine and Hünigs base (DIPEA) were tested as alternative bases in our reductive Heck system (Table 3, entries 16 and 17). Unfortunately, both of the alternative bases (Table 3, entries 16 and 17) significantly reduced the yield of the reaction, with poor conversion leaving 60 - 70% **61a** starting material even after 17 hours.

Table 3. Second round of optimisations: bases.



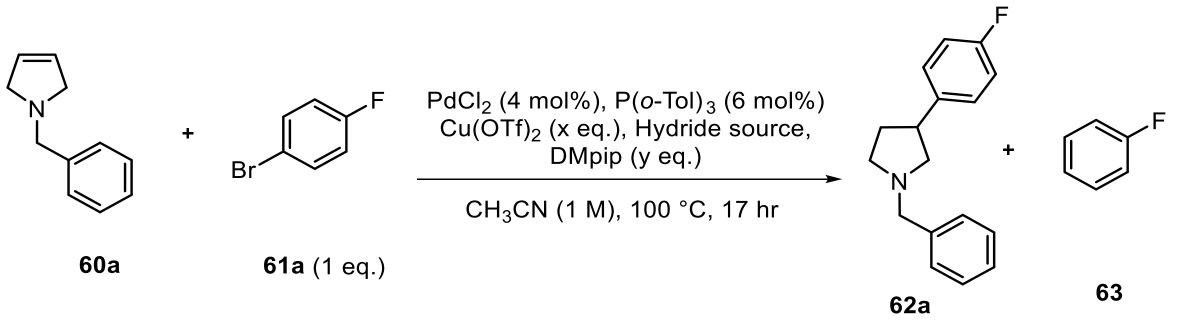
Entry	**60a** (eq.)	$PdCl_2$ (mol%)	P(*o*-Tol)₃ (mol%)	Additive	Hydride source	Base	**62a** yield (%)*	**61a** yield (%)*	**63** yield (%)*
10 *(Previous relevant entry for comparison)*	1.2	4	6	Cu(OTf)₂ 1 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	82	-	3
12	1.2	4	4	Cu(OTf)₂ 1 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	81	-	2

13	1.2	4	8	Cu(OTf)$_2$ 1 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	74	2	2
14	1.2	4	6	Cu(OTf)$_2$ 1 eq.	Hantzsch Ester 2 eq.	DMPip 3 eq.	79	-	3
15	**1.2**	**4**	**6**	**Cu(OTf)$_2$ 1 eq.**	**Hantzsch Ester 2 eq.**	**DMPip 1 eq.**	**84**	**-**	**4**
16	1.2	4	6	Cu(OTf)$_2$ 1 eq.	Hantzsch Ester 2 eq.	Et$_3$N 1 eq.	19	67	2
17	1.2	4	6	Cu(OTf)$_2$ 1 eq.	Hantzsch Ester 2 eq.	Hünigs base 1 eq.	17	62	3

*yields determined by ^{19}F NMR

For the third round of optimisations, we turned our attention to the hydride source. The amount of Hantzsch ester used in the reaction was studied first (compare Table 2, entry 1 to Table 4, entries 18 and 19), showing that excess Hantzsch ester was crucial to maximising our yields, even with 2 equivalents of Cu(OTf)$_2$. Previous work exploring alternative hydride sources had already been performed with N-propyl pyrroline, however, as shown by results presented in table 1, 2 and 3 the N-benzyl pyrroline series, behaves somewhat differently. As a result, it was decided to test some alternative hydride sources (Table 4, entries 20-23) informed by previous work in the group and the literature discussed. Sodium formate (Table 4, entry 22) performed similarly as in the N-propyl series giving 43% yield after 17 hours whilst using ammonium formate (Table 4, entry 21) afforded products **62a** in only 22% yield. Inspired by Kaufmann and coworkers proposal that PMHS could be a more selective hydride source than formates[32], PMHS was used in our system but **62a** was obtained in only 13% yield and of all hydride sources tested (Table 4, entries 20-23), PMHS gave the highest amount of **63** obtained 9%. Kaufmann and coworkers proposed that a 'selective' hydride source would lead to lower amounts of protodehalogenation as it would be selectively acting as a hydride source to form the reductive Heck product. As shown by the amount of **63** (protodehalogenation product) produced, this shows Kaufmann and coworkers proposed use of PMHS was proven to be not as selective as Hantzsch ester in our system. Ultimately the most successful hydride source was still the Hantzsch ester (Table 4, entry 15).

Table 4. Third round of optimisations: hydride sources.



Entry	**60a** (eq.)	$PdCl_2$ (mol%)	P(*o*-Tol)$_3$ (mol%)	Additive	Hydride source	Base	**62a** yield (%)*	**61a** yield (%)*	**63** yield (%)*
1 (Previous relevant entry for comparison)	1.2	4	6	$Cu(OTf)_2$ 2 eq.	Hantzsch Ester 2 eq.	DMPip 5 eq.	85	2	3
18	1.2	4	6	$Cu(OTf)_2$ 2 eq.	Hantzsch Ester 1 eq.	DMPip 5 eq.	35	20	3
19	1.2	4	6	$Cu(OTf)_2$ 2 eq.	Hantzsch Ester 1.5 eq.	DMPip 5 eq.	52	22	4
15 (Previous relevant entry for comparison)	1.2	4	6	$Cu(OTf)_2$ 1 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	84	-	4
20	1.2	4	6	$Cu(OTf)_2$ 1 eq.	$PhSiH_3$ 2eq.	DMPip 1 eq.	-	100	-
21	1.2	4	6	$Cu(OTf)_2$ 1 eq.	HCO_2NH_4 2eq.	DMPip 1 eq.	22	65	2
22	1.2	4	6	$Cu(OTf)_2$ 1 eq.	HCO_2Na 2eq.	DMPip 1 eq.	43	39	4
23	1.2	4	6	$Cu(OTf)_2$ 1 eq.	PMHS 2eq.	DMPip 1 eq.	13	78	9

*yields determined by ^{19}F NMR

Due to the commercial expense of $Cu(OTf)_2$ and the increased effectiveness of using excess Hantzsch ester allowing for $Cu(OTf)_2$ to be reduced, the fourth round of optimisations entailed reducing the copper additive equivalents further (Table 5, entries 24-29). As a result, we were extremely gratified to find that the reaction was marginally improved when only 0.5 equivalents of $Cu(OTf)_2$ was used and **62a** was obtained in 88% yield with full conversion and the lowest protodehalogenation observed of all entries so far (Table 5, entry 24). Following this finding, we thought it would also be valuable to explore some alternative copper additives and evaluate the effect of different counterions on our reductive Heck system (entries 30-35). $CuCl_2$ and $CuSO_4$ (entries 31 & 35) both produced **62a**, with complete conversion and in good yields of 80 and 68% respectively. Other $Cu^{(II)}$ additives (Table 5, entries 32-34) proceeded with moderate success and conversion, obtaining the product in 50-65% yield whilst CuI, the $Cu^{(I)}$ additive, only managed to produce 20% of the desired product **62a**, with a very poor conversion leaving 74% of the starting material **61a** after 17 hours. Although all the of the alternative additives successfully yielded the desired product, none were as effective as 0.5 equivalents of $Cu(OTf)_2$.

An interesting observation was made whilst testing the alternative copper additives to $Cu(OTf)_2$ (entries 31-35), as for all of the alternatives, except CuI, diarylated product **64** (Figure 5)) was formed in small amounts (2-8% yield) which unfortunately was not isolated in pure form. This novel diarylated compound had been detected in previous work from the Sweeney group, but had not been present in the reductive Heck system since introducing Hantzsch ester as the hydride source. It would be interesting and extremely valuable if the reaction could perhaps be optimised differently to give only the diarylation product. One alternative copper additive that could have been explored is $Cu(NTf_2)_2$ however, due to its commercial expense and availability it was not used for this project.

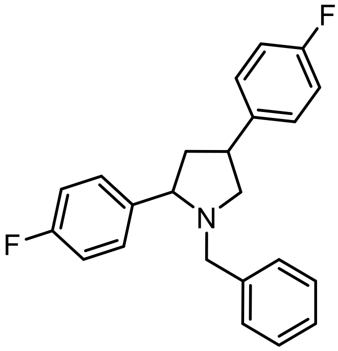


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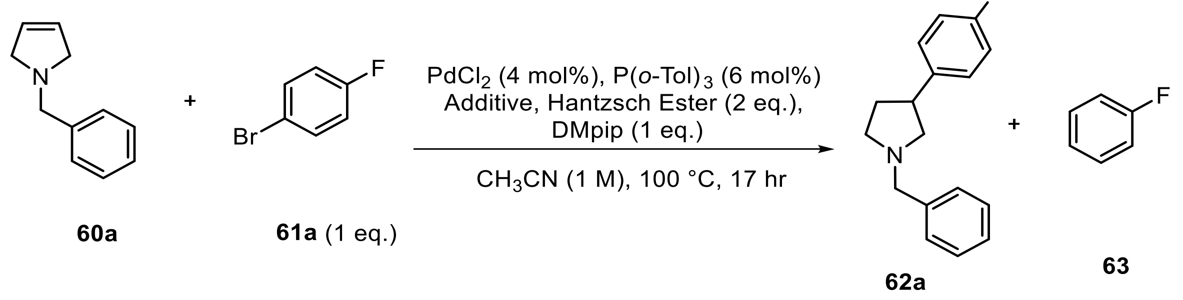
Figure 5. Novel diarylated compound, which unfortunately was not able to be isolated from this reductive Heck system whilst exploring alternative copper additives.

Table 5. Fourth round of optimisations: Cu additives.



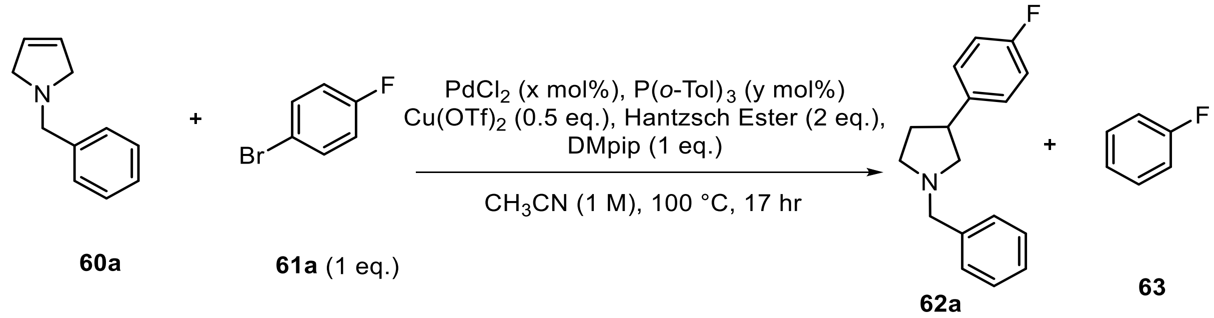
Entry	**60a** (eq.)	$PdCl_2$ (mol%)	P(*o*-Tol)$_3$ (mol%)	Additive	Hydride source	Base	**62a** yield (%)*	**61a** yield (%)*	**63** yield (%)*
15 *(Previous relevant entry for comparison)*	1.2	4	6	$Cu(OTf)_2$ 1 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	84	-	4
24	**1.2**	**4**	**6**	**$Cu(OTf)_2$ 0.5 eq.**	**Hantzsch Ester 2 eq.**	**DMPip 1 eq.**	**88**	**-**	**2**
25	1.2	4	6	$Cu(OTf)_2$ 0.4 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	77	1	1
26	1.2	4	6	$Cu(OTf)_2$ 0.3 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	71	-	1
27	1.2	4	6	$Cu(OTf)_2$ 0.2 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	71	10	1
28	1.2	4	6	$Cu(OTf)_2$ 0.1 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	64	5	1
29	1.2	10	15	$Cu(OTf)_2$ 0.1 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	69	-	2
30	1.2	4	6	CuI 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	20	74	-
*31***	1.2	4	6	$CuCl_2$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	80	-	1
*32***	1.2	4	6	$Cu(OAc)_2$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	63	6	1
*33***	1.2	4	6	$Cu(acac)_2$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	65	-	1
*34***	1.2	4	6	$CuCO_3$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	50	17	15
*35***	1.2	4	6	$CuSO_4$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	68	-	4

*yields determined by ^{19}F NMR

**Low amounts of diarylation products observed.

The fifth and final round of optimisations were performed to study the catalyst loading (Table 6, entries 36-38). To our delight the study showed that palladium could be reduced to 1 mol% with no negative impact on the efficiency of the reaction. In fact, the reaction showed a slight increase in obtained yield from 88 to 93% yield when the catalyst loading was lowered from 4 to 1 mol% (Table 6, entry 38). This observation reflects the success of this reductive Heck system, as the new optimised conditions provides **62a** in excellent yield, while reducing the waste generated (low Pd loading and sub stoichiometric amounts of Cu additive) and making the reaction more economically viable, which is highly desirable for potential industrial applications. Overall, the current best optimised conditions for this reductive Heck system are found in entry 38 and were then progressed into the next stages of the project for the screening of aryl bromides.

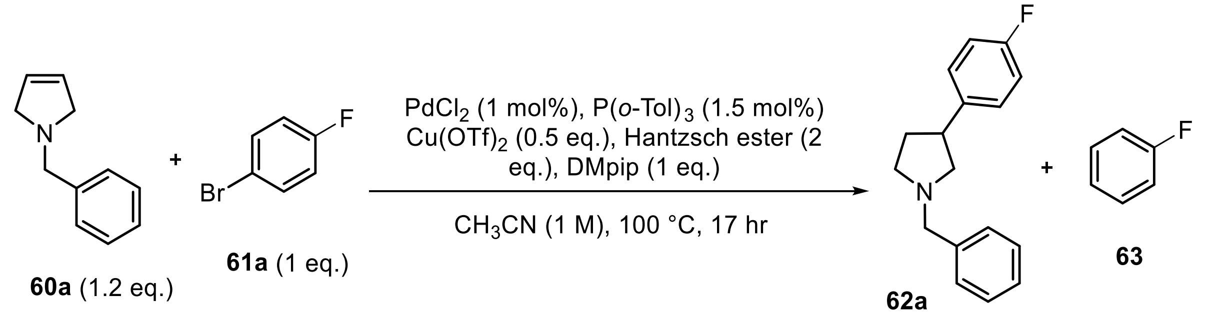
Table 6. Fifth round of optimisations: Pd catalyst loading.



Entry	**60a** (eq.)	PdCl$_2$ (mol%)	P(o-Tol)$_3$ (mol%)	Additive	Hydride source	Base	**62a** yield (%)	**61a** yield (%)	**63** yield (%)
24 *(Previous relevant entry for comparison)*	1.2	4	6	Cu(OTf)$_2$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	88	-	2
36	1.2	3	4.5	Cu(OTf)$_2$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	92	-	2
37	1.2	2	3	Cu(OTf)$_2$ 0.5 eq.	Hantzsch Ester 2 eq.	DMPip 1 eq.	91	-	2
38	**1.2**	**1**	**1.5**	**Cu(OTf)$_2$ 0.5 eq.**	**Hantzsch Ester 2 eq.**	**DMPip 1 eq.**	**93**	**4**	**1**

7.1.2 Reaction Monitoring

The reaction progress was monitored by using ^{19}F NMR (by taking the integration of all signals, then calculating the yield based on the ratio of integration of product/overall integration) to track a 2.5 mmol scale reaction of **60a** with **61a** under the newly optimised conditions. NMR samples were taken at 15 minutes, 30 minutes as well as 1, 2, 3, 5, 7 and 24 hours in order to see if the reaction, with its improved yield and efficiency, could reach its maximum yield in less than the 17 hours previously required with N-propyl analogues. Unfortunately, although the reaction does proceed much faster than shown in previous work, reaching 86% yield in 7 hours, the reaction then plateaus at 90% yield after 24 hours meaning that overnight (17 hours) are still optimal. As shown by the 10% starting material **61a** left after 24 hours, full conversion was not achieved in this reaction, however, this could be due the aliquots being taken throughout the reaction. One interesting observation can be made by following the unwanted by-product 4-fluorobenzene (**63**) formed by protodehalogenation. After 1 hour, **63** could be obtained in 2% yield and, as shown in Figure 6, this does not increase for the next 23 hours of the reaction. This indicates excellent selectivity for the Hantzsch ester to act as a hydride source in our reductive Heck system, where other hydride sources, with poor selectivity, lead to increased protodehalogenation.[32]



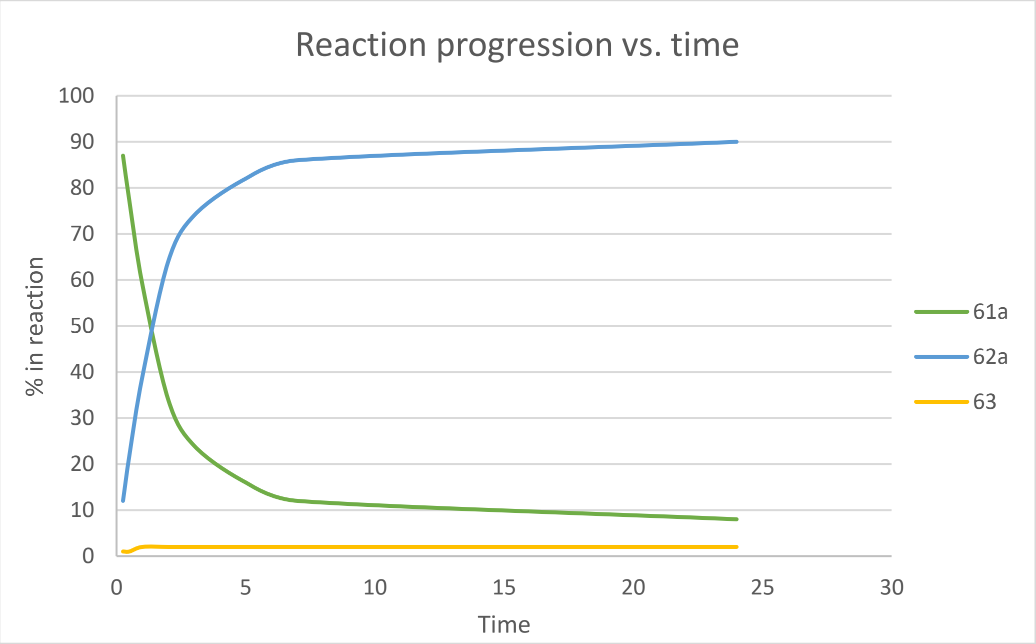


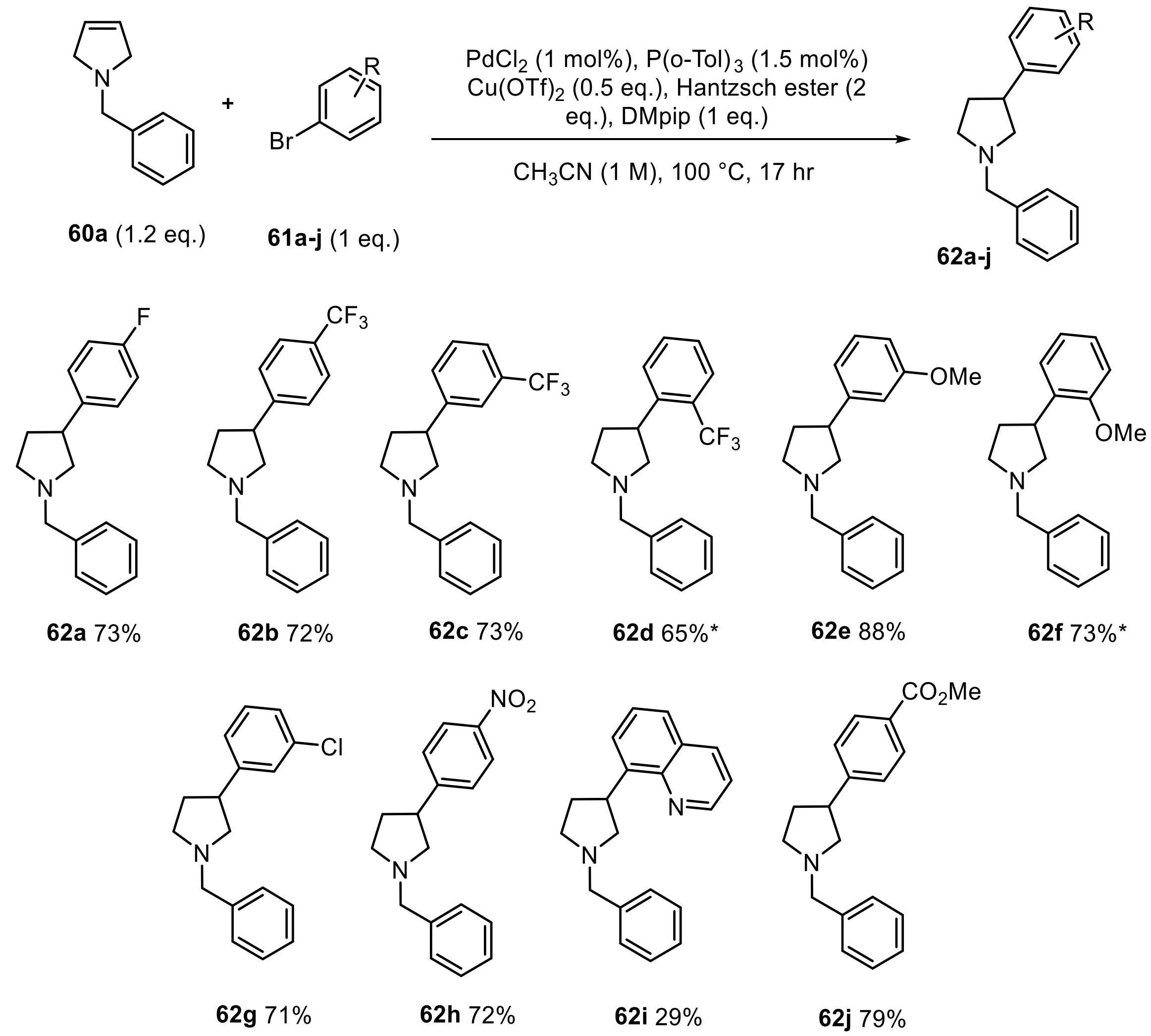
Figure 6. Reaction progression profile of the optimisation reductive Heck reaction between N-benzyl pyrroline and 4-Fluoro bromobenzene.

7.1.3 Synthesis of target compounds

The scope of the reaction was first assessed by exploring the electronic and steric effects of substituents on aryl bromide starting materials. For this ortho, meta and para bromobenzotrifluoride and ortho/meta bromoanisole were reacted with N-benzyl pyrroline (**60a**) using the optimised conditions (Scheme 15), with para bromoanisole still needing to be performed. Ortho-substituents and strong electronically donating groups were thought to have the worst yield as theoretically they would hinder/slow the oxidative addition. The synthesis of compounds (**62b-f**) showed that electronic effects had little influence on the reaction outcome whether the aryl bromide was substituted with either an electron withdrawing or donating group, obtaining good to excellent isolated yields (65-88%).

Although ortho methoxy and trifluoride **62d** and **f** could not be isolated in pure fashion, their estimated NMR yields (65 and 73% respectively) demonstrate the compatibility of sterically hindered ortho-substituted aryl-bromides, although as expected, these are slightly less successful than their meta and para-analogues. The small screening sample of chemical functionalities showed overall very good compatibility with ether, nitro, ester and halide functional groups **62a-h** and **j** (65 – 88% yield). Only the quinoline substituted product, **62i** was isolated in poor yield (29%), which would be expected to suffer from chelation of the quinoline nitrogen to the palladium catalyst, as well as steric hindrance. The highest yield was obtained with meta bromoanisole and the product **62e** was obtained in 88% isolated yield, however, there are no clear observational trends to explain this. It is important to note that isolated yields do not completely represent the outcome of the reaction, as purification was difficult and as a result, variation in yields might be caused by the purification rather than electronic effects. This is shown, by the optimised reaction yield 93% (Table 6, entry 38) where the expected isolated yield of **62a** should be higher than the 73% yield obtained. The challenging purification has led to lower isolated yields for **62a** and other target compounds in which both the Hantzsch by-products and pyrroline starting material were often difficult to separate from the desired product. These challenging purifications have been common throughout the N-Benzyl series but were not as prevalent in the N-propyl series.

To further probe the compatibility of this system other standard heteroaryl bromides will need to be investigated, such as 2-/3-bromo thiophene, furan, 4-bromopyridine and 3-bromo-1-methylindazole. Importantly yields overall were greatly improved in this system (using Hantzsch ester) over almost all reactions in the comparable N-propyl pyrroline system where no Hantzsch was used. One key comparative example is the synthesis of compound **62a**, which was obtained in both screenings and was previously only isolated in 54% yield using 2 equivalents of $Cu(OTf)_2$ with no hydride source[27], but was gratifyingly isolated in 73% yield using our current optimised conditions (Scheme 15).

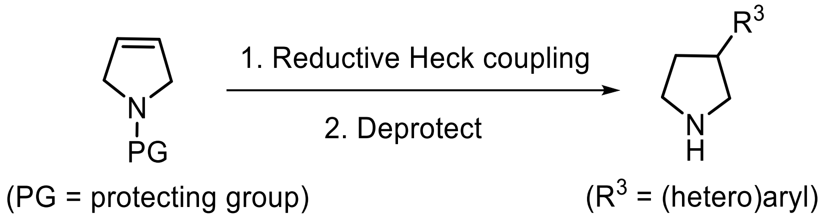


*yield estimated by NMR, pure compounds isolated following deprotection of Benzyl group

Scheme 15. Screening of (hetero)aryl bromides showing isolated yield after purification.

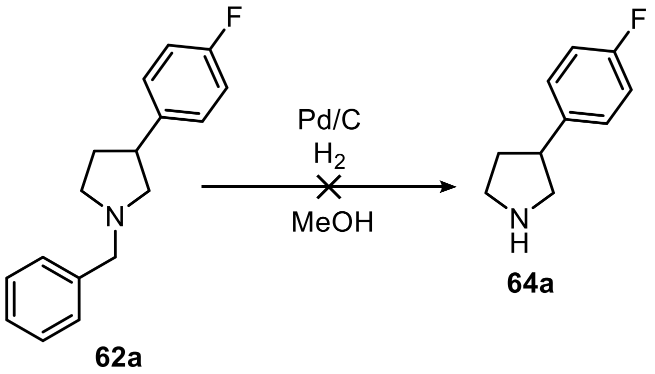
7.1.4 Removal of protecting group

The next step in the project was to develop a robust deprotection method to produce the N-H pyrrolidine analogues of our successful reductive Heck arylations (Scheme 16). Dealkylation of the propyl protecting group, although possible, as discussed is much harder to remove than a benzyl group, which can be removed by a hydrogenation. Other protecting groups such as para methoxybenzyl (PMB) and *t*-Butyl carbamate (Boc) were also considered with Boc and CO_2Me having already been extensively covered as a protecting group in Heck-Matsuda arylations by Correia *et* al.[53–55] Previous research in the Sweeney group had discounted Boc as a possible protecting group as the N-Boc pyrroline did not act as a hydride source under the original conditions. However, now that we are using an external hydride source, the reaction no longer necessarily requires electron rich amines (i.e. N-benzyl/N-propyl pyrroline) to provide the hydride, so it would be valuable to make the N-Boc pyrroline and test it in our system.



Scheme 16. Synthesis of target templates via 1. the reductive Heck coupling of N-benzyl pyrroline with (hetero)aryl bromides followed by 2. the deprotection of the benzyl group.

With this information taken into account and the availability/relative inexpensive nature of N-benzyl pyrroline, it was determined that we would optimise our system to produce 3-(hetero)aryl substituted N-benzyl pyrrolidines and then deprotect these via hydrogenation to yield the target compounds (Scheme 16). All hydrogenation reactions during our testing and optimised conditions were performed using a balloon to supply the hydrogen and therefore not carried out using a pressure hydrogenation system. Unfortunately, in our initial tests using general hydrogenation conditions, with 10 wt.% palladium on carbon at room temperature, debenzylation proved unsuccessful (Scheme 17). However, further literature delving revealed that Pearlman's catalyst ($Pd(OH)_2$ on carbon) could be successfully used for the selective N-debenzylation of pyrrolidines even in the presence of benzyl ethers.[56] A first pass application of these synthetic conditions to 3-(4-methoxyphenyl)-1-benzylpyrrolidine led to approximately 70% conversion to the desired deprotected pyrrolidine. It was therefore decided that increased catalyst loading (from approximately 1 mol% to 5 mol%) and heating to 50 °C should help encourage the debenzylation to occur more efficiently. As a result, we were extremely pleased to see that indeed, upon changing the conditions, full conversion was achieved and crude **64a** was obtained, as shown in Figure 6 by the loss of the benzyl -CH_2- peak at 3.70 ppm and 5 aromatic hydrogens from the aromatic region.



Scheme 17. Trial conditions for initial unsuccessful debenzylation attempt (H_2 was supplied by hydrogen balloon).

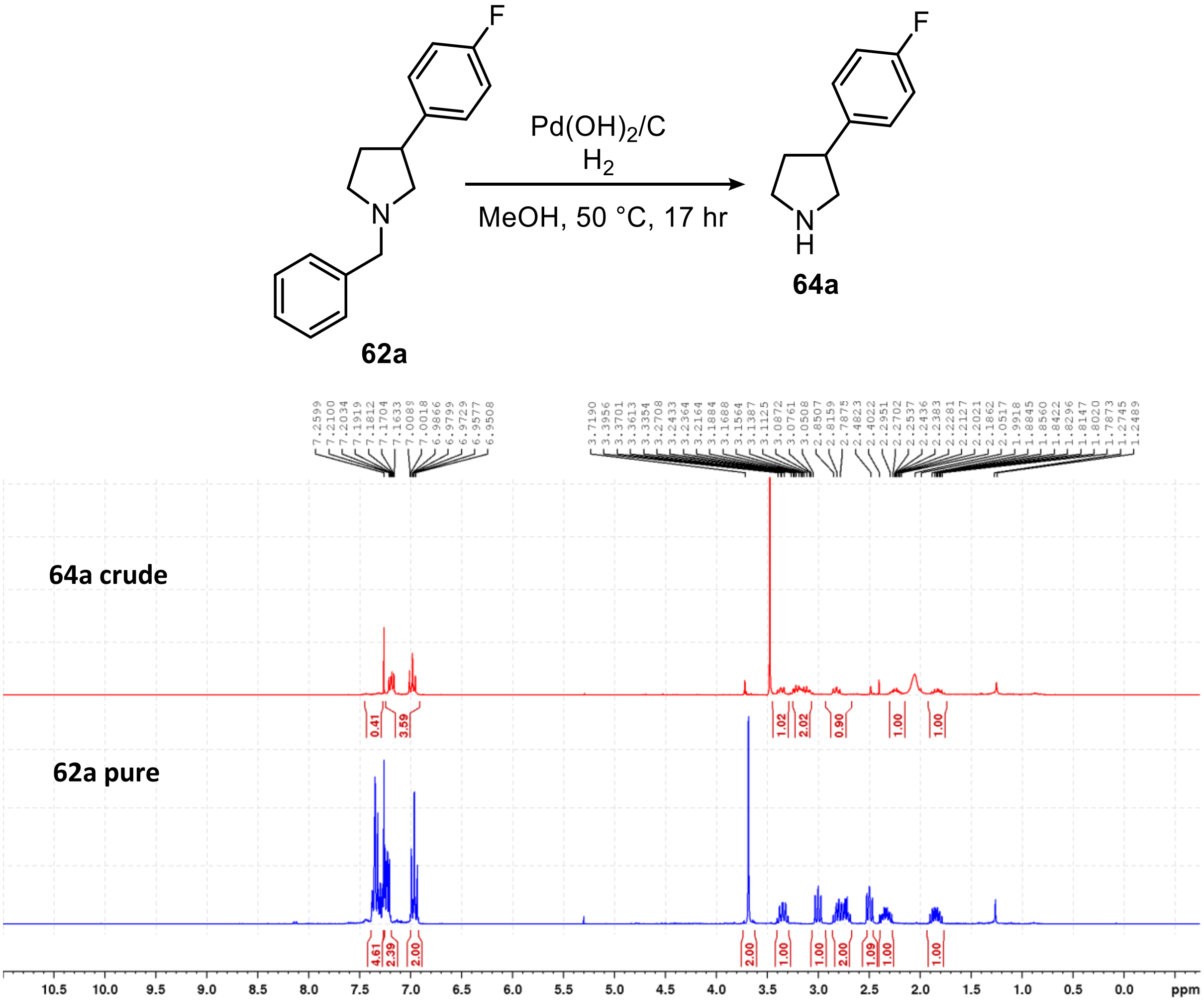
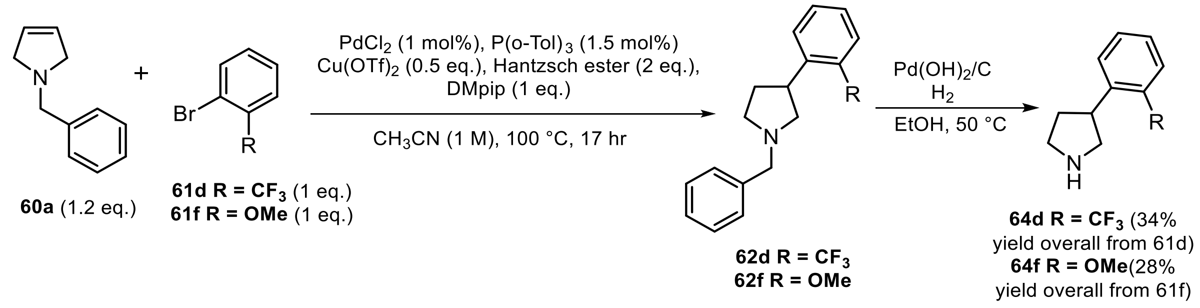


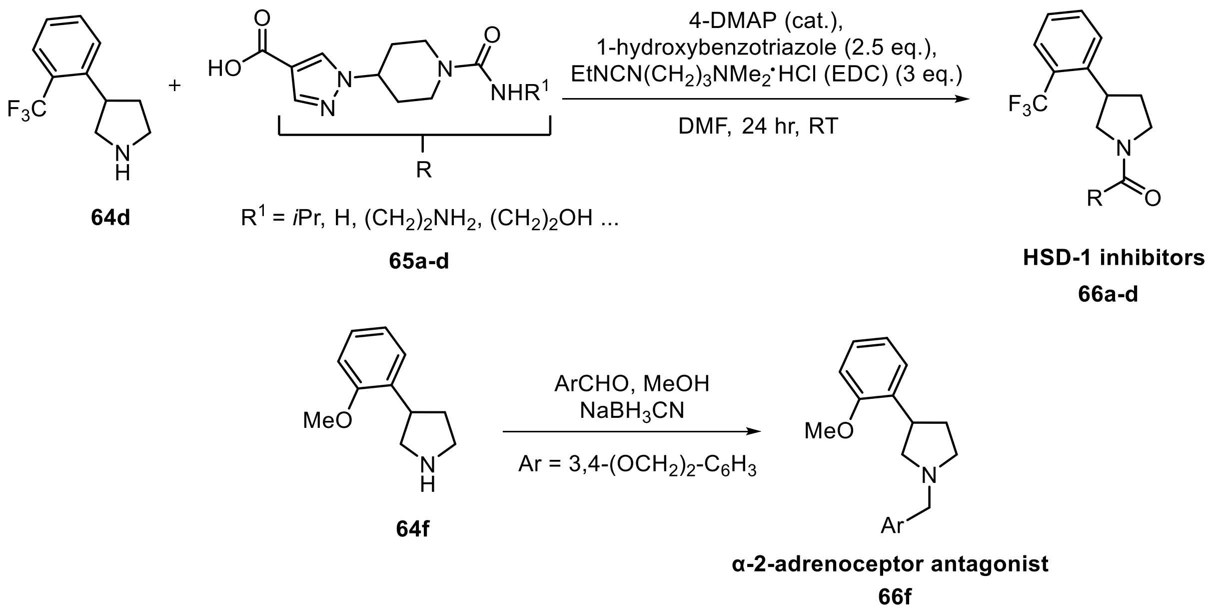
Figure 6. Successful debenzylation of pyrrolidine 62a to yield crude pyrrolidine 64a, with NMR comparison (H_2 was supplied by hydrogen balloon).

The ortho methoxy and trifluoride compounds **62d** and **62f** are valuable target compounds as shown by the biologically active α-2-adrenoceptor antagonist and HSD-1 inhibitors discussed previously (Figure 4).[13–16] Unfortunately, as mentioned in Scheme 15, isolation of their N-benzyl pyrrolidine analogues proved challenging, as the compounds coeluted with the N-benzyl pyrroline starting material despite varied column conditions tested. Thankfully, given our success in optimising a set of deprotecting conditions, we were able to debenzylate **62d/f** and purify the deprotected pyrrolidines **64d** and **64f** (Scheme 18). This allowed for the yield determination of the overall 2-step reaction based on the 2.5 mmol of aryl bromide starting material (Scheme 18). **64d** and **64f** were successfully isolated in 34 and 28% yield respectively. These yields are lower than expected, due to repeated column efforts, and given more time, repeating the reaction and performing the debenzylation on the crude, followed by column of the NH pyrrolidine compound, would most definitely give higher yields.



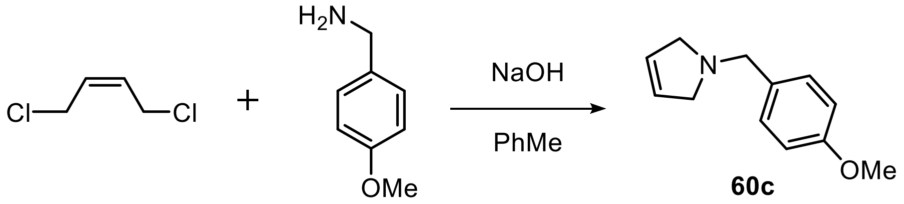
Scheme 18. Optimised conditions for the synthesis of deprotected pyrrolidines **64d** and **f** (H_2 was supplied by hydrogen balloon).

Incorporation of **64d** and **f** into established methods to synthesise these biologically active drug templates (Scheme 19) provides a plausible alternative synthetic route to produce both the α-2-adrenoceptor antagonist and a range of HSD-1 inhibitors using our reductive Heck system.[13,57] **66f** could also be synthesised from the pyrroline bearing the appropriate benzyl group without the need for deprotection or functionalisation. The α-adrenoceptor antagonist **66f**, developed by Novartis in 2006[15], was synthesised as a racemic mixture and without a specified enantiomer given for the drug. However as enantiopure compounds have since been synthesised[13,14], work to make our reaction asymmetric, or to separate the two enantiomers is a target for future study. Similarly, the HSD-1 inhibitors **66a-d** were all synthesised in their (*S*)-enantiomeric conformations, which further increases our desire to develop an asymmetric reductive Heck system in the future.

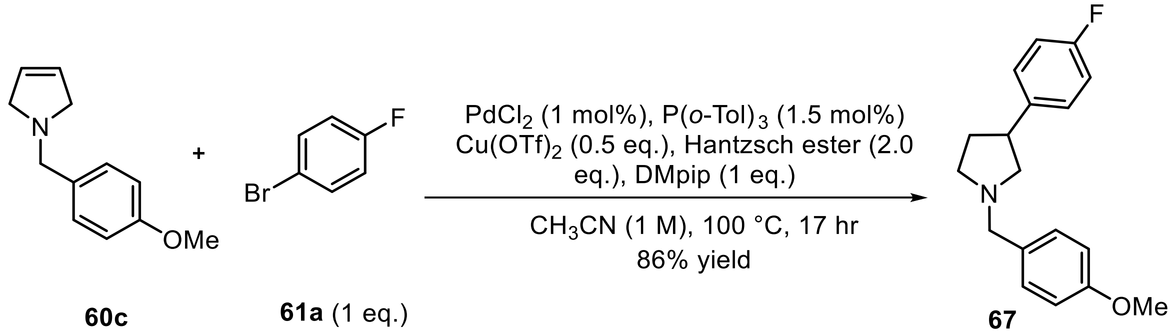


Scheme 19. Synthetic routes to produce the biologically active α-2-adrenoceptor antagonist and HSD-1 inhibitors using from **64d** and **f**.[13,57]

Alternatively, as discussed, the para methoxybenzyl (PMB) protecting group is also an extremely interesting option as it would be more labile than the regular benzyl protecting group, resulting in hypothetically easier hydrogenation. We were therefore extremely gratified when the N-PMB pyrroline **60c** (synthesis shown in Scheme 20)[58] underwent successful reductive Heck arylation using **61a** (4-Fluoro bromobenzene), under our optimised conditions, the product **67** was obtained in an excellent 86% yield (Scheme 21) (yield determined by ^{19}F NMR in the same was as in the optimisations section). It should be noted that the product **67**, similar to the N-Benzyl series, was very challenging to purify. As shown in Figure 7, after column chromatography only, 20% yield could be obtained as pure compound, with the other 66% yield expected coeluting with the Hantzsch ester by-products. Usually, if this was the case, compounds in the N-benzyl series underwent a second column and the combined isolated yield was quoted. However, as performing multiple columns has led to a loss in isolated yield (see **64d** and **f**), it would be better to perform the hydrogenation on the 'crude' **67** (mixture of Hantzsch ester by-products and **67** (Figure 7B)) followed by column purification of the NH pyrrolidine compound **62a**.



Scheme 20. Synthesis of N-PMB pyrroline (**60c**) following Takae and Haruyo.[58]



Scheme 21. Performing reductive Heck arylation on N-PMB pyrroline under optimised conditions (yield determined by ^{19}F NMR).

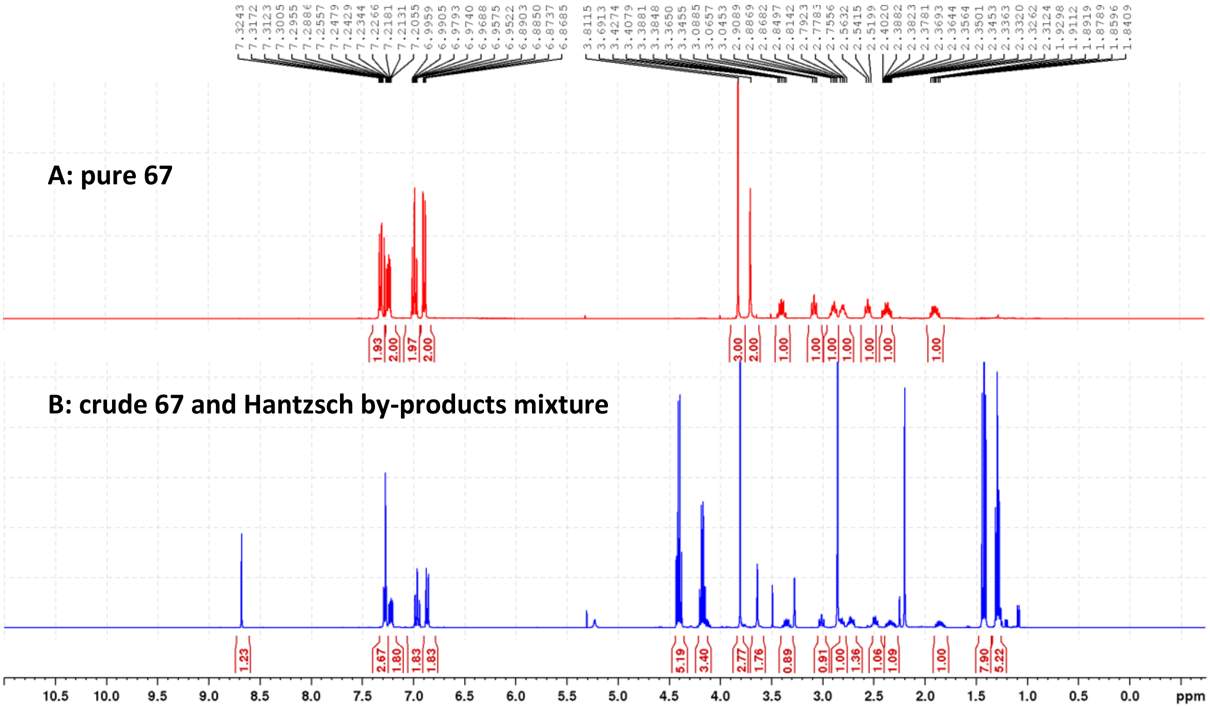
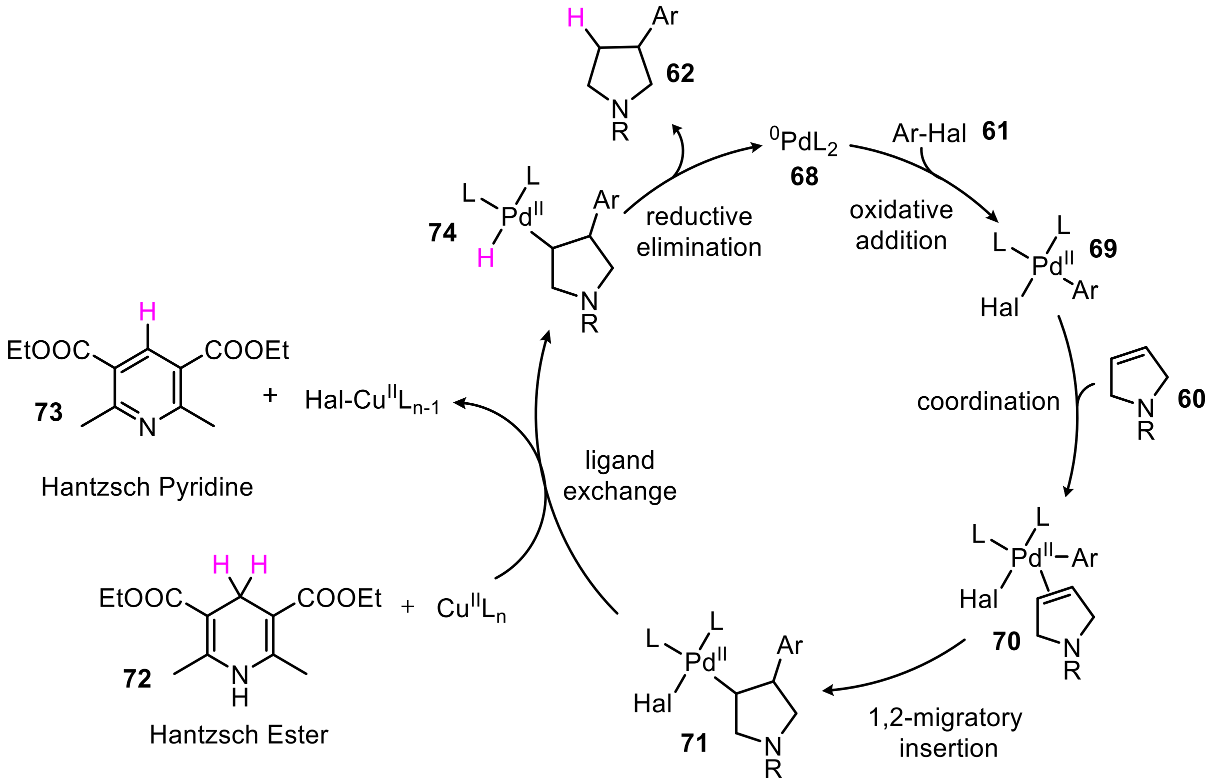


Figure 7. **A**: Pure 3-(4-fluorophenyl)-1-*p*-methoxybenzylpyrrolidine (**67**), **B**: 'crude' mixture of Hantzsch ester by-products and **67.**

7.1.5 Plausible mechanism for reductive Heck

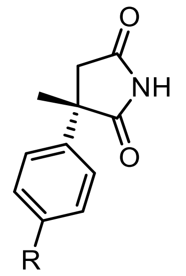
The mechanism by which Hantzsch ester can act as a hydride source has been extensively studied in both chiral phosphoric acid catalysed hydrogenation reactions[59,60] and also in palladium photoirradiation systems where the mechanism follows a radical pathway[61,62]. However, how the Hantzsch ester acts as a hydride source in a palldium catalysed reductive Heck reactions reamains unstudied. As a result, the precise mechanism for this reductive Heck system is not completely understood, however one would assume the plausible mechanism that this reductive Heck system follows is a similar mechanism to that proposed by the Sweeney group in 2018 (Scheme 20).[27] The key step in the cycle is the ligand exchange, where the copper additive can abstract the bromide anion from the alkyl palladium(II) complex **71**, followed by subsequent interception by the Hantzsch ester **72** to form the palladium complex **74**, which can underdo reductive elimination releasing the product. Hantzsch pyridine is released as a by-product following hydrogen transfer and can be seen in the crude NMR (Figure 7). A reaction using deuterated Hantzsch ester could be especially helpful to shed some light on the mechanism and this is definitely one of the first targets for future work on this system.



Scheme 22. Plausible mechanism for the Reductive Heck reaction of aryl halides where Hantzsch ester is acting as a hydride source.

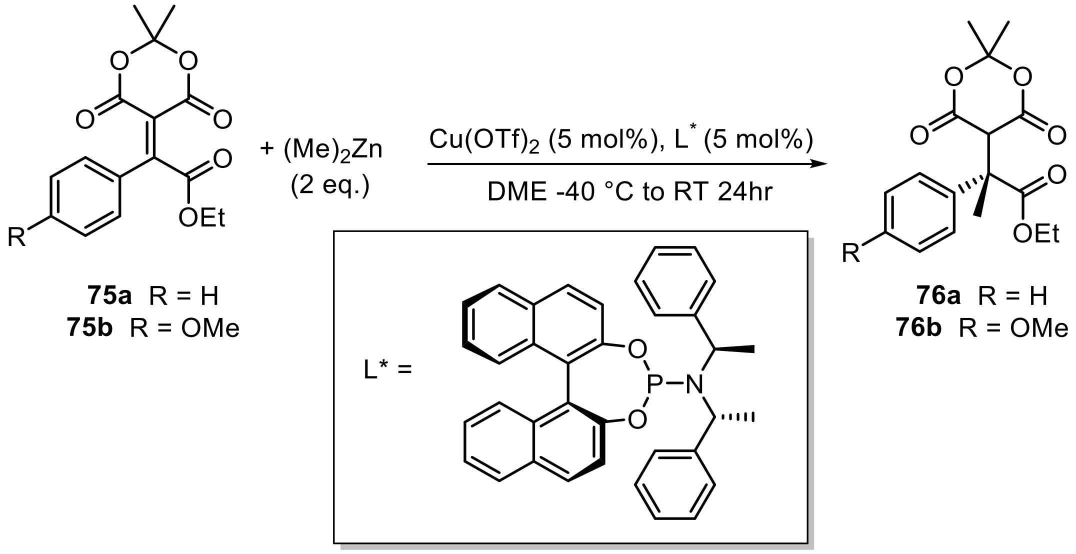
7.2. Reduction of Chiral Succinimides

Whilst working on a different project, trying to synthesise quaternary stereogenic centre succinimides **79a and b** (Figure 8), we found another way to generate highly functionalised chiral pyrrolidines. The project involved following literature conditions to perform an asymmetric 1,4-conjugate addition, to alkylidene Meldrum's acid adducts **76a** and **b** (Scheme 23).[63] However, the following cyclisation, to form the succinimide, bearing a quaternary stereogenic centre at the C-3 position proved problematic. A variety of ammonia sources were unsuccessfully tested under microwave conditions in order to cyclise the Medrum's adducts **76a** and **b** (Scheme 24). Previous work within the group to synthesise the quaternary stereogenic centre succinimides, bearing an ethyl group instead of a methyl, had used urea to cyclise their respective compounds, but this, unfortunately was not successful with the methyl group.



79a R = H
79b R = OMe

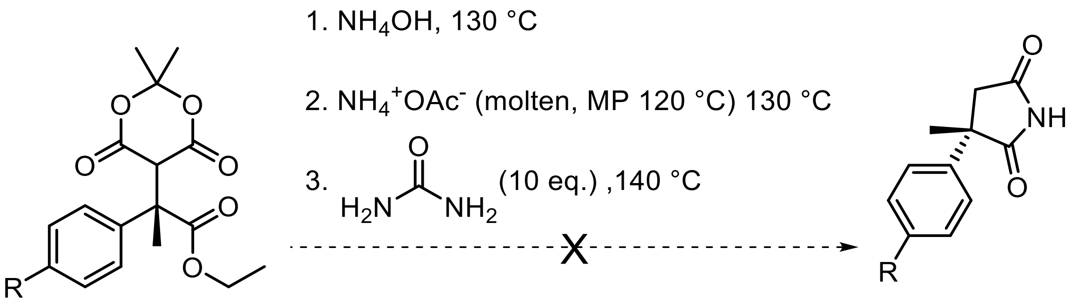
Figure 8. Structure of succinimide target compounds **79a** and **b**.



75a R = H
75b R = OMe

76a R = H
76b R = OMe

Scheme 23. Asymmetric copper catalysed 1,4-conjugate addition of dimethyl zinc to alkylidene Meldrum's acids **75a** and **b**.[63]

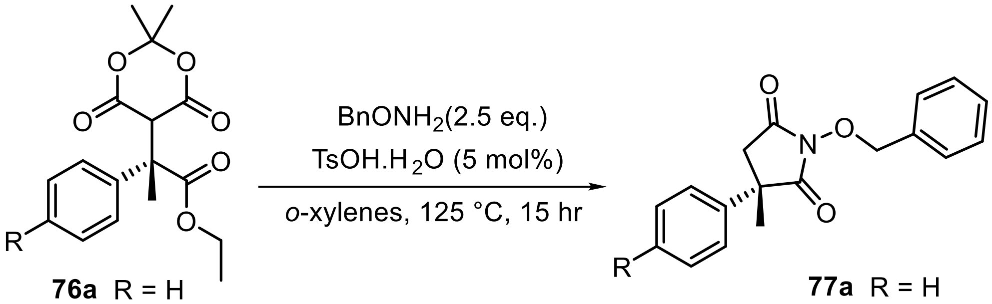


76a R = H
76b R = OMe

79a R = H
79b R = OMe

Scheme 24. Unsuccessful cyclisation attempts of Meldrum's adducts **76a** and **b**.

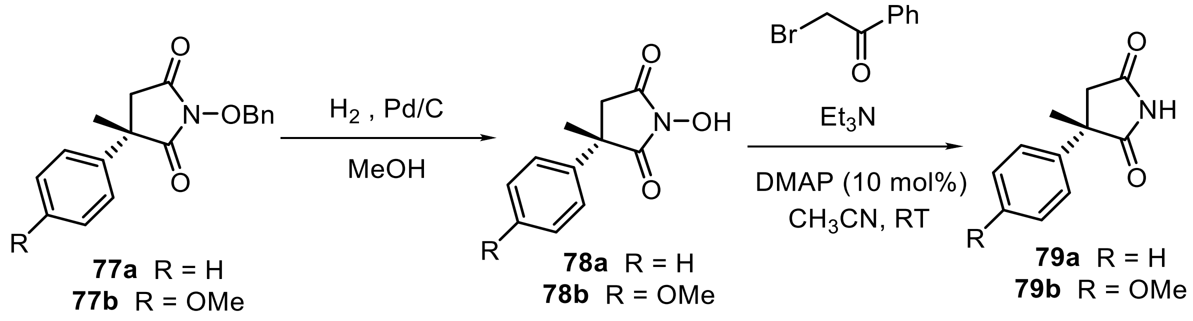
Whilst retro synthetically analysing the struggling ring closure against other literature methods we postulated an alternative starting material in O-benzylhydroxylamine to react with the Meldrum's adducts (Scheme 25). We firstly attempted the ring closing with benzylamine to check that the cyclisation worked in the methyl series. Although this was successful, previous work by the Sweeney group showed that using benzylamine to cyclise the adducts was not a viable route for our synthesis as hydrogenation of the benzyl succinimides requires high pressures, which we did not have access to. Our use of O-benzylhydroxylamine, when coupled with Dixon and co-workers' deprotection method[64], importantly provided a synthetic route to successfully deprotect compounds **77a** and **b** to yield the target succinimide compounds **79a** and **b** in 16 and 59% yields respectively (Scheme 26, yields were based on the overall reaction from alkylidene Meldrum's acids **75a** and **b** as crude products were carried on in each step in the synthetic route). Future work could definitely improve upon the yield of **79a** as purification methods were developed during the course of synthesising **79b**, namely the purification by recrystallisation for **79b**, which led to a much higher yield being obtained.



76a R = H
76b R = OMe

77a R = H
77b R = OMe

Scheme 25. Successful cyclisation of Meldrum's adduct **76a** and **b** to yield the protected succinimides **77a** and **b**.[64]

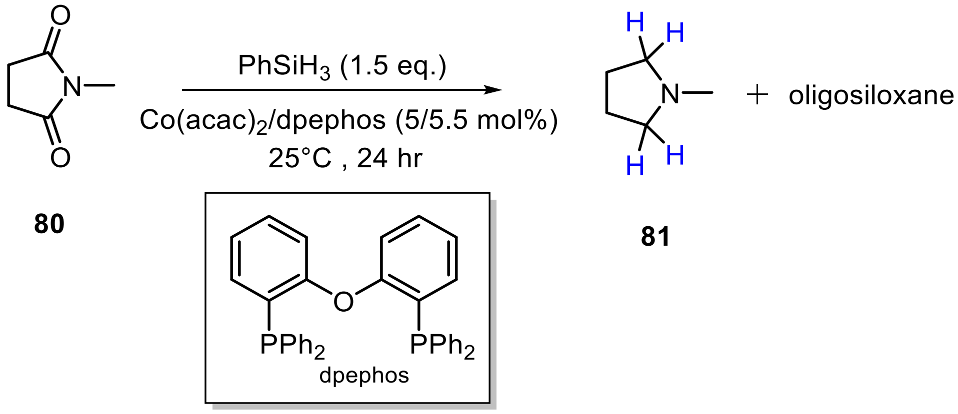


77a R = H
77b R = OMe
78a R = H
78b R = OMe
79a R = H
79b R = OMe

Scheme 26. Literature hydrogenolysis of benzyl group to from N-hydroxy succinimides **78a** and **b** followed by elimination of the hydroxyl group to obtain the desired succinimides **79a** and **b**, which were obtained in 15 and 59% yield respectively based on the overall synthesis from the alkylidene Meldrum's acids **75a** and **b** .[64]

As a follow up to the chiral succinimides synthesis project it was determined that for added value, the chiral succinimides already synthesised could be reduced from the imide to the amine. This would generate chiral pyrrolidines where the chiral centre has already been incorporated, at an earlier stage, by asymmetric 1,4-conjugate addition to the Meldrum's adducts **75a** and **b**.

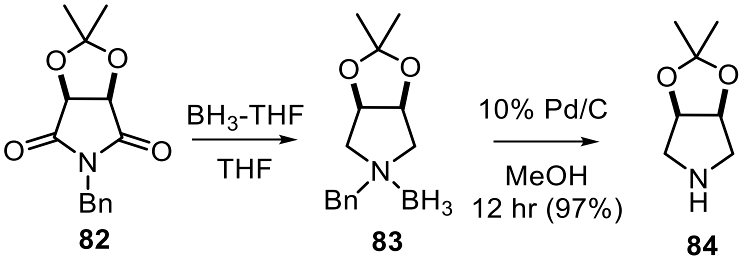
Recently, in 2019, Nerseiit and co-workers developed a mild hydrosilylative reduction of tertiary imides to amines (Scheme 27).[65] This was achieved following work from Dombray and co-workers who, in 2013, carried out the first example of a cobalt catalysed hydrosilylative reduction of amides using a low catalytic amount (0.5 mol%) of $Co_2(CO)_8$ in conjunction with 2.2 equivalents of PMHS at 100 °C for 3 hours.[66] Nurseiit and co-workers' specific reduction conditions of imides were optimised using bench stable and commercially available $Co(acac)_2$ (5 mol%) with dpephos ligand (5.5 mol%) at 25 °C for 24 hours which gave 90% yield.[65]



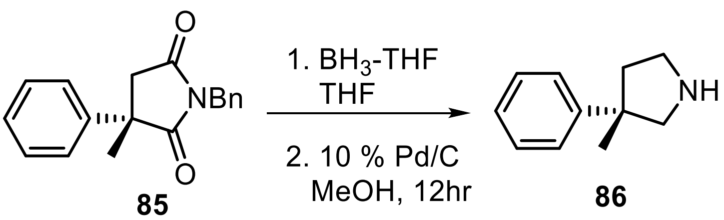
80
81

Scheme 27. Co-catalyzed hydrosilative reduction of imide to an amine using dpephos ligand under mild conditions.[65]

Couturier and co-workers' also developed a two-step method of reducing imides to amines, using borane to reduce the carbonyl groups followed by either palladium or Raney nickel catalysed methanolic cleavage of stable borane-amine complexes, which, until then had proven difficult to cleave (Scheme 28).[67] Previously to that report, cleavage of the borane-amine complex, required harsh reaction conditions, most commonly refluxing in aqueous HCl, which had not been popular in industry as it often promoted side reactions.[68] Unfortunately, due to time constraints on the project, only one imide to amine reduction could be attempted. The imide reduction via a borane-amine complex was chosen for this as, whilst testing the O-benzylhydroxylamine cyclisation, the conditions were first tested using benzylamine and as a result, we had already synthesised the required starting material benzyl succinimide (**85**). Much to our disappointment, this proved to be unsuccessful when following the literature conditions (Scheme 29). Future work should involve testing the alternative imide reduction conditions proposed and should allow for the synthesis of the aforementioned pyrrolidines, thus providing a valuable and alternative route to our target templates with added functionalisation.



Scheme 28. Reduction of imide followed by tandem methanoloysis-hydrogenolysis of a stable borane-benzylamine complex.[67]



Scheme 29. Unsuccessful reduction of N-Benzyl succinimide bearing quaternary stereogenic centre following Couturier and co-worker's synthetic conditions. [67]

8. Conclusion

In conclusion, this project has successfully established a set of optimised conditions for the reductive Heck reaction of N-Bn pyrroline with (hetero)aryl bromides. The work has further proven that the use of Hantzsch ester as a hydride source allows for the lowering of many of the reaction components namely N-Benzyl pyrroline (from 3.0 eq. to 1.2 eq.), DMpip (base) (from 5.0 eq. to 1.0 eq.), $Cu(OTf)_2$ (additive) (from 2.0 eq. to 0.5 eq.) and $PdCl_2/P(o\text{-}Tol)_3$ (Catalyst loading) (from 4/6 mol% to 1/1.5 mol%). This reduction in the equivalents of expensive components, with an increase in efficiency of the reaction has vastly improved the industrial viability of our reaction system. These conditions have been tested using a limited substrate screening providing a small library of racemic chiral pyrrolidines (9 examples with good to excellent yields 65-88% and 1 example with poor yield 29%) suitable for my partner company with the potential for diverse expansion. Further work on separation of enantiomers and the development of an asymmetric reaction is highly desirable based on reaction conditions developed in this report. As part of the project another method to produce pyrrolidines bearing a quaternary stereogenic centre via succinimides (2 examples in 16 and 59 % yield) was established, however although there are many examples in literature, a successful set of conditions for the imide reduction still needs to be established for our succinimides.

Despite the reductive Heck's synthetic appeal, it still remains largely unexplored within the pharmaceutical industry with routes favouring the MH reaction followed by a reduction. The development of intramolecular asymmetric reductive Heck systems (discussed in the introduction chapter) in the past two decades are key milestones, and further mechanistic understanding should unveil the full potential of the reductive Heck reaction and allow it to become a standard tool in the toolkit for synthetic chemists. [17,37]

8.1. Further questions and future work

As a result of our findings additional questions have been raised that would be of extreme interest for future study. Firstly, this includes developing an asymmetric version of the reaction, using chiral Hantzsch ester, a chiral benzyl group and/or chiral ligands for palladium catalyst (and possibly to the Cu additive). Alternatively, a method which one could use to separate the enantiomers would be just as valuable (i.e. chiral auxiliaries[69]). Development of an asymmetric version of this would be extremely significant in the pharmaceutical industry and allow for greater use of the currently unexploited reductive Heck reaction. Another key question raised that should be explored in future work is to better understand the roles of both the Hantzsch ester and $Cu(OTf)_2$ in the mechanism of the reaction. Especially of interest is to understand the hydride delivery and binding of the Hantzsch ester to the palladium, which could also prove useful in the development of an asymmetric reductive Heck reaction using chiral Hantzsch ester. Finally, other optimisations of this system that would be of great interest would include testing alkenyl bromides instead of (hetero)aryl bromides and, as previously discussed, trying to change the conditions of the reaction to only produce diarylated compounds.

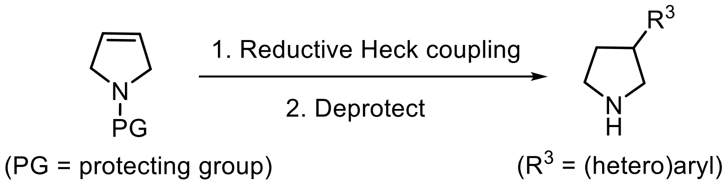
9. Experimental

9.1 General methods

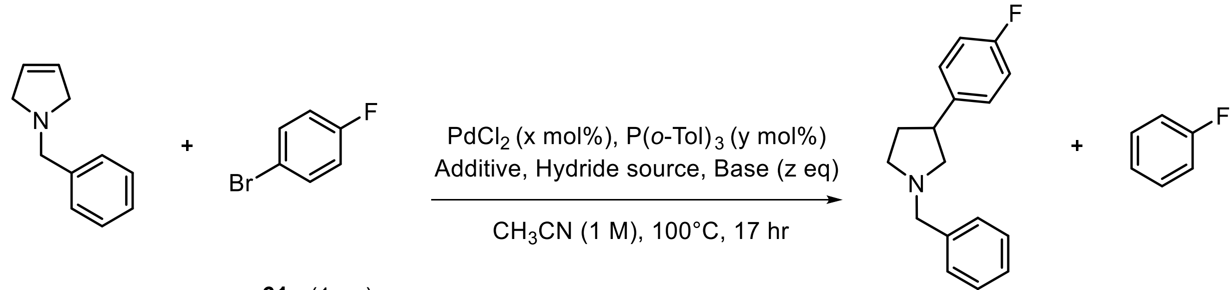
Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, Fluorochem and Tokyo Chemical Industry UK, and were not purified except where stated. Dry solvents were purchased from Acros (acroseal) and used as such. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, phosphomolybdic acid and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (40-63 microns) supplied by vwr and later supplied by Fluorochem.

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, ^{19}F at 376 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR and in ^{13}C NMR spectra are relative to the respective residual NMR solvent and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). The ^{19}F NMR of crude samples are relative to the standard, 1,3-difluorobenzene, with a chemical shift of -110.81 ppm in MeCN. Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.1 Hz. Mass spectrometry was performed using a Shimadzu Axima iDplus Performance MALDI-TOF instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Agilent Cary 630 FTIR benchtop spectrometer with Agilent MicroLab software with wavenumbers being reported in cm^{-1}.

9.2 Reductive Heck: Hydroarylation



9.2.1 Optimisation and H source determination



60a **61a** (1 eq) **62a** **63**

Optimised conditions were achieved by varying equivalents, base, additive and hydride source of the reaction mixture (as shown in tables in results and discussion chapter). The yield was measured using ^{19}F NMR (the T1 for fluorine containing species 2, 3 and 4 were measured and a d1 of 5 x the longest T1 value was used to record the ^{19}F NMR spectra).

General procedure 1: Optimisation of the Heck reaction of *N*-benzyl-3-pyrroline

In a 3-mL vial was added, $PdCl_2$ (see tables), P(*o*-Tol)$_3$ (see tables), Base (see tables), 4-fluorobenzene (1 mmol, 1 eq.), an additive (see tables), *N*-benzyl-1H-pyrroline (see tables), and acetonitrile (1 mL/mmol (hetero)arylbromide). The vial was tightly closed and then heated at 100 °C for 17 hours. The reaction mixture was then allowed to cool down to room temperature and a solution of 1,3-difluorobenzene standard in acetonitrile was added (1 mL, 0.5 M). The resulting solution was well stirred and a small amount (~0.1 mL) was taken for NMR analysis; to prepare the NMR sample, the reaction mixture taken out was filtered over celite, and washed with MeCN directly into the NMR tube).

9.2.2 Synthesis of target compounds

General procedure 2: Reductive Heck reaction of *N*-benzyl-3-pyrroline with screened (hetero)aryl bromides

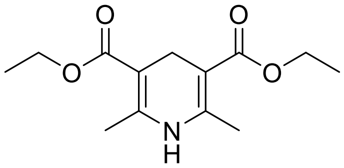
In a 20-mL microwave vial was added sequentially, $PdCl_2$ (4.4 mg, 0.025 mmol, 0.01 eq.), P(*o*-Tol)$_3$ (11.4 mg, 0.00375 mmol, 0.015 eq.), Hantzsch ester (1.2665 g, 5 mmol, 2 eq.), Cu(OTf)$_2$ (0.4521 g, 1.25 mmol, 0.5 eq.), acetonitrile (2.5 mL), arylbromide (2.5 mmol, 1 eq.), *N*-benzyl-3-pyrroline (0.57 mL, 3 mmol, 1.2 eq.) and *N*,*N*-dimethylpiperazine (0.34 mL, 2.5 mmol, 1 eq.). The vial was closed and then heated at 100 °C for 17 hours. For the work up, the reaction mixture was then allowed to cool down to room temperature and was then diluted with DCM

(10 mL). Then, Et_2O (80 mL) was added and the mixture was washed with NH_4OH_{aq} (28%, 80 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 80 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography, conditions are discussed for each compound.

General procedure 3: Debenzylation of 3-((hetero)aryl)-1-benzylpyrrolidine

To a 50 mL RBF pure or crude 3-((hetero)aryl)-1-benzylpyrrolidine), was dissolved in EtOH (25 mL). 20 wt. % $Pd(OH)_2/C$ (5 mol%) was added and the reaction mixture was stirred for 30 minutes before being placed under an atmosphere of H_2 and the reaction was heated to 50 °C and left to stir overnight. The crude product was filtered through a celite cake, and the solvent was removed under vacuum to yield the crude product which was purified by column chromatography (100 g silica, gradient DCM:7N NH_3 in MeOH, 99.5:0.5 to 95:5 v/v) affording the pure title compound.

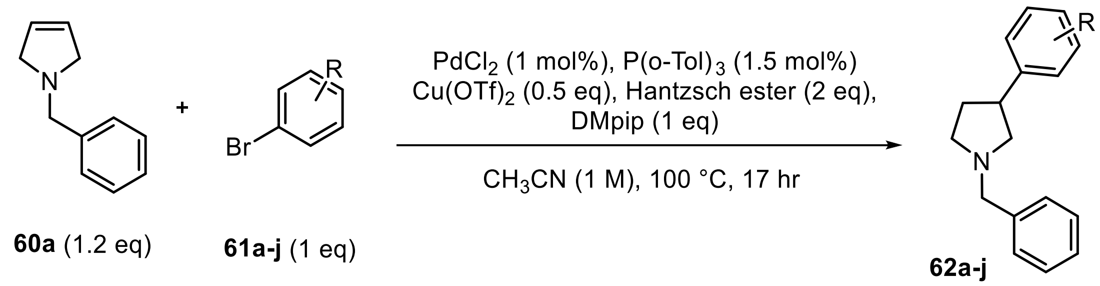
Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch ester)[70]



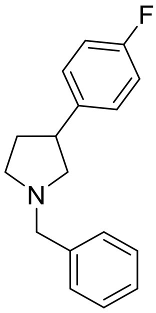
A mixture of ethyl acetoacetate (50.6 mL, 400 mmol, 2 eq.), ammonium acetate (23.12 g, 300 mmol, 1.5 eq.), paraformaldehyde (6.0 g, 200 mmol, 1 eq.) was heated at 70 °C for 10 min. The reaction mixture was then allowed to cool down to RT and cold water (320 mL) were added. The resulting mixture was stirred for 10 min and filtered. The precipitate was recrystallized twice from EtOH (500 mL followed by a second recrystallisation using 800 mL) to afford pure Hantzsch ester as a bright yellow solid (27 g, 106.6 mmol, 53 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* 7.2 Hz, 4H), 3.28 (s, 2H), 2.20 (s, 6H), 1.29 (t, *J* 7.2 Hz, 6H).

Screened (hetero)aryl bromides data



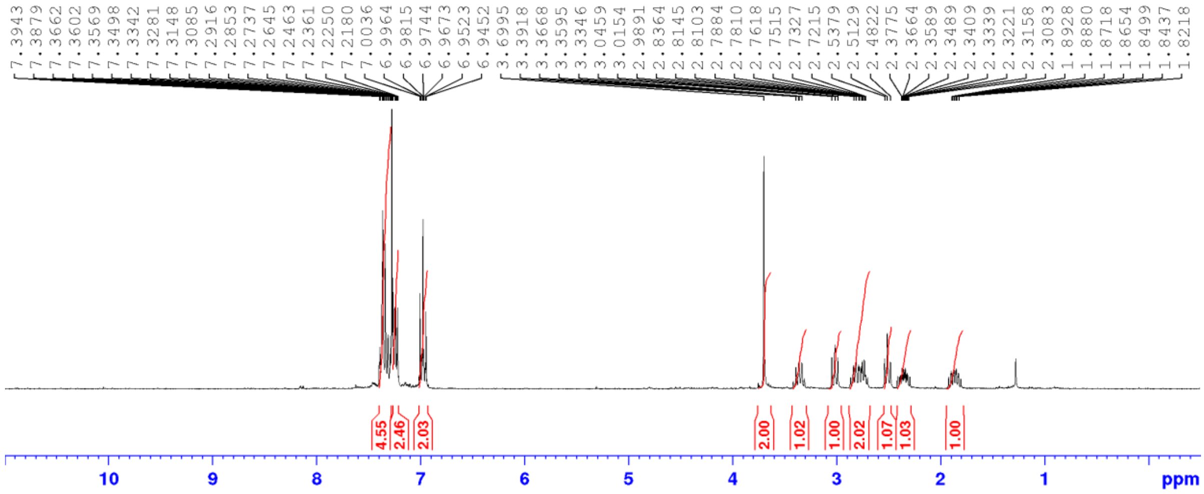
3-(4-fluorophenyl)-1-benzylpyrrolidine (**62a**)[27]



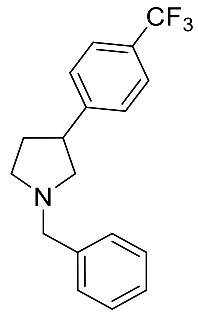
Chemical Formula: $C_{17}H_{18}FN$
Molecular Weight: 255.34

Following general procedure 2, using 4-fluorobromobenzene, the title compound **62a** was isolated by column (Conditions: 50 g silica, gradient DCM:7N NH_3 in MeOH, 99.5:0.5 to 95:5 v/v), as an orange oil (465 mg, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.39-7.22 (m, 7H), 7.00-6.95 (m, 2H), 3.68 (s, 2H), 3.32-3.31 (m, 1H), 3.02 (dd, *J* 8.1 Hz, 7.9 Hz, 1H), 2.87-2.70 (m, 2H), 2.51 (dd, *J* 7.3 Hz, 7.8 Hz, 1H), 2.41-2.29 (m, 1H), 1.92-1.80 (m, 1H).



3-(4-(trifluoromethyl)phenyl)-1-benzylpyrrolidine (**62b**)



Chemical Formula: $C_{18}H_{18}F_3N$
Molecular Weight: 305.34

Following general procedure 2, using 4-bromotrifluorobenzene, the title compound **62b** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 14:1 to 1:1 v/v followed by a second column conditions: 100 g silica gradient DCM:EtOAc, 18:1 to 1:1 v/v), as an orange oil (547 mg, 72%).

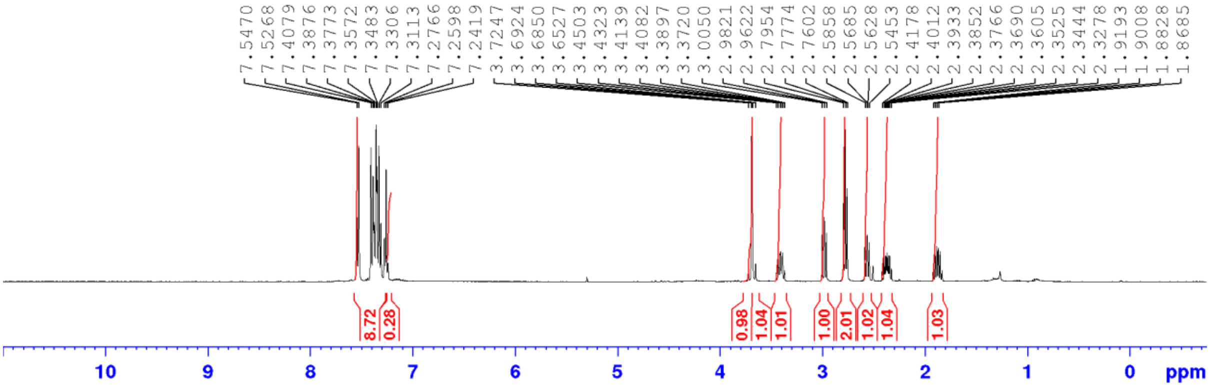
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.55-7.24 (m, 9H), 3.71 (d, *J* 12.8 Hz, 1H), 3.67 (d, *J* 12.8 Hz, 1H), 2.98 (dd, *J* 8.0 Hz, 7.8 Hz, 1H), 2.78 (t, *J* 7.3 Hz, 2H), 2.56 (dd, *J* 7.0 Hz, 6.7 Hz, 1H), 2.42-2.33 (m, 1H), 1.92-1.83 (sext, *J* 7.0 Hz, 1H).

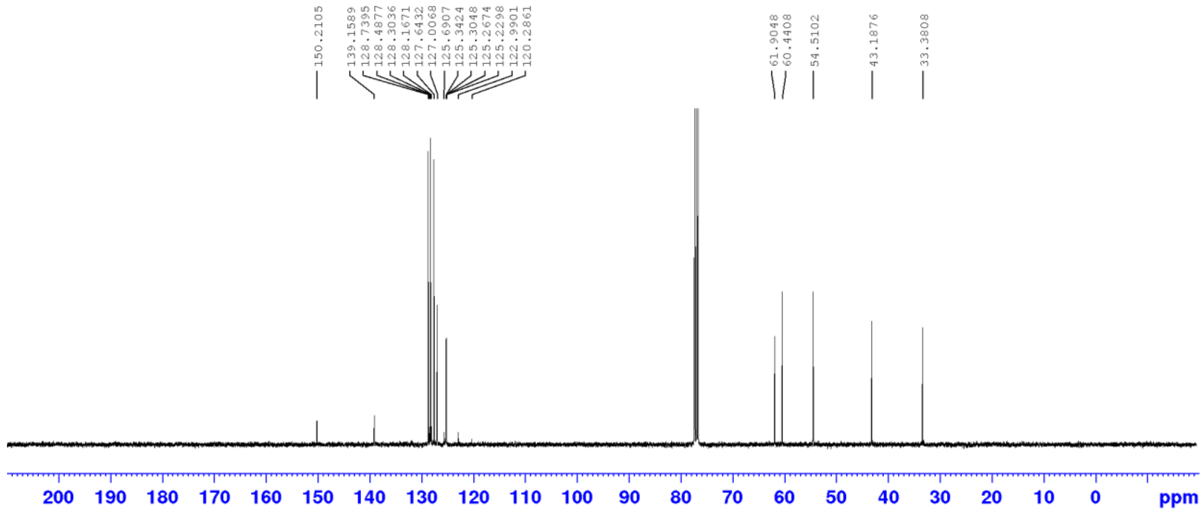
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 150.2 (1C), 139.2 (1C), 128.7 (2CH), 128.3 (2CH), 127.6 (2CH), 127.0 (2CH), 125.3 (q, *J* 3.7 Hz, 2CH), 124.3 (q, *J* 271.4 Hz, 1C), 61.9 ($1CH_2$), 60.4 ($1CH_2$), 54.5 ($1CH_2$), 43.2 (1CH), 33.4 ($1CH_2$)

19F {1H} NMR ($CDCl_3$, 376 MHz) δ_F –62.3.

IR ν_{max} (thin film, cm^{-1}): 3028 (C-H, Ar), 2957 (C-H), 2920 (C-H), 2790 (C-H), 2734 (C-H), 1494 (Ar), 1321 (C-N).

HRMS *m/z* (ESI$^+$) calculated for $C_{18}H_{18}F_3N$ [M+H]$^+$: 306.1464, found 306.1456.

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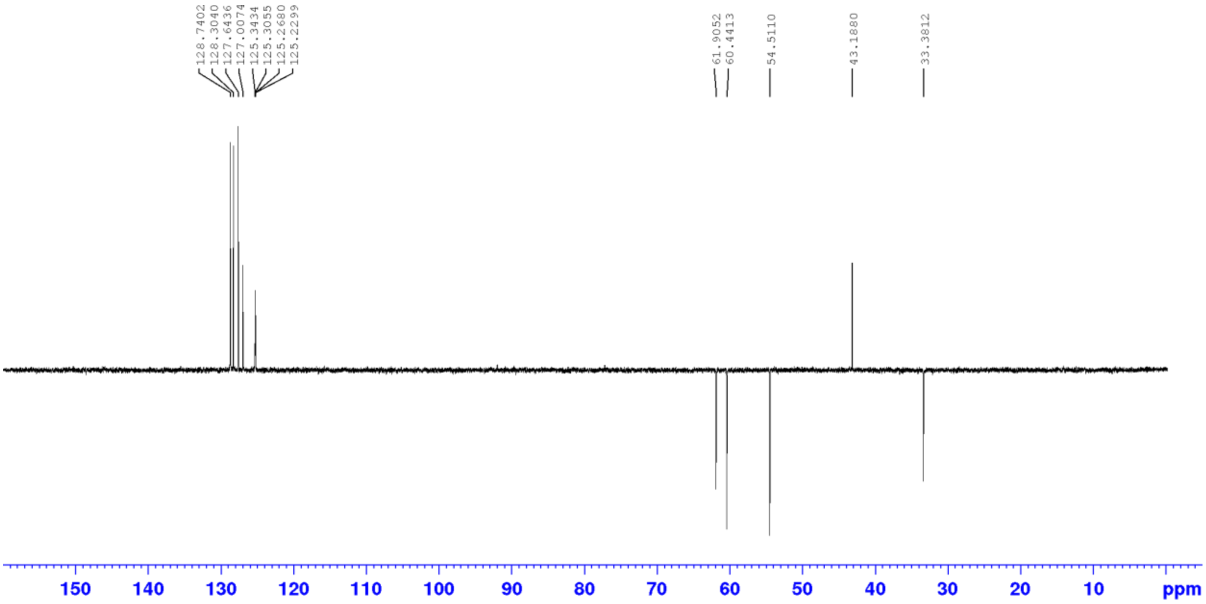
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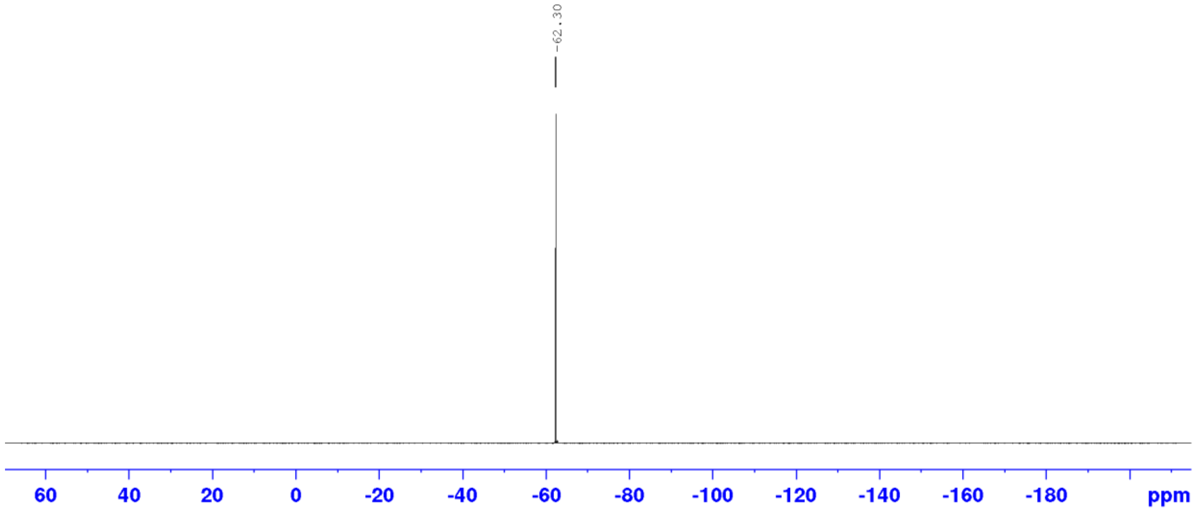
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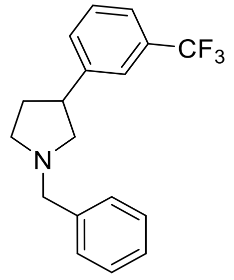
3-(3-(trifluoromethyl)phenyl)-1-benzylpyrrolidine (**62c**)



Chemical Formula: $C_{18}H_{18}F_3N$
Molecular Weight: 305.34

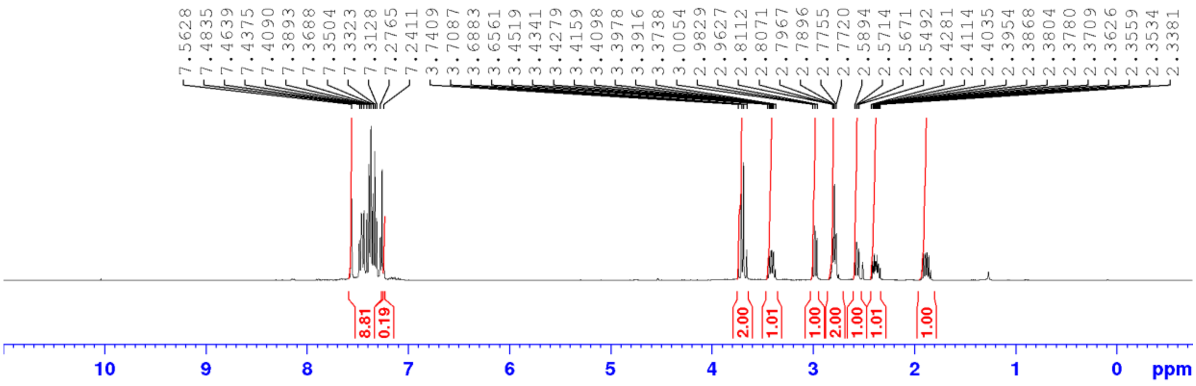
Following general procedure 2, using 3-bromotrifluorobenzene, the title compound **62c** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 14:1 to 1:1 v/v followed by a second column conditions: 100 g silica gradient DCM:EtOAc, 18:1 to 1:1 v/v), as a pale orange oil (556 mg, 73%).

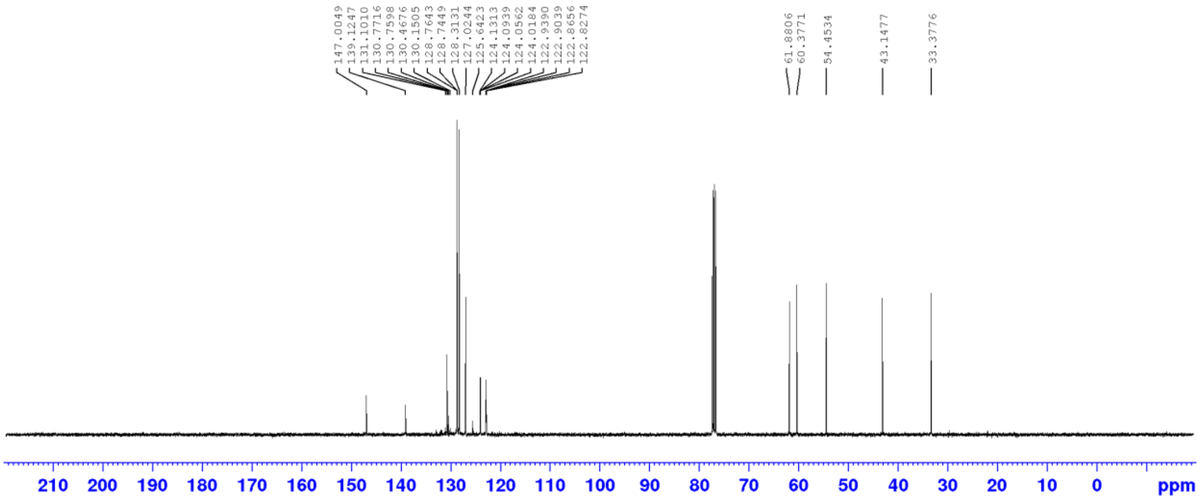
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.56-7.24 (m, 9H), 3.72 (d, *J* 13.2 Hz, 1H), 3.67 (d, *J* 13.2 Hz, 1H), 3.45-3.37 (m, 1H), 2.98 (dd, *J* 8.3 Hz, 8.3 Hz, 1H), 2.81-2.77 (m, 2H), 2.57 (dd, *J* 7.3 Hz, 7.1 Hz, 1H), 2.43-2.34 (m, 1H), 1.93-1.84 (m, 1H).

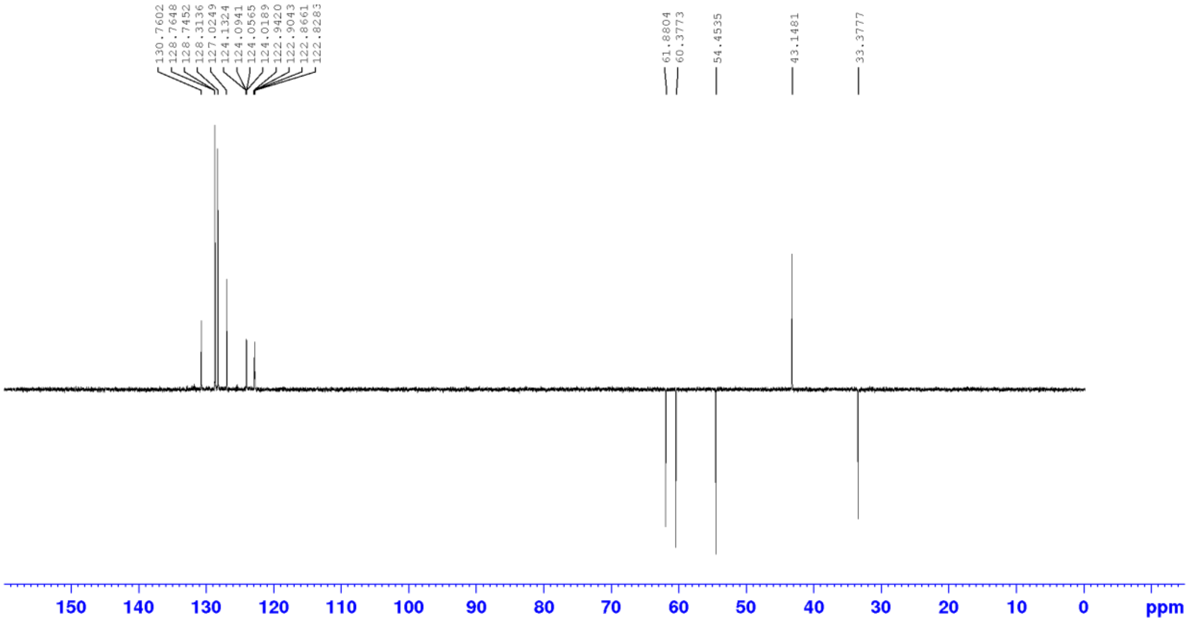
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 147.0 (1C), 139.1 (1C), 130.8 (1CH), 130.6 (q, *J* 29.3 Hz, 1C), 128.8 (1CH), 128.7 (2CH), 128.3 (2CH), 127.0 (1CH), 124.3 (q, *J* 271.3 Hz, 1C), 124.1 (q, *J* 3.9 Hz, 1CH), 122.9 (q, *J* 3.7 Hz, 1CH), 61.9 ($1CH_2$), 60.4 ($1CH_2$), 54.5 ($1CH_2$), 43.1 (1CH), 33.4 ($1CH_2$).

IR ν_{max} (thin film, cm^{-1}): 3064 (C-H, Ar), 3029 (C-H, Ar), 2959 (C-H), 2922 (C-H), 2878 (C-H), 2790 (C-H), 2734 (C-H), 1492 (Ar), 1323 (C-N).

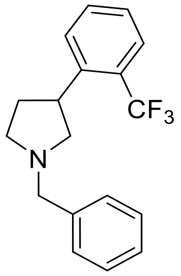
HRMS *m/z* (ESI^+) calculated for $C_{18}H_{18}F_3N$ $[M+H]^+$: 306.1464, found 306.1454.







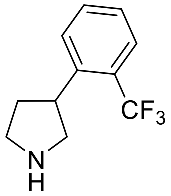
3-(2-(trifluoromethyl)phenyl)-1-benzylpyrrolidine (**62d**)



Chemical Formula: $C_{18}H_{18}F_3N$
Molecular Weight: 305.34

Following general procedure 2, using 2-bromotrifluorobenzene, the title compound **62d** was isolated as a mixture of product, the Hantzsch ester and Hantzsch pyridine by-products. The impure mixture was hydrogenated as and afforded the NH pyrrolidine compound after silicagel column chromatography.

3-(2-(trifluoromethyl)phenyl)-pyrrolidine (**64d**)



Chemical Formula: $C_{11}H_{12}F_3N$
Molecular Weight: 215.22

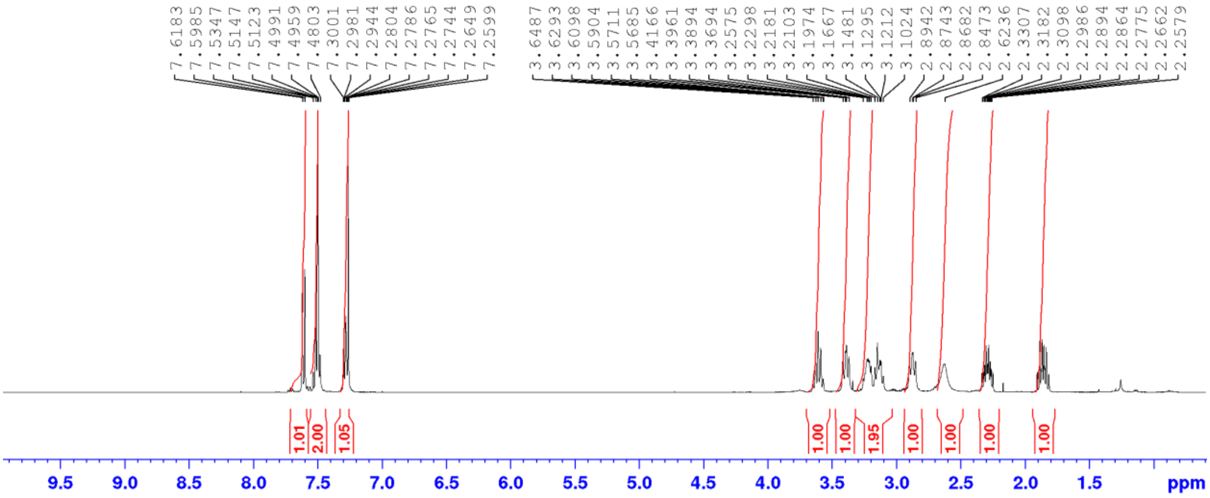
Crude 3-(2-(trifluoromethyl)phenyl)-1-benzylpyrrolidine (1.4 g, **62d**) underwent debenzylation following general procedure 3, affording the pure title compound **64d** as a pale orange oil (180 mg, overall, 34% yield based on aryl bromide in step 1 before deprotection).

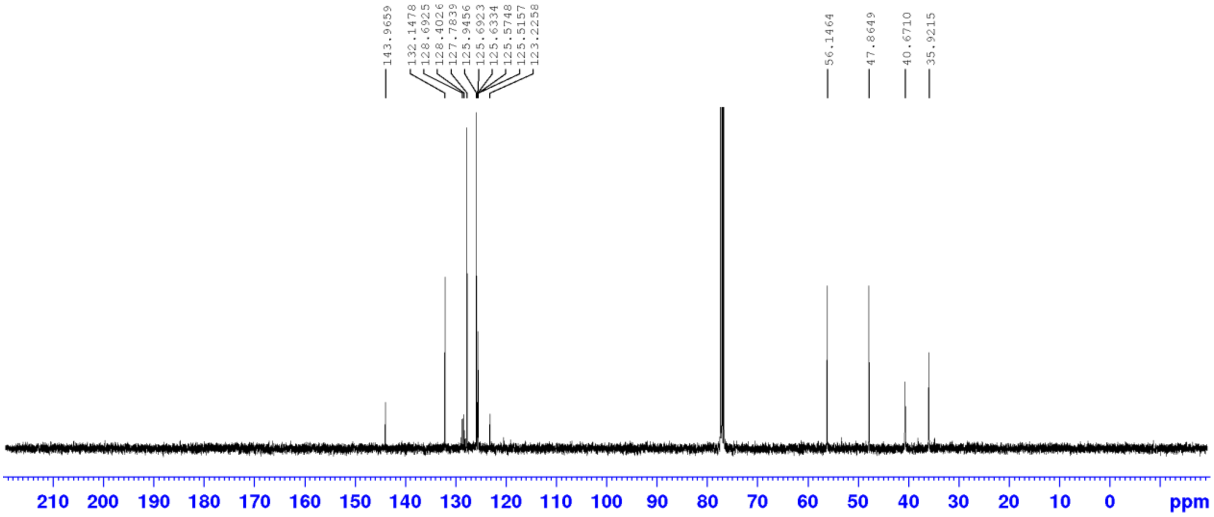
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.61 (d, *J* 7.5 Hz, 2H), 7.53-7.48 (m, 2H), 7.30-7.26 (m, 1H), 3.61 (quint, *J* 8.0 Hz, 1H), 3.39 (dd, *J* 8.1 Hz, 8.1 Hz 1H), 3.26-3.10 (m, 2H), 2.87 (dd, *J* 8.7 Hz, 8.7 Hz 1H), 2.62 (s, 1H), 2.33-2.25 (m, 1H), 1.86 (dq, *J* 8.1 Hz, 8.1 Hz, 1H).

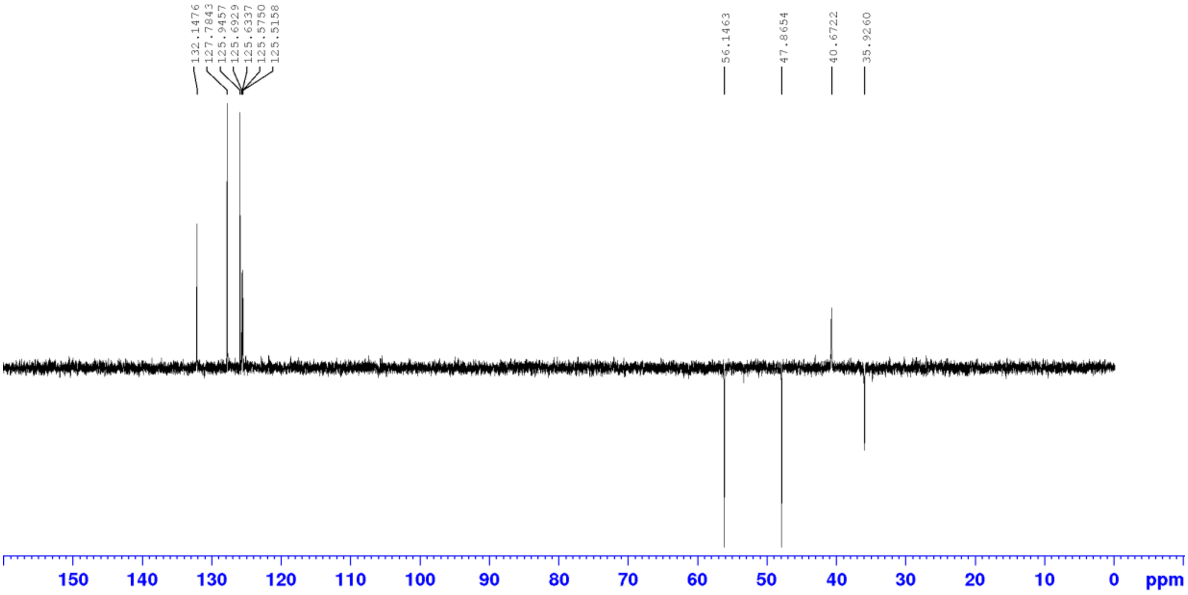
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 144.0 (1C), 132.1 (1CH), 128.5 (q, *J* 29.5 Hz,1C), 127.8 (1CH), 125.9 (1CH), 125.6 (q, *J* 5.8 Hz, 1CH), 124.6 (q, *J* 274.0 Hz,1C), 56.1 ($1CH_2$), 47.9 ($1CH_2$), 40.7 (1CH), 35.9 ($1CH_2$).

IR ν_{max} (thin film, cm^{-1}): 3267 (N-H), 3038 (C-H, Ar), 2963 (C-H), 2876 (C-H), 1456 (Ar).

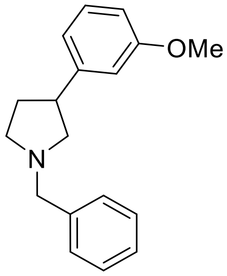
HRMS *m/z* (ESI$^+$) calculated for $C_{11}H_{12}F_3N$ $[M+H]^+$: 216.0995, found 216.0986.







3-(3-methoxyphenyl)-1-benzylpyrrolidine



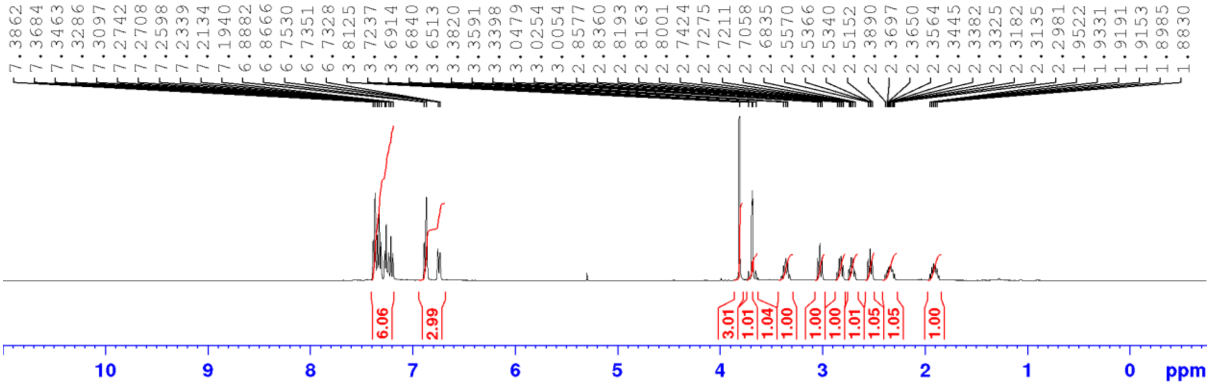
Chemical Formula: $C_{18}H_{21}NO$
Molecular Weight: 267.37

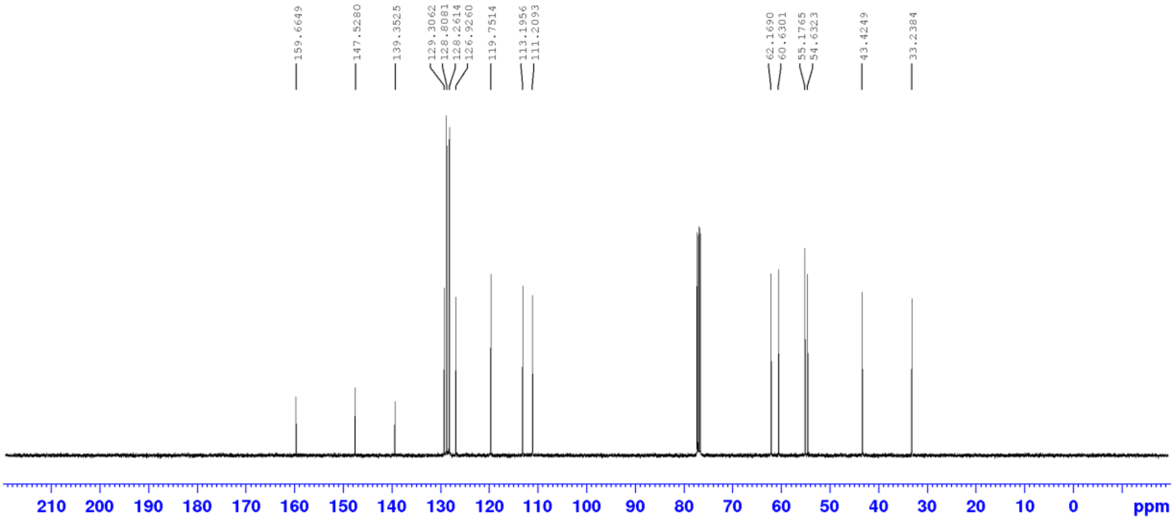
Following general procedure 2, using 3-bromo methoxybenzene, the title compound **62e** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 18:1 to 1:1 v/v followed by a second column conditions: 100 g silica gradient DCM:EtOAc, 14:1 to 1:1 v/v), as an orange oil (588 mg, 88%).

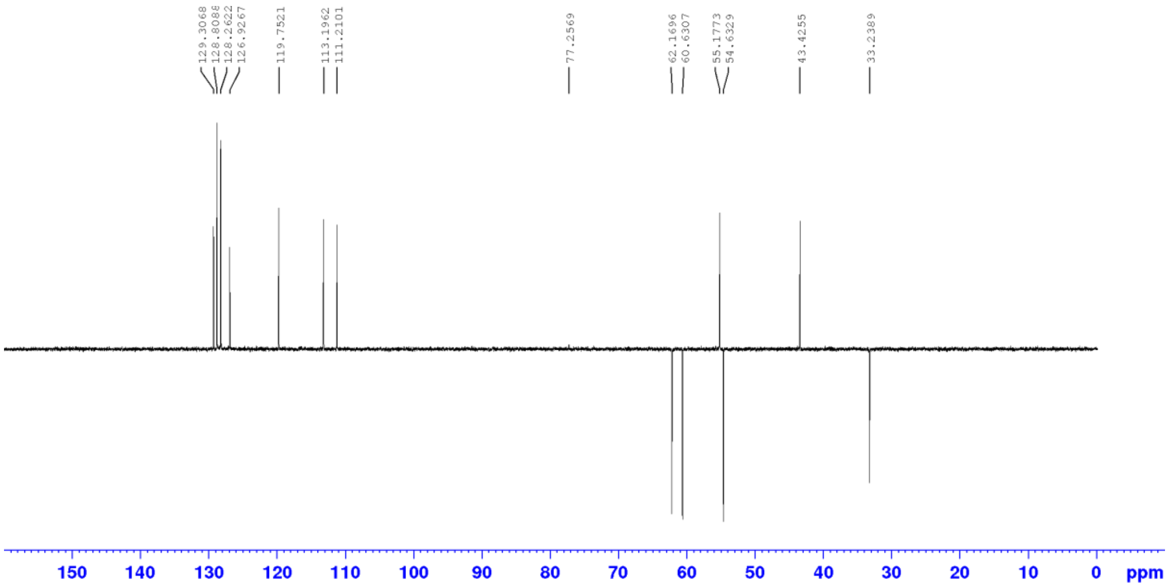
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.39-7.19 (m, 6H), 6.89-6.74 (m, 3H), 3.81 (s, 3H), 3.71 (d, *J* 12.8 Hz, 1H), 3.67 (d, *J* 12.2 Hz, 1H), 3.36 (quint, *J* 7.9 Hz, 1H), 3.03 (t, *J* 9.2 Hz, 1H), 2.84-2.80 (m, 1H), 2.74-2.68 (m, 1H), 2.54 (dd, *J* 7.7 Hz, 1H), 2.39-2.30 (m, 1H), 1.95-1.87 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 159.7 (1C), 147.5 (1C), 139.4 (1C), 129.3 (1CH), 128.8 (2CH), 128.3 (2CH), 126.9 (1CH), 119.8 (1CH), 113.2 (1CH), 111.2 (1CH), 62.2 ($1CH_2$), 60.6 ($1CH_2$), 55.2 ($1CH_3$), 54.6 (1CH), 43.4 (1CH), 33.2 (1CH).

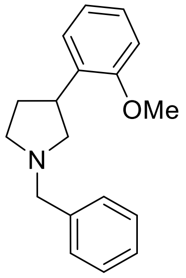
IR ν_{max} (thin film, cm^{-1}): 3060 (C-H, Ar), 3025 (C-H, Ar), 2953 (C-H), 2833 (C-H), 2786 (C-H), 2784 (C-H), 1601 (Ar), 1157 (C-O).







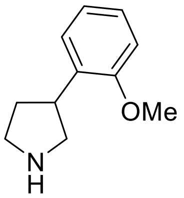
3-(2-methoxyphenyl)-1-benzylpyrrolidine (**62f**)



Chemical Formula: $C_{18}H_{21}NO$
Molecular Weight: 267.37

Following general procedure 2, using 2-bromo methoxybenzene, the title compound **62f** was isolated as a mixture of product, Hantzsch ester and Hantzsch pyridine by-products. The impure mixture was hydrogenated as and afforded the NH pyrrolidine compound after silicagel column chromatography.

3-(2-(trifluoromethyl)phenyl)-pyrrolidine (**64f**)

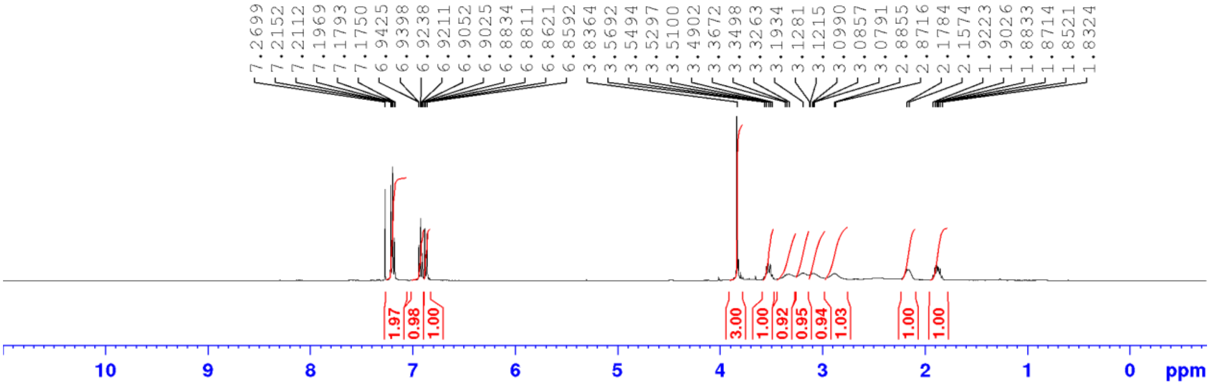


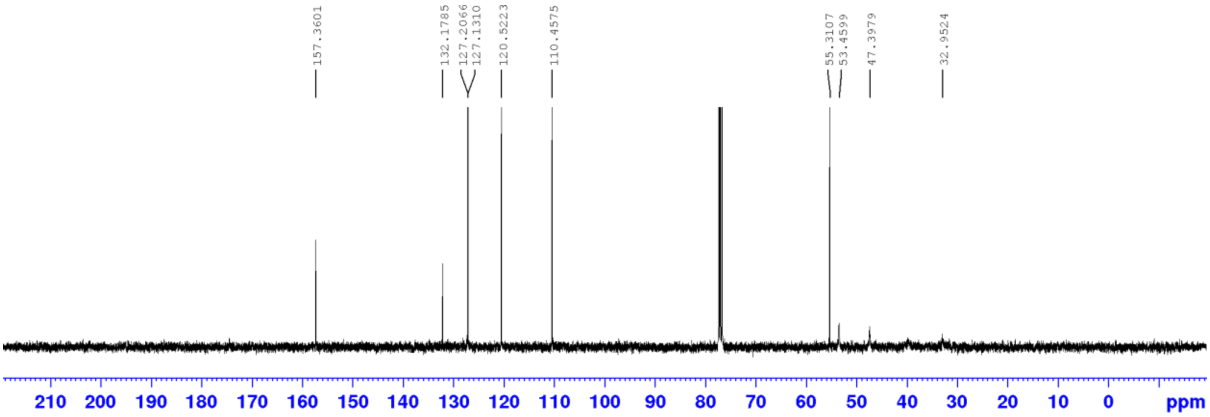
Chemical Formula: $C_{11}H_{15}NO$
Molecular Weight: 177.25

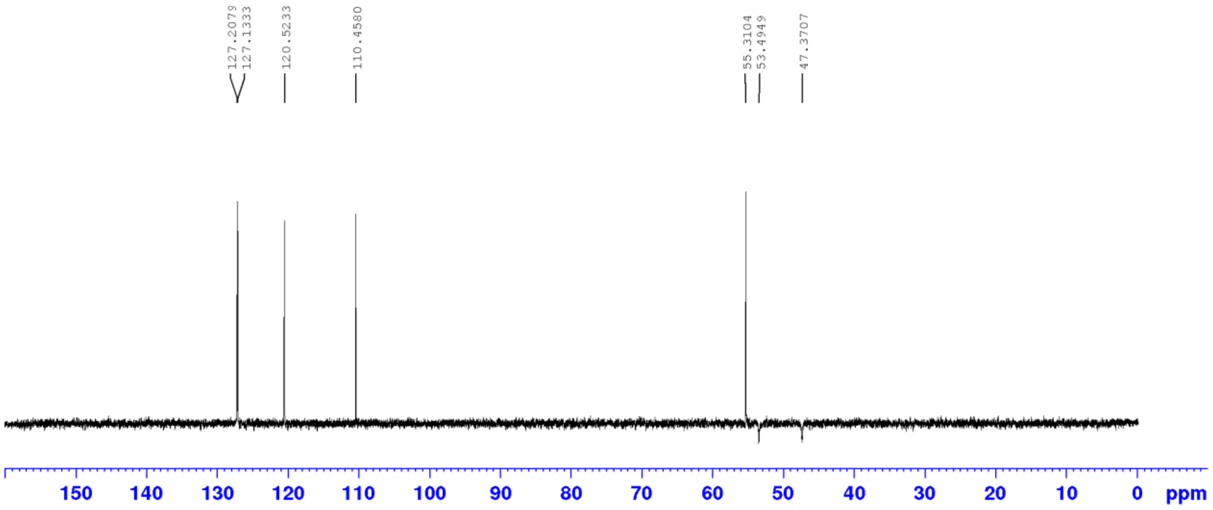
Crude 3-(2-methoxyphenyl)-1-benzylpyrrolidine (0.351 g, **62f**) underwent debenzylation following general procedure 3, affording the pure title compound **64f** as a yellow oil (124 mg, overall, 28% yield based on aryl bromide in step 1 before deprotection).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.22-7.18 (m, 2H), 6.92 (td, *J* 7.7 Hz, 1.1 Hz, 1H), 6.87 (dd, *J* 8.8, 8.5 Hz, 1H), 3.84 (s, 3H), 3.57-3.49 (m, 1H), 3.37-3.23 (m, 1H), 3.19 (m, 1H), 3.13-3.08 (m, 1H), 2.89-2.87 (m, 1H), 2.18-2.16 (m, 1H), 1.92-1.83 (m, 1H).

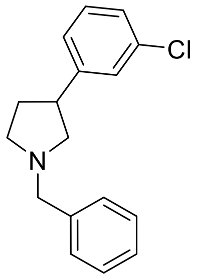
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 157.4 (1C), 132.2 (1C), 127.2 (1CH), 127.1 (1CH), 120.5 (1CH), 110.5 (1CH), 55.3 ($1CH_3$), 53.5 ($1CH_2$), 47.4 ($1CH_2$), 33.0 ($1CH_2$).







3-(3-chlorophenyl)-1-benzylpyrrolidine (**62g**)



Chemical Formula: $C_{17}H_{18}ClN$
Molecular Weight: 271.79

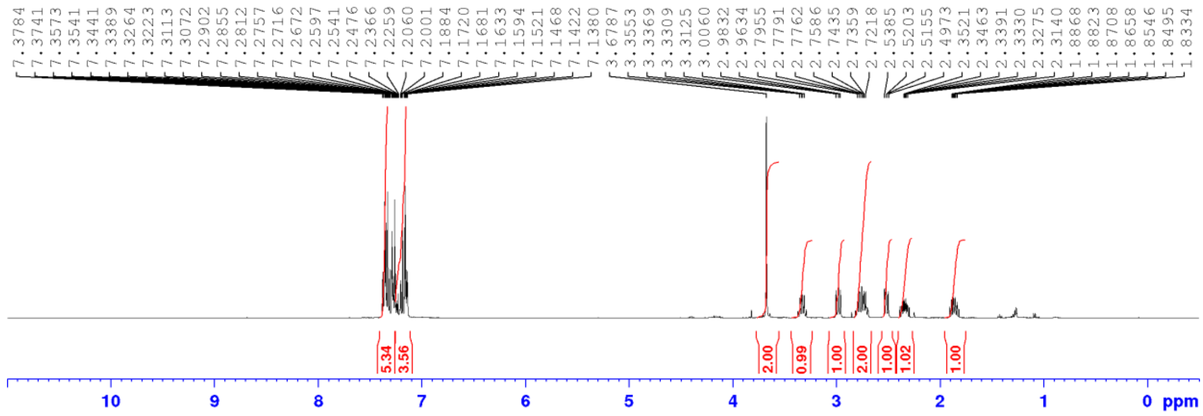
Following general procedure 2, using 3-bromo chlorobenzene, the title compound **62g** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 18:1 to 1:1 v/v followed by a second column conditions: 100 g silica under the same solvent conditions), as a yellow oil (483 mg, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.37-7.13 (m, 9H), 3.68 (s, 2H), 3.37-3.29 (m, 1H), 2.98 (dd, *J* 7.7 Hz, 8.0 Hz, 1H), 2.82-2.70 (m, 2H), 2.52 (dd, *J* 7.5 Hz, 7.0 Hz, 1H), 2.38-2.29 (m, 1H), 1.90-1.82 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 148.0 (1C), 139.2 (1C), 134.1 (1C), 129.6 (1CH), 128.8 (2CH), 128.3 (2CH), 127.5 (1CH), 127.0 (1CH), 126.2 (1CH), 125.6 (1CH), 61.9 ($1CH_2$), 60.5 ($1CH_2$), 54.5 ($1CH_2$), 43.1 (1CH), 33.2 ($1CH_2$).

IR ν_{max} (thin film, cm^{-1}): 3062 (C-H, Ar), 3027 (C-H, Ar), 2958 (C-H), 2920 (C-H), 2786 (C-H), 2734 (C-H), 1597 (Ar), 749 (C-Cl).

HRMS *m/z* (ESI^+) calculated for $C_{17}H_{18}ClN$ $[M+H]^+$: 272.1201, found 272.1193.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2.7218
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2.3521
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2.3391
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2.3140
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1.8495
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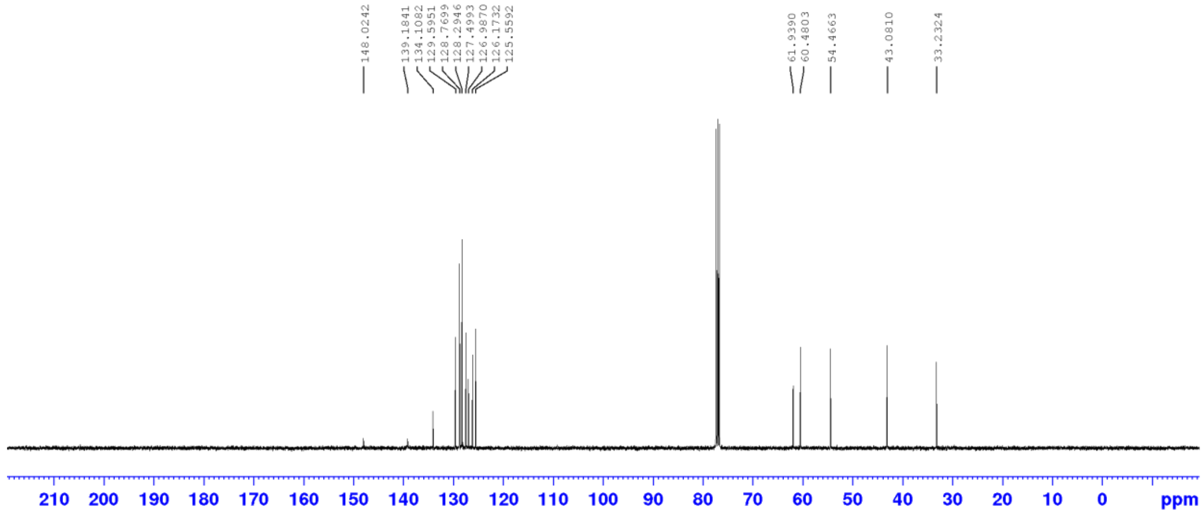
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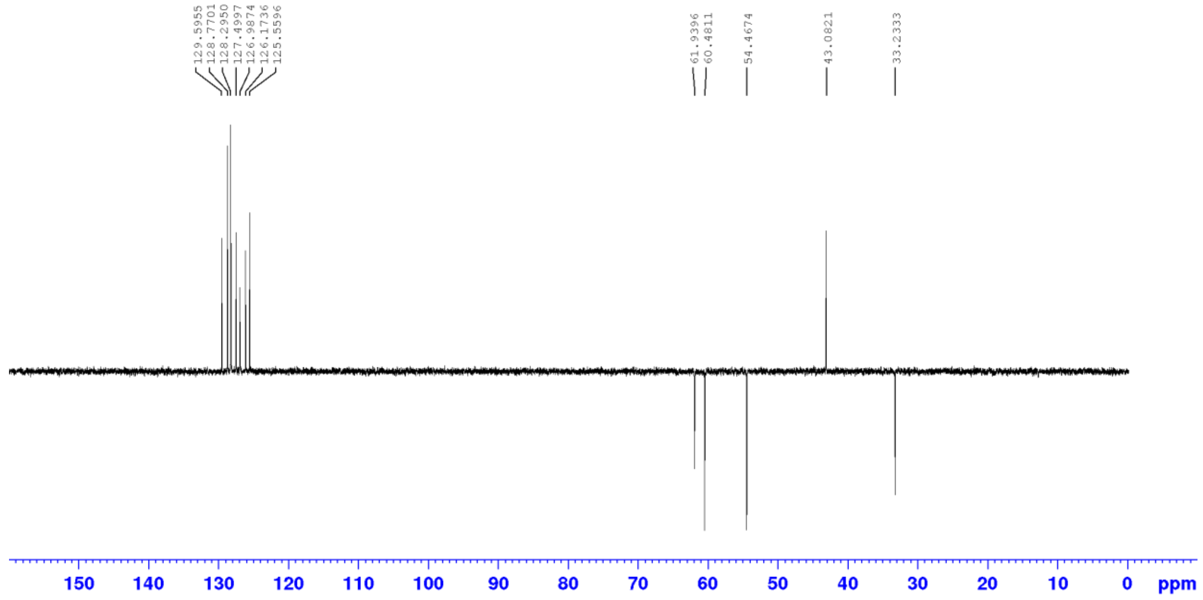
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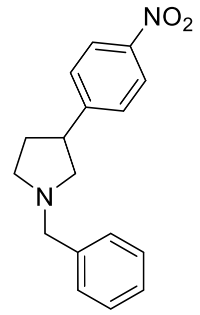
3-(4-nitrophenyl)-1-benzylpyrrolidine (**62h**)



Chemical Formula: $C_{17}H_{18}N_2O_2$
Molecular Weight: 282.34

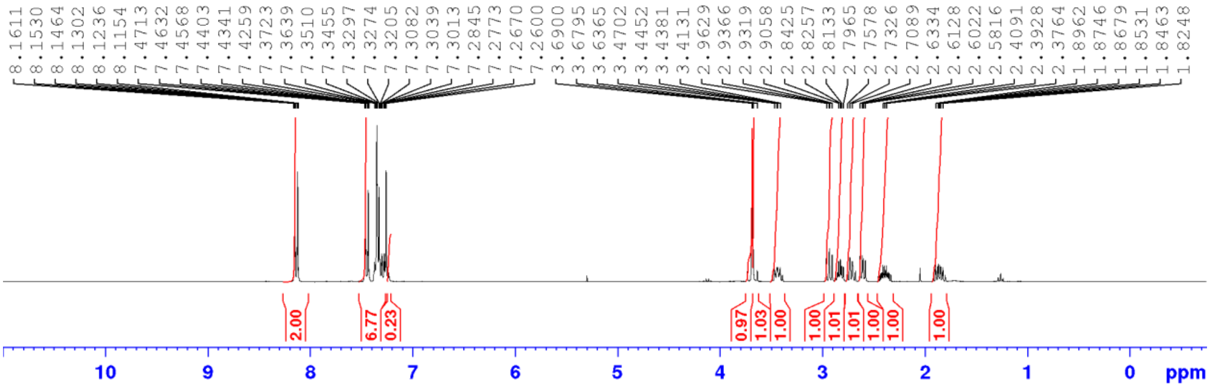
Following general procedure 2, using 4-bromo nitrobenzene, the title compound **62h** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 18: followed by a second column conditions: 100 g silica under the same solvent conditions), as a blood orange oil (506 mg, 72%).

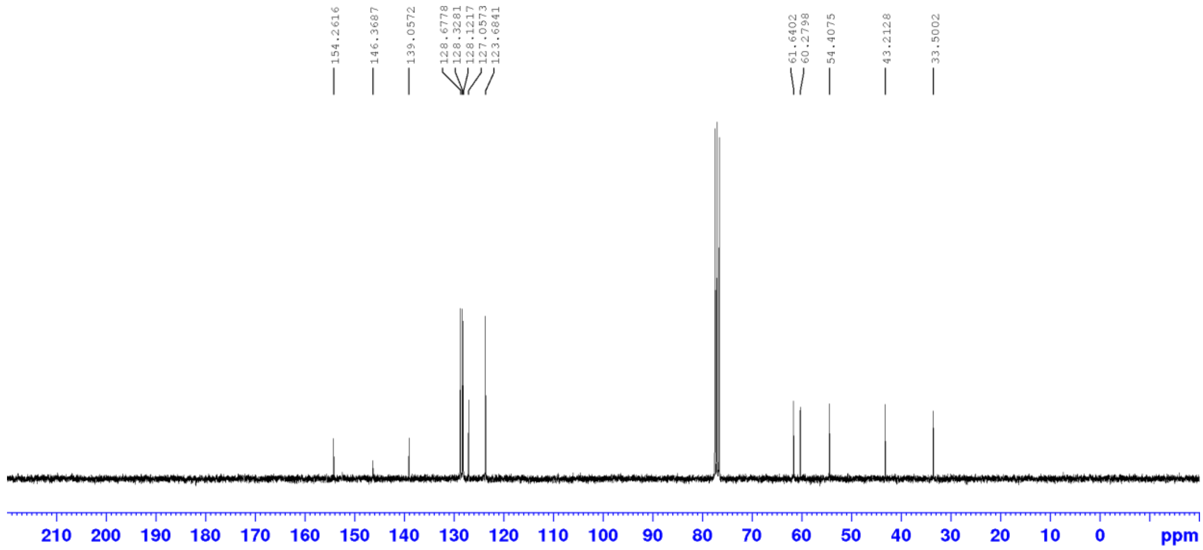
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.16-8.12 (m, 2H), 7.46-7.23 (m, 7H), 3.71 (d, *J* 13.0 Hz, 1H), 3.66 (d, *J* 12.9 Hz, 1H), 3.49-3.39 (m, 1H), 2.93 (dd, *J* 8.0 Hz, 7.7 Hz, 1H), 2.87-2.80 (m, 1H), 2.76-2.68 (m, 1H), 2.93 (dd, *J* 6.0 Hz, 6.3 Hz, 1H), 2.44-2.33 (m, 1H), 1.92-1.80 (m, 1H).

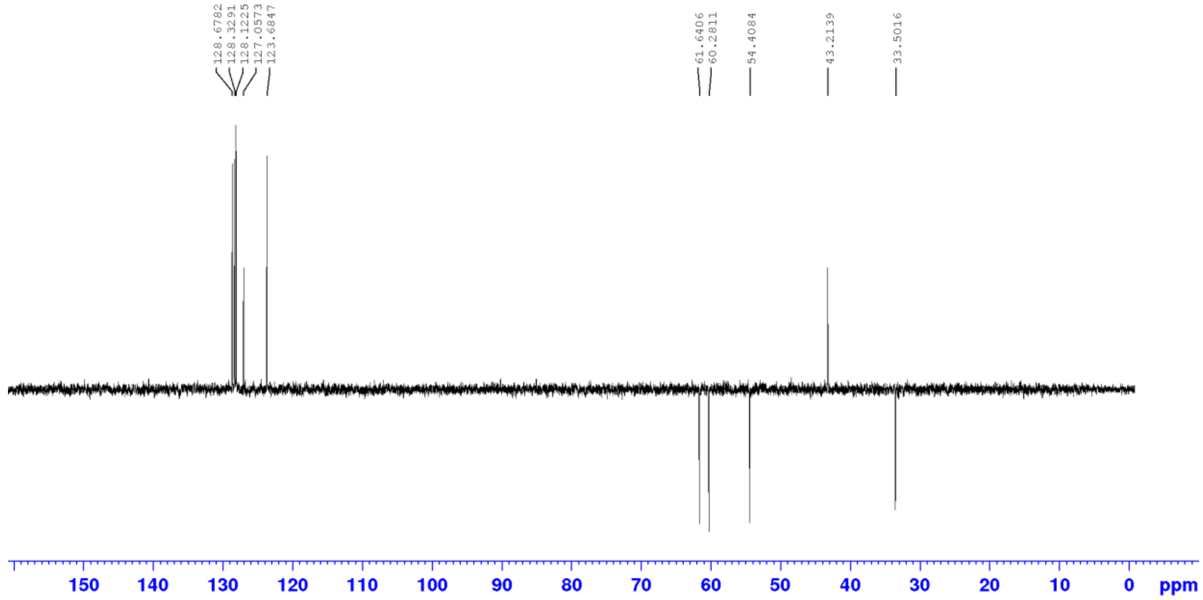
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 154.3 (1C), 146.4 (1C), 139.1 (1C), 128.7 (2CH), 128.3 (2CH), 128.1 (2CH), 127.0 (1CH), 123.7 (2CH), 61.6 ($1CH_2$), 60.3 ($1CH_2$), 54.4 ($1CH_2$), 43.4 (1CH), 33.2 ($1CH_2$).

IR ν_{max} (thin film, cm^{-1}): 3062 (C-H, Ar)3029 (C-H, Ar), 2960 (C-H), 2917 (C-H), 2788 (C-H), 2734 (C-H), 1451 (Ar), 1515 (N-O), 1342 (N-O).

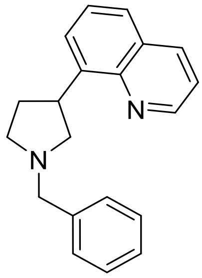
HRMS *m/z* (ESI$^+$) calculated for $C_{17}H_{18}N_2O_2$ $[M+H]^+$: 283.1441, found 283.1436.







3-(8-quinlone)-1-benzylpyrrolidine (**62i**)



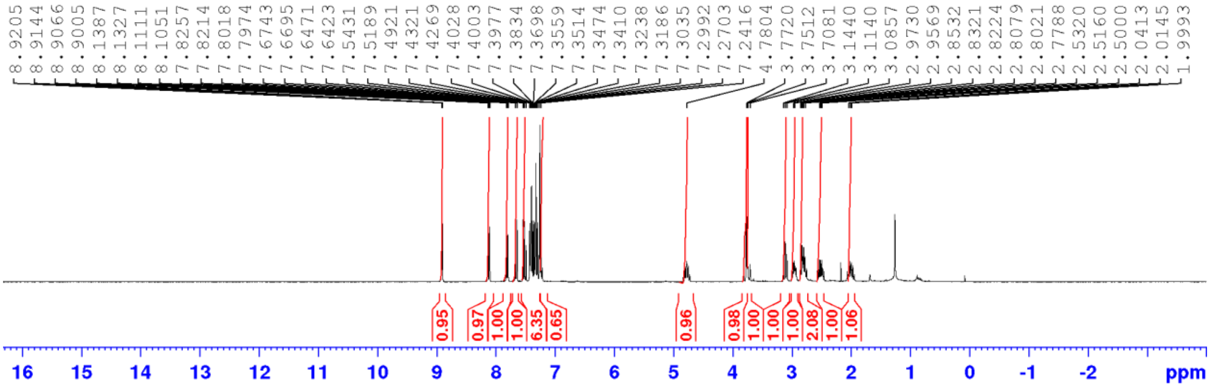
Chemical Formula: $C_{20}H_{20}N_2$
Molecular Weight: 288.39

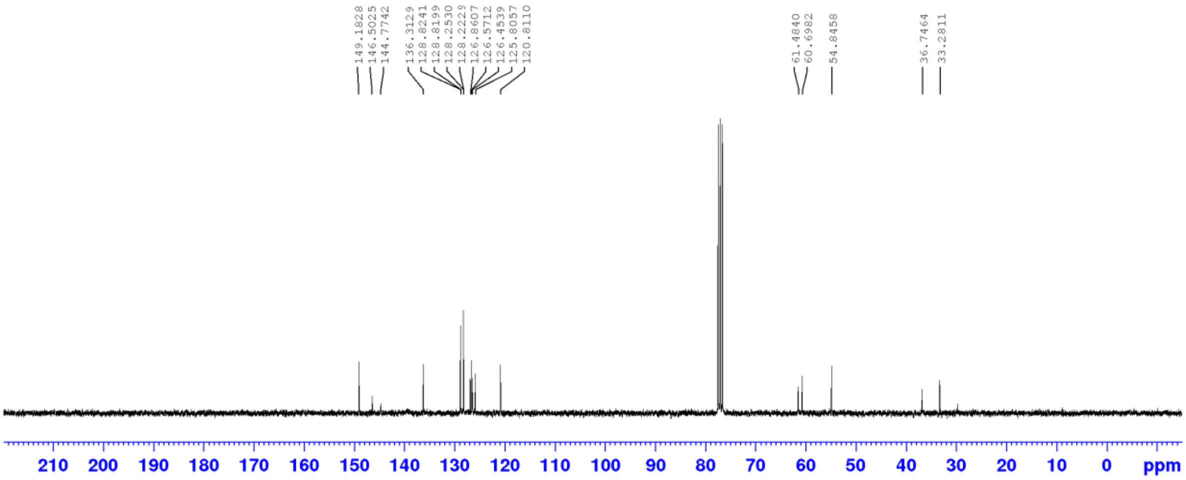
Following general procedure 2, using 8-bromoquinoline, the title compound **62i** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 18:1 to neat DCM to gradient DCM:7N NH_3 in MeOH, 99.5:0.5 to 95:5 v/v), as a dark orange oil (209 mg, 29%).

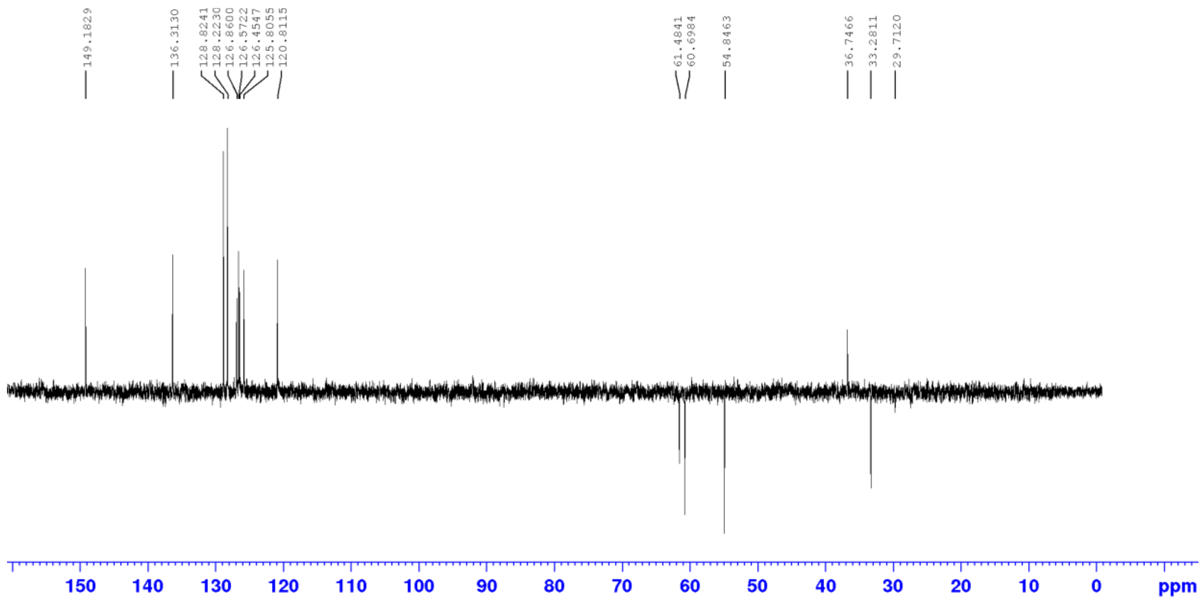
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.91 (dd, *J* 4.2 Hz, 4.3 Hz, 1H), 8.12 (dd, *J* 8.3 Hz, 8.3 Hz, 1H), 7.81 (dd, *J* 6.9 Hz, 7.3 Hz, 1H), 7.66 (dd, *J* 8.3 Hz, 8.0 Hz, 1H), 7.54-7.21 (m, 6H), 4.83-4.73 (m, 1H), 3.79 (d, *J* 13.0 Hz, 1H), 3.73 (d, *J* 13.0 Hz, 1H), 3.11 (dd, *J* 9.0 Hz, 9.0 Hz, 1H), 3.00-2.93 (m, 1H), 2.85-2.75 (m, 2H), 2.57-2.46 (m, 1H), 2.07-1.95 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 149.2 (1CH), 146.5 (1C), 144.8 (1C), 136.3 (1CH), 128.8 (2CH), 128.8 (1C), 128.3 (1C), 128.2 (2CH), 126.9 (1CH), 126.6 (1CH), 126.5 (1CH), 125.8 (1CH), 61.5 (1CH_2), 60.7 (1CH_2), 54.8 (1CH_2), 36.7 (1CH), 33.3 (1CH_2), 29.7 (1CH_2).

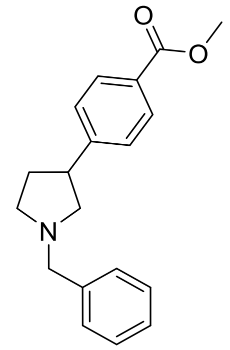
IR ν_{max} (thin film, cm^{-1}): 3058 (C-H, Ar), 3029 (C-H, Ar), 2954 (C-H), 2919 (C-H), 2783 (C-H), 2730 (C-H), 2113 (C=N), 1496 (Ar), 1370 (C-N).







3-(methylbenzonate)-1-benzylpyrrolidine (**62j**)



Chemical Formula: $C_{19}H_{21}NO_2$
Molecular Weight: 295.38

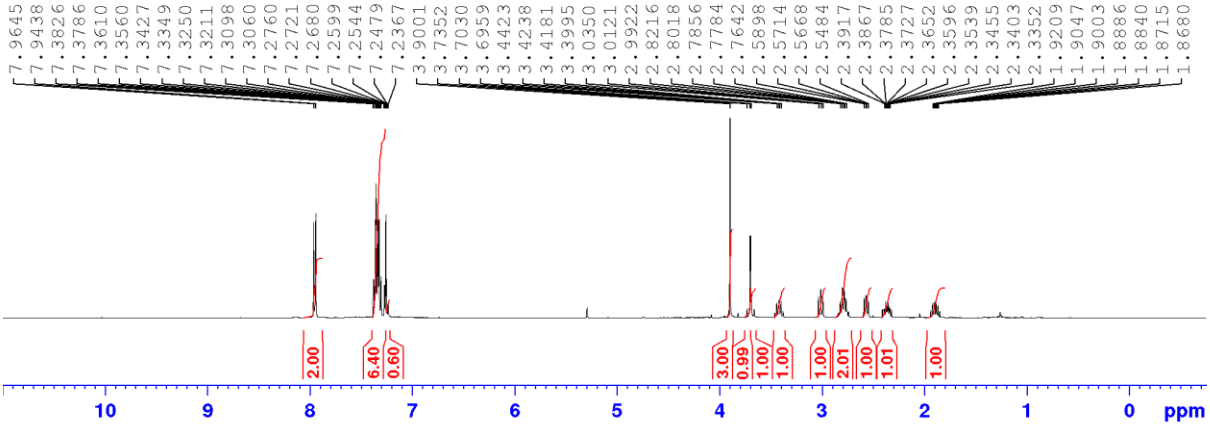
Following general procedure 2, using 4-bromo methylbenzoate, the title compound **62j** was isolated by column chromatography (Conditions: 50 g silica, gradient DCM:EtOAc, 18:1 to neat DCM to gradient DCM:7N NH_3 in MeOH, 99.5:0.5 to 95:5 v/v), as a dark orange oil (587 mg, 79%).

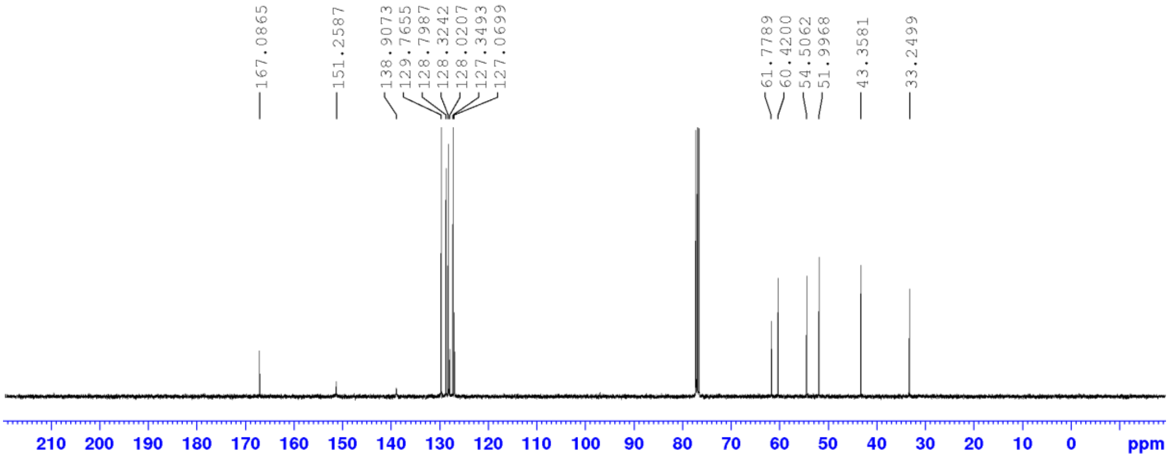
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.95 (d, *J* 8.3 Hz, 2H), 7.38-7.23 (m, 7H), 3.90 (s, 3H), 3.72 (d, *J* 13.0 Hz, 1H), 3.68 (d, *J* 13.0 Hz, 1H), 3.46-3.38 (m, 1H), 3.01 (dd, *J* 8.0 Hz, 8.2 Hz, 1H), 2.84-2.74 (m, 2H), 2.57 (dd, *J* 7.0 Hz, 7.4 Hz, 1H), 2.41-2.32 (m, 1H), 1.94-1.85 (m, 1H).

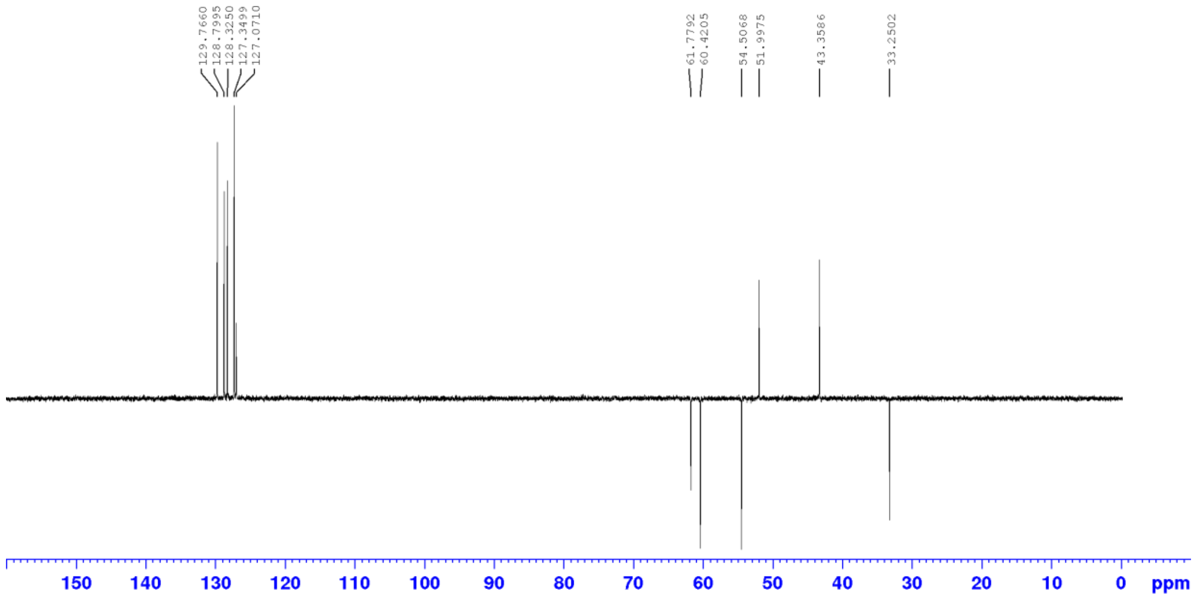
^{13}C NMR (CDCl$_3$, 100 MHz) δ_C 167.1 (1C), 152.3 (1C), 138.9 (1C), 129.8 (2CH), 128.8 (2CH), 128.3 (2CH), 128.0 (1C), 127.3 (2CH), 127.1 (1CH), 61.8 (1CH$_2$), 60.4 (1CH$_2$), 54.5 (1CH$_2$), 52.0 (1CH$_3$), 43.4 (1CH), 33.2 (1CH$_2$).

IR ν_{max} (thin film, cm^{-1}): 3062 (C-H, Ar), 3029 (C-H, Ar), 2950 (C-H), 2929 (C-H), 2796 (C-H), 1718 (C=O), 1435 (Ar), 1275 (C-O).

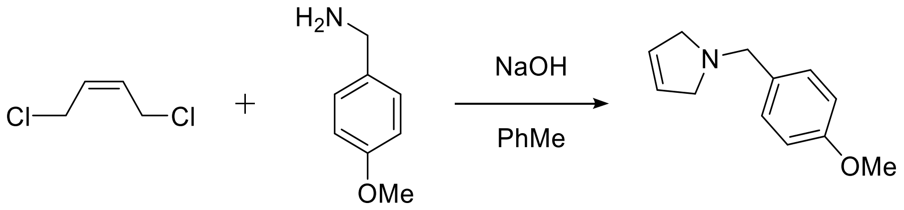
HRMS *m/z* (ESI$^+$) calculated for $C_{19}H_{21}NO_2$ [M+H]$^+$: 296.1645, found 296.1635.





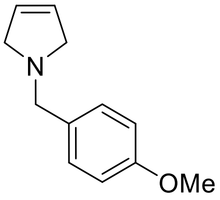


9.2.3 Synthesis of N-PMB pyrroline[58]



(*Z*)-1,4-dichlorobut-2-ene (1.58 mL) and 4-methoxylbenzylamine (7.06 mL) were dissolved in toluene (7 mL). 50% (w/w) aq. NaOH (0.92 mL) was added the and reaction mixture was stirred at room temperature overnight. After 15 hours water (30 mL) was added and the crude product was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield the crude product (5.131 g). The crude product was purified by column chromatography hexane/EtOAc (1:1) to yield the pure product.

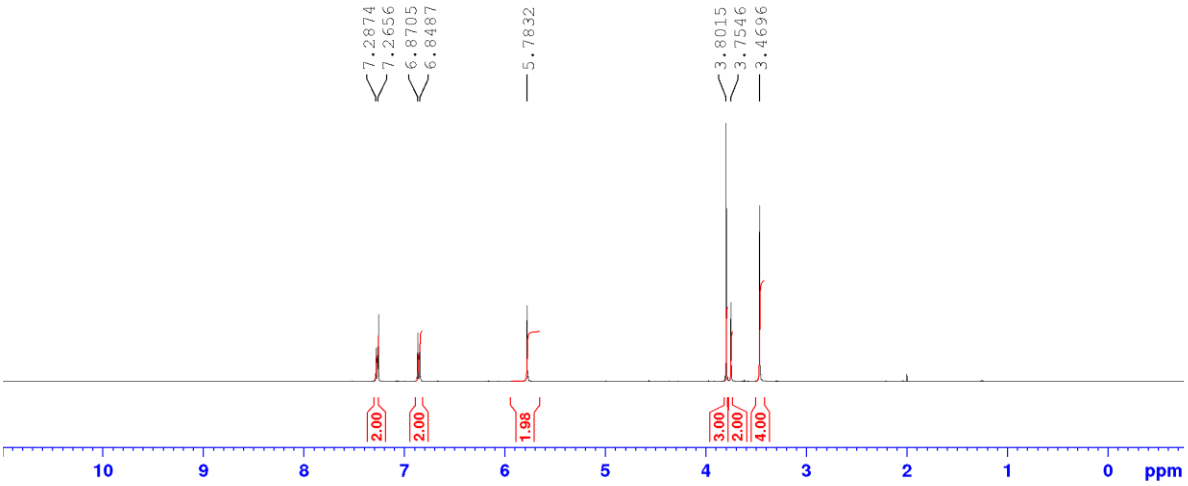
1-(4-methoxybenzyl)-pyrroline (**60c**)



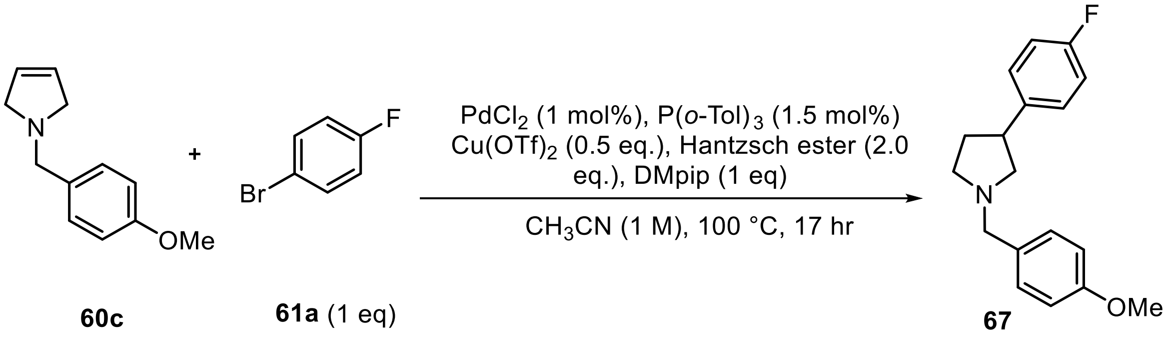
Chemical Formula: $C_{12}H_{15}NO$
Molecular Weight: 189.26

60c was isolated as a dark orange/yellow oil (2.138 g, 75%).

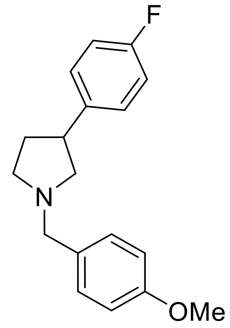
^{1}**H NMR** ($CDCl_3$, 400 MHz) δ_H 7.28 (d, *J* 8.8 Hz, 2H), 6.86 (d, *J* 8.8 Hz, 2H), 5.78 (s, 2H), 3.80 (s, 3H), 3.75 (s, 2H), 3.47 (s, 4H).



9.2.4 Application of the reductive Heck system to N-PMB pyrroline



3-(4-fluorophenyl)-1-*p*-methoxybenzylpyrrolidine (**67**)

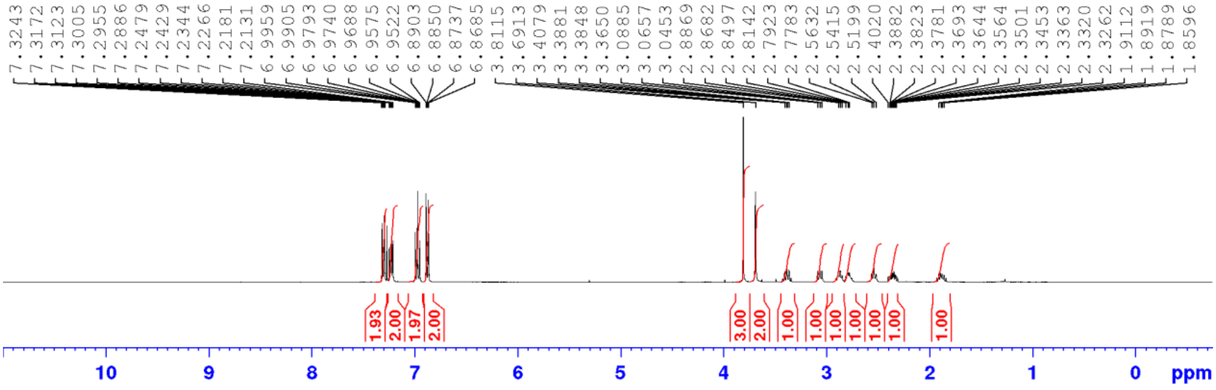


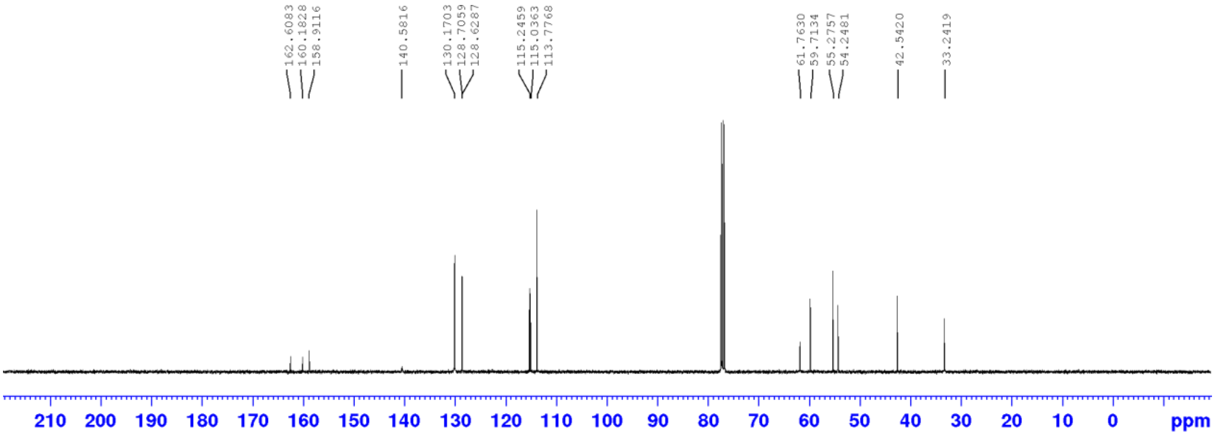
Chemical Formula: $C_{18}H_{20}FNO$
Molecular Weight: 285.36

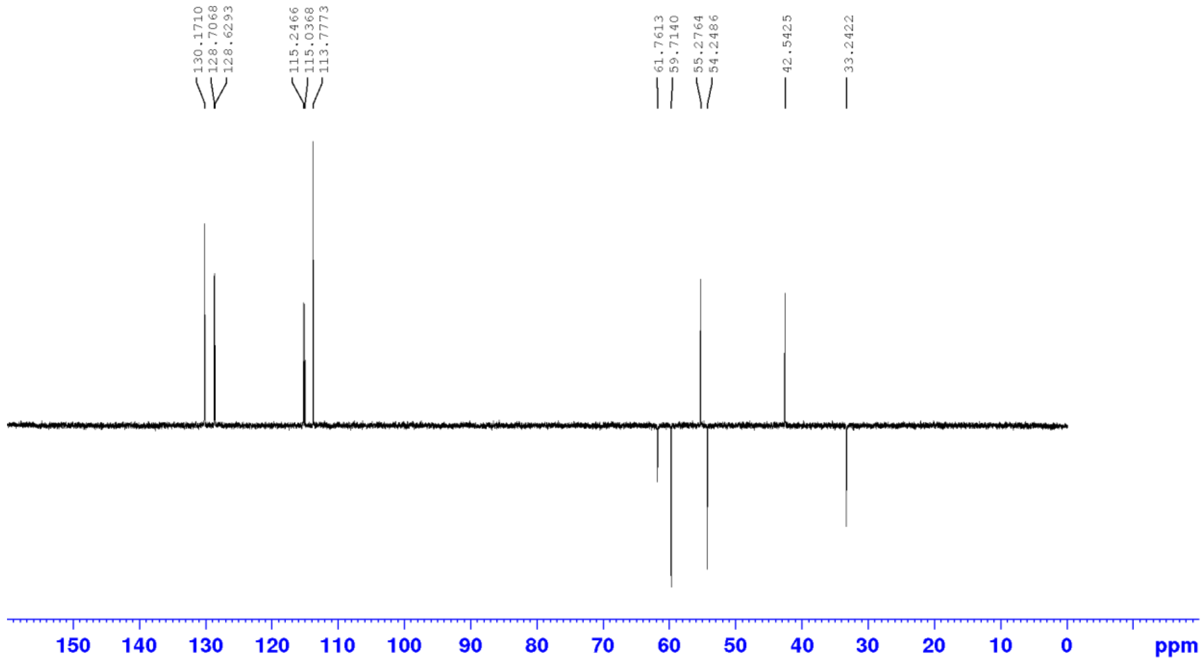
Using 4-fluorobromobenzene and N-PMB pyrroline, under the optimised general procedure for the reductive Heck reaction of N-benzyl-3-pyrroline, the title compound **67** was isolated by column (Conditions: 100 g silica, gradient DCM:EtOAc, 18:1 to neat DCM to gradient DCM:7N NH_3 in MeOH, 99.5:0.5 to 95:5 v/v), as an orange oil (140 mg, 20%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.31 (d, *J* 8.8 Hz, 2H), 7.38-7.23 (dd, *J* 5.5 Hz, *J* 5.5 Hz, 2H), 3.81 (s, 3H), 3.69 (s, 2H), 3.42-3.35 (m, 1H), 3.07 (dd, *J* 8.0 Hz, 8.2 Hz, 1H), 2.91-2.85 (m, 1H), 2.81-2.76 (m, 1H), 2.54 (dd, *J* 8.4 Hz, 8.4 Hz, 1H), 2.40-2.31 (m, 1H), 1.93-1.84 (m, 1H).

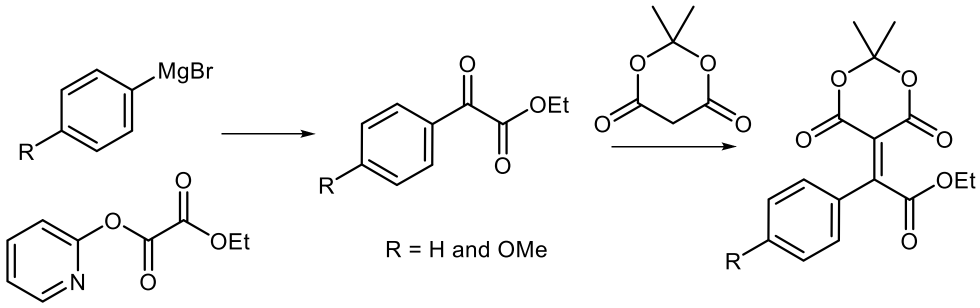
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 162.6 (1C), 160.2 (1C), 158.9 (1C), 140.6 (1C), 130.2 (2CH), 128.7 (1CH), 128.6 (1CH), 115.2 (1CH), 115.0 (1CH), 113.8 (2CH), 61.8 (1CH_2), 59.7 (1CH_2), 55.3 (1CH_3), 54.3 (1CH_2), 42.5 (1CH), 33.2 (1CH_2).



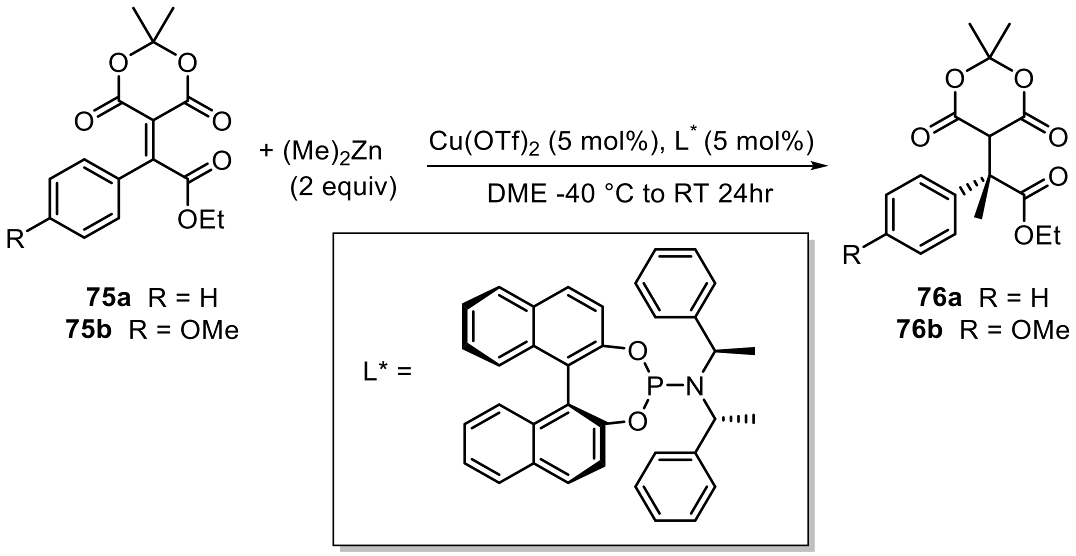




9.3 Chiral Succinimides



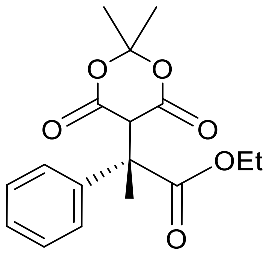
Alkylidene Meldrum's acids **75a** and **b** were supplied at the start of the project and had been synthesised using aryl Grignard's that were reacted with ethyl 2-pyridinyl oxalate to form ethyl arylglyoxylates which can undergo a Knoevenagel condensation with Meldrum's acid. The resulting alkylidene Meldrum's acids were then carried on in the synthetic route following Wilsily and co-worker's methods.[63]



9.3.1 General procedure 4: Conjugate 1,4-addition of Me_2Zn to alkylidene Meldrum's acids (75a and b)[63]

An alkylidene Meldrum's acids (1.0 eq.) solution in anhydrous DME (10 mL) was added to an oven dried RBF. Under an argon blanket $Cu(OTf)_2$ (5 mol %) and phosphoramidite chiral ligand (5 mol %) were weighed out and added to the reaction mixture. Anhydrous DME (2 mL) was used to wash down the sides of the RB flask and the reaction mixture was stirred under nitrogen at RT before being cooled to -40˚C. $(Me)_2Zn$ (2.0 eq.) was added dropwise to the reaction mixture and the resulting solution was stirred for a further 30 mins. The reaction mixture was allowed to warm up to RT and stirred for a further 24 hours. After 24 hours aqueous HCl (5% v/v, 25 mL) and Et_2O (25 mL) were added to the reaction mixture. The aqueous layer was separated and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

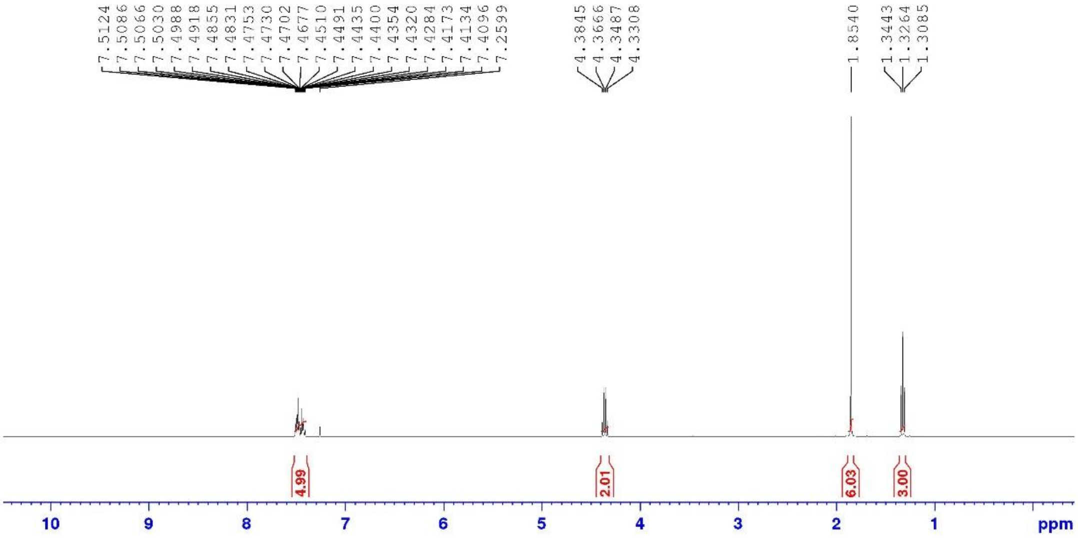
(S)-Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpropanoate (**76a**)



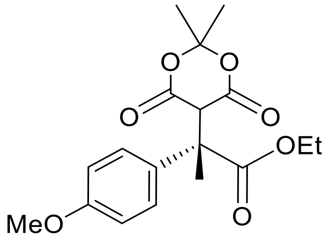
Chemical Formula: $C_{17}H_{20}O_6$
Molecular Weight: 320.34

Using general procedure 4, Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-phenylacetate (0.5519, 1 eq.) and $(Me)_2Zn$ were reacted to afford the crude product as a white powder (0.6013 g) and was then used in the next step of the of the synthetic route. Data obtained matches previously reported data on this compound.[63]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.51- 7.26 (m, 5H), 4.36 (q, *J* 7.2 Hz, 2H), 1.85 (s, 6H), 1.33 (t, *J* 7.2 Hz, 2H).



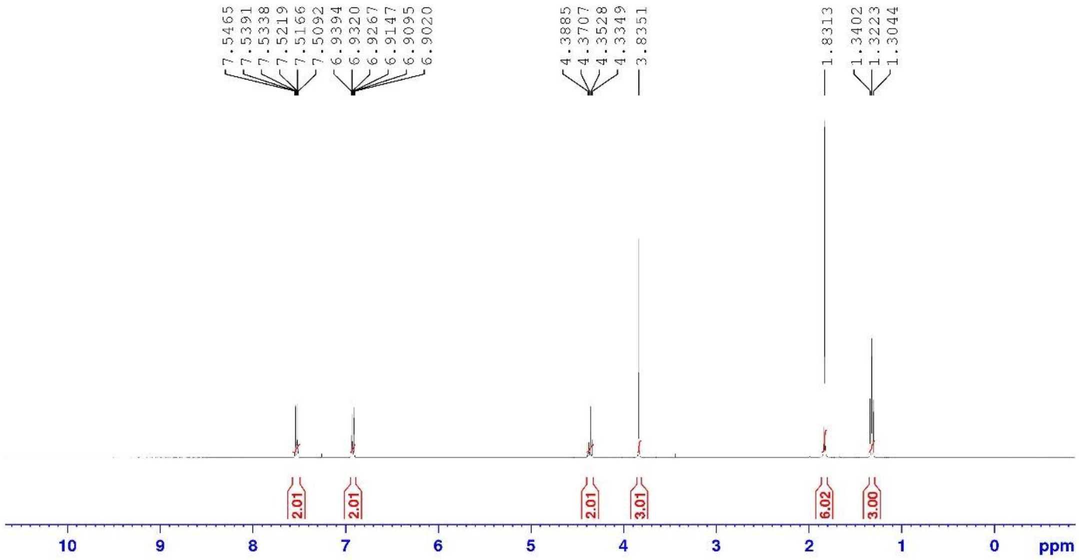
(S)-Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-(4-methoxyphenyl) propanoate (**76b**)



Chemical Formula: $C_{18}H_{22}O_7$
Molecular Weight: 350.37

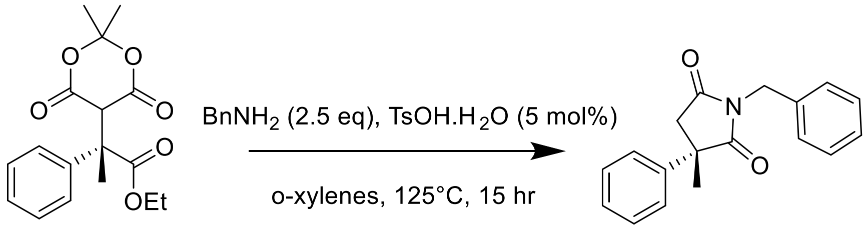
Using general procedure 4, Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-(4-methoxyphenyl) acetate (0.5499 g) and $(Me)_2Zn$ were reacted to afford the crude product as a cream white powder (0.6191 g) which was carried straight on to the next step in the reaction.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.55- 7.51 (m, 2H), 6.94- 6.90 (m, 2H), 4.36 (q, *J* 7.2 Hz, 2H), 3.84 (s, 3H), 1.83 (s, 6H), 1.32 (t, *J* 7.2 Hz, 2H).

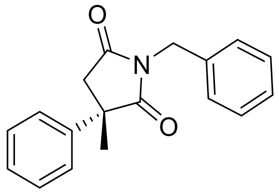


9.3.2 Synthesis of chiral succinimides by cyclisation

Successful cyclisation of (S)-Ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpropanoate with benzylamine using Wilsily and co-worker’s method.[63]



(S)-1-Benzyl-3-methyl-3-phenylpyrrolidine-2,5-dione

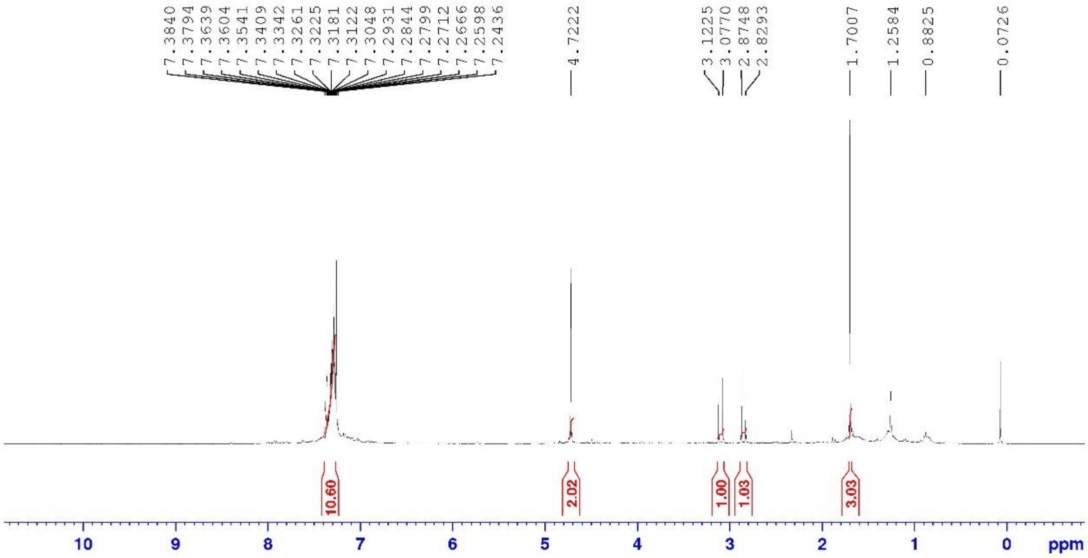


Chemical Formula: $C_{18}H_{17}NO_2$
Molecular Weight: 279.34

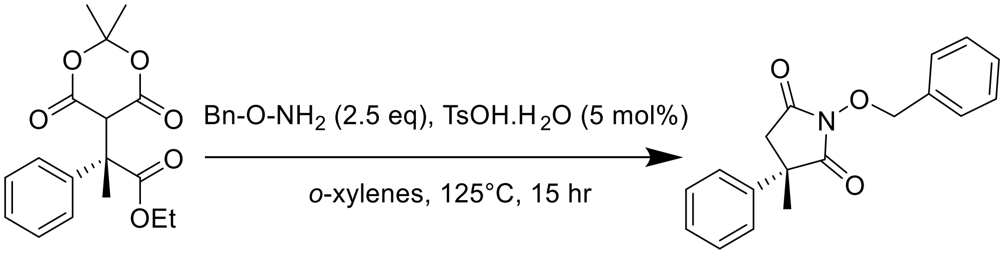
$BnNH_2$ (0.12 mL, 2.5 eq.) was added to a solution of (S)-ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpropanoate (0.1018 g, 1.0 eq.) in *o*-xylene (2.5 mL). At room temperature $TsOH.H_2O$ (4.3 mg, 0.05 eq.) was added the reaction mixture was heated to 125 °C and stirred for 15 hours. The sample was heated to 100 °C and had N_2 blown over it to evaporate *o*-xylene to yield crude product as a dark orange oil (55 mg).

Data obtained matches previously reported data on this compound.[63]

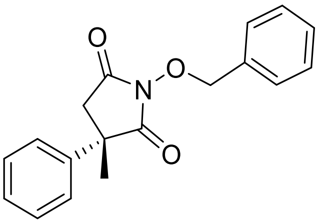
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.38- 7.24 (m, 10H), 4.72 (s, 2H), 3.10 (d, *J* 18.2 Hz, 2H), 2.85 (d, *J* 18.2 Hz, 2H), 1.70 (s, 3H).



9.3.3 Adapting Wilsily and coworkers method using O-hydroxybenzylamine[63,64]



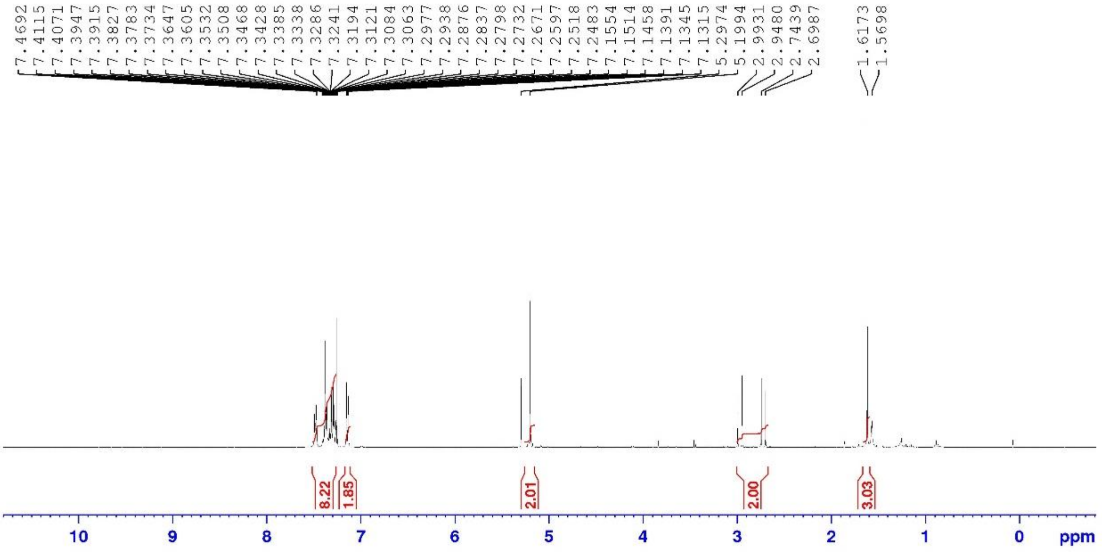
(S)-3-methyl-3-phenyl-N-(benzyloxy) succinimide (**77a**)



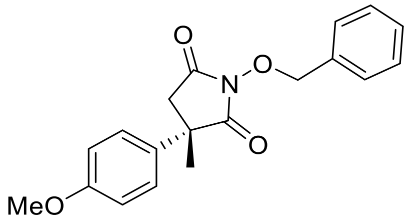
Chemical Formula: $C_{18}H_{17}NO_3$
Molecular Weight: 295.34

$BnONH_2$ (0.36 mL, 2.5 eq.) was added to a solution of crude (S)-ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpropanoate (0.427 g, 1.0 eq.) in *o*-xylene (10 mL). At room temperature TsOH.H_2O (12 mg, 0.05 eq.) added the reaction mixture was heated to 125 °C and stirred for 15 hours. After 15 hours $BnONH_2$ (1 eq.) was added and the reaction mixture was stirred for a further 15 hours at 125°C. After 15 hours the reaction mixture was heated at 100 °C and had N_2 blown over it to evaporate *o*-xylene. The crude product was purified by column chromatography using DCM:Hexanes (80:20) to yield the product as an orange/brown oil (148 mg, 40%) which was carried straight on to the next step in the synthetic route.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.47- 7.13 (m, 10H), 5.20 (s, 2H), 2.97 (d, *J* 18.2 Hz, 1H), 2.72 (d, *J* 18.2 Hz, 1H), 1.62 (s, 3H).



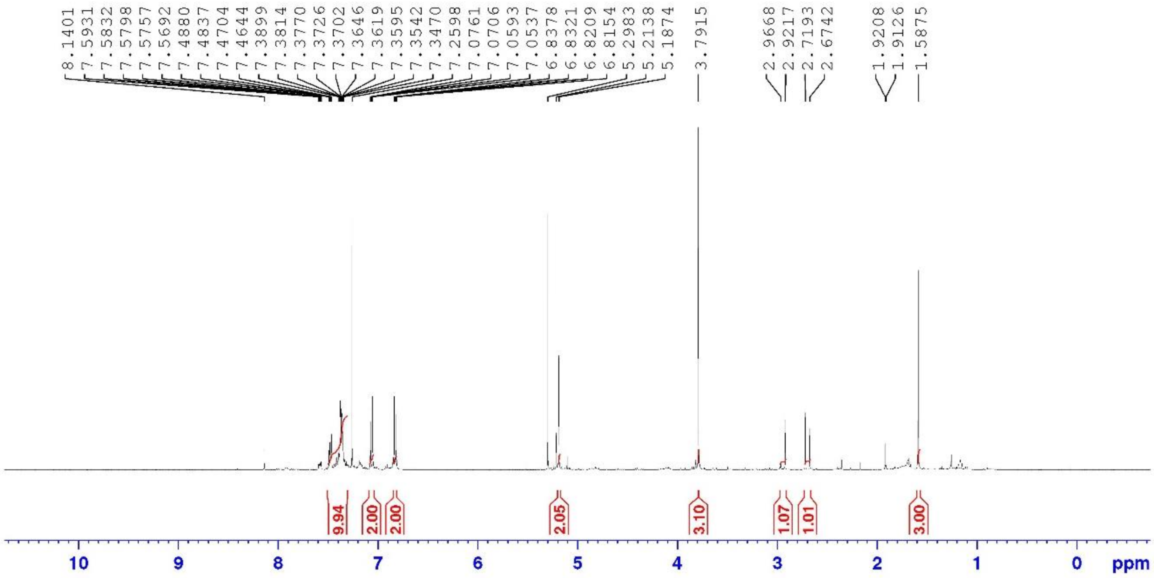
(S)-3-methyl-3-(4-methoxyphenyl)-N-(benzyloxy)-succinimide (**77b**)



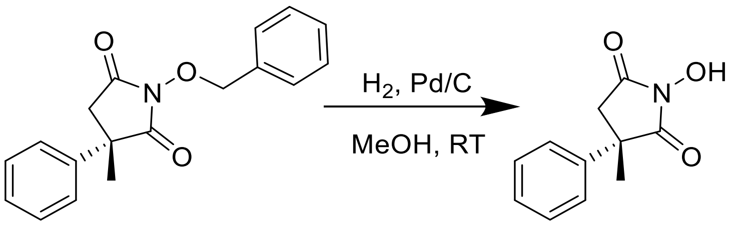
Chemical Formula: $C_{19}H_{19}NO_4$
Molecular Weight: 325.36

$BnONH_2$ (0.52 mL, 2.5 eq.) was added to a solution of crude (S)-ethyl 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenylpropanoate (0.6191 g, 1.0 eq.) in *o*-xylene (25 mL). At room temperature TsOH.H_2O (18 mg, 0.05 eq.) was added the reaction mixture was heated to 125 °C and stirred for 24 hours. After 24 hours $BnONH_2$ (1 eq.) was added and the reaction mixture was stirred for a further 15 hours at 125°C. After 15 hours the reaction mixture was heated at 100 °C and had N_2 blown over it to evaporate *o*-xylene yielding the crude product (0.715 g) which was checked by ^1H NMR before being carried on straight on to the next step.

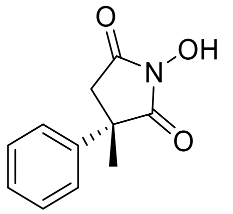
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.59- 7.35 (m, 10H), 7.08- 7.05 (m, 2H), 6.84- 6.82 (m, 2H), 5.19 (s, 2H), 3.79 (s, 3H), 2.94 (d, *J* 18.2 Hz, 1H), 2.70 (d, *J* 18.2 Hz, 1H), 1.59 (s, 3H).



Hydrogenolysis of benzyl group following Dixon and co-worker's route[64]



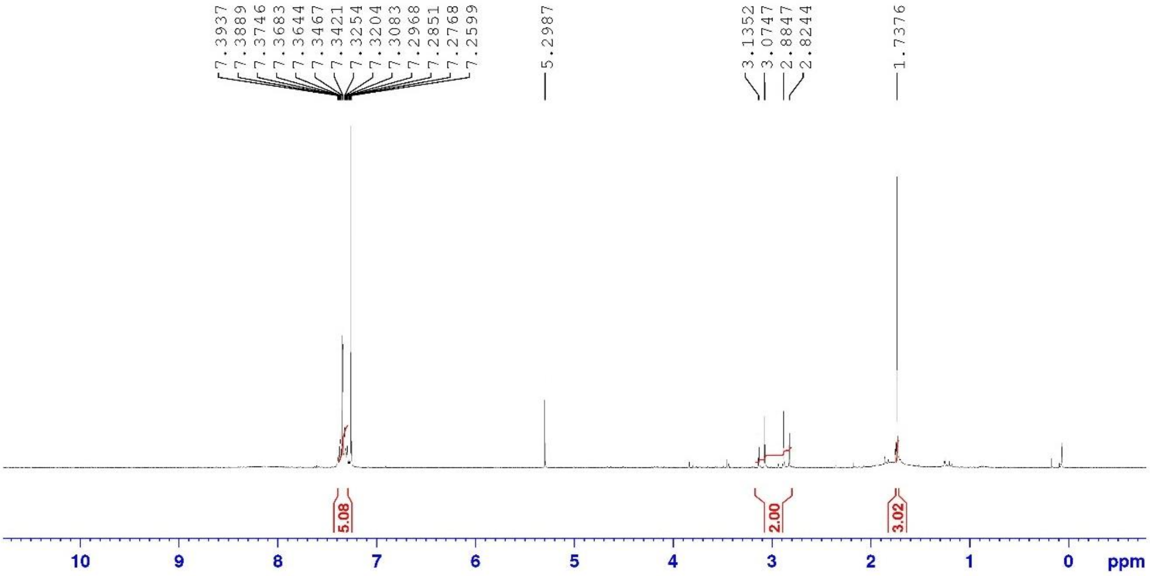
(S)-3-methyl-3-phenyl-N-hydroxysuccinimide (**78a**)



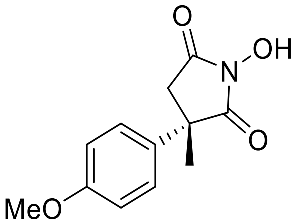
Chemical Formula: $C_{11}H_{11}NO_3$
Molecular Weight: 205.21

(S)-3-methyl-3-phenyl-N-(benzyloxy) succinimide (148 mg, 1 eq.), was dissolved in MeOH (10 mL). 10 wt. % Pd/C (56mg, 10 mol%) was added and the reaction mixture was stirred for 30 minutes before being placed under an atmosphere of H_2 and the reaction was left to stir overnight. The crude product was filtered through a celite cake, and the solvent was removed under vacuum to yield the crude product (107 mg) which was carried straight on to the next step in the synthesis.

^{1}**H NMR** ($CDCl_3$, 400 MHz) δ_H 7.39- 7.28 (m, 5H), 3.10 (d, J 18.1 Hz, 1H), 2.86 (d, *J* 18.1 Hz, 1H), 1.74 (s, 3H).



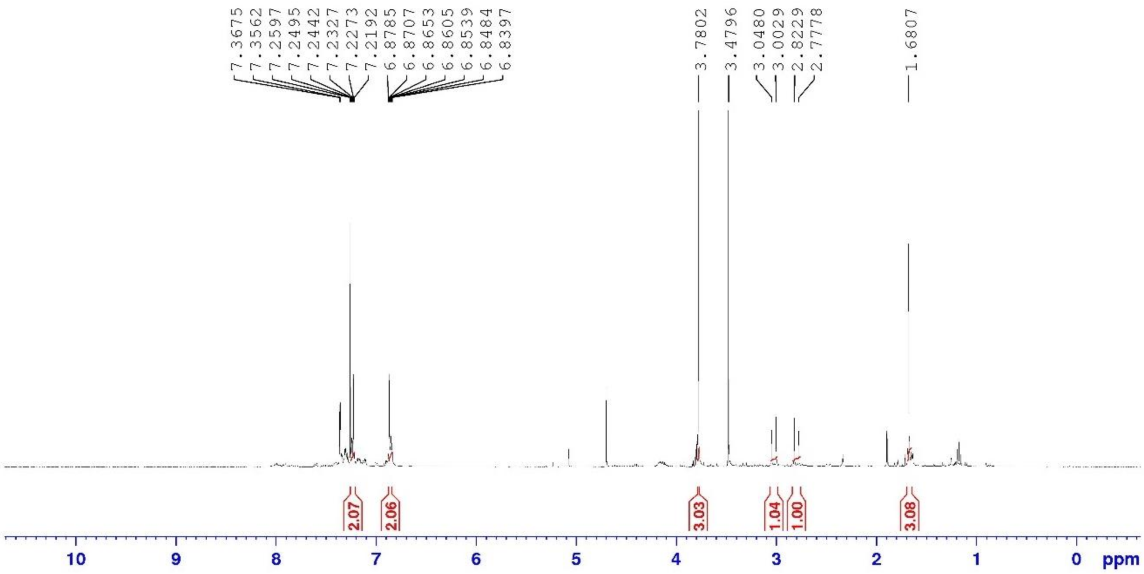
(S)-3-methyl-3-(4-methoxyphenyl)-N-hydroxysuccinimide (**78b**)



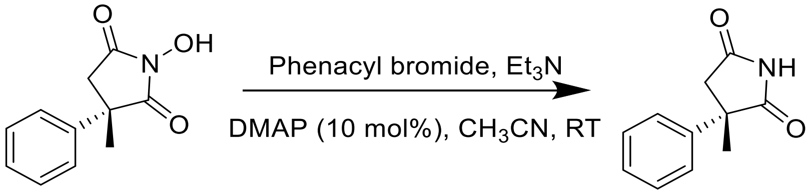
Chemical Formula: $C_{12}H_{13}NO_4$
Molecular Weight: 235.24

(S)-3-methyl-3-(4-methoxyphenyl)-N-(benzyloxy)-succinimide (0.715 g, 1 eq.), was dissolved in MeOH (50 mL). 10 wt. % Pd/C (80 mg, 3 mol%) was added and the reaction mixture was stirred for 30 minutes before being placed under an atmosphere of H_2 and the reaction was left to stir overnight. The crude product was filtered through a celite cake, and the solvent was removed under vacuum to yield the crude product (461 mg). Which following NMR analysis was not purified and instead carried on to the next step in the synthesis.

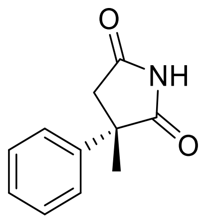
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.37-7.22 (m, 2H), 6.88-6.84 (m, 2H), 3.78 (s, 3H) 3.03 (d, *J* 18.1 Hz, 1H), 2.80 (d, *J* 18.1 Hz, 1H), 1.68 (s, 3H).



Removal of hydroxyl group by nucleophilic cleavage of a phenacyl ether following Dixon and co-worker's route[64]



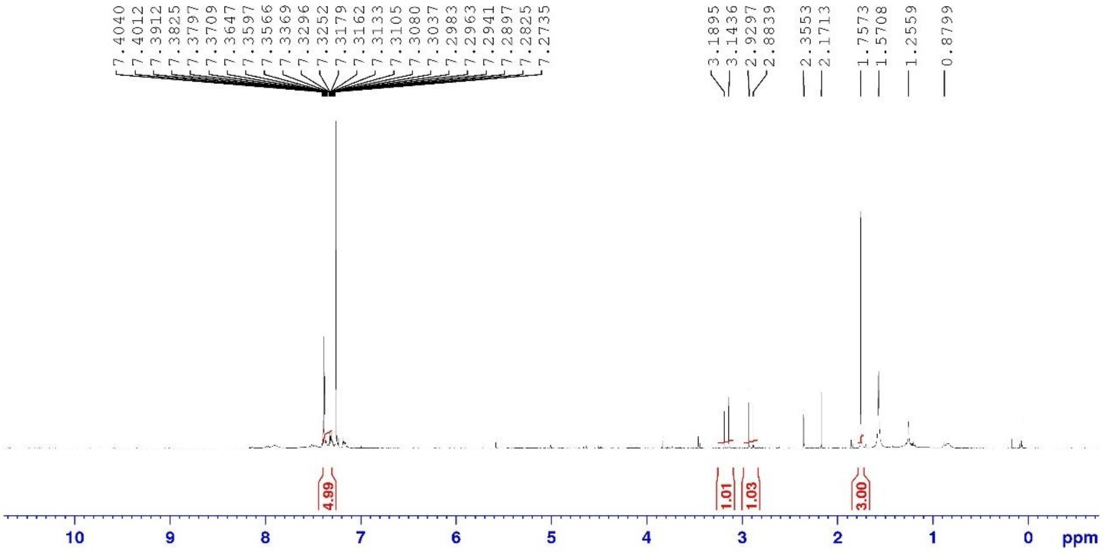
(S)-3-methyl-3-phenyl-succinimide (**79a**)



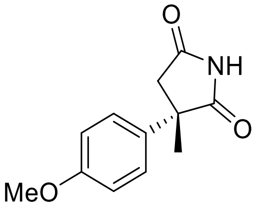
Chemical Formula: $C_{11}H_{11}NO_2$
Molecular Weight: 189.21

(S)-3-methyl-3-phenyl-N-hydroxysuccinimide (95 mg, 1 eq.) was dissolved in CH_3CN (20 mL). Phenacyl bromide (97 mg, 1 eq.) and Et_3N (65 µL, 1 eq.) were added before addition of DMAP (6 mg, 0.1 eq.). The reaction mixture was stirred at RT overnight. The crude NMR showed that a column was required but indicated that desired product had been produced with the downfield shift of the geminal coupled CH_2 peak. The crude product was washed with 1M HCl (20 mL) and a saturated potassium bicarbonate solution (20 mL). The compound crashed out in toluene and therefore was triturated in toluene (3 x 25 mL) at reflux to extract maximum product in toluene. The organic layers were combined, and solvent was removed by rotary evaporation. The compound was purified by column chromatography (4:1 Petroleum ether:EtOAc) to obtain the pure product (53 mg, 16% yield over 3 steps, based on overall cyclisation and deprotection steps from Meldrum's acid adducts, as all crude products were carried on to each relevant next step once checked by NMR).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.40- 7.27 (m, 5H), 3.17 (d, *J* 18.3 Hz, 1H), 2.90 (d, *J* 18.3 Hz, 1H), 1.76 (s, 3H).



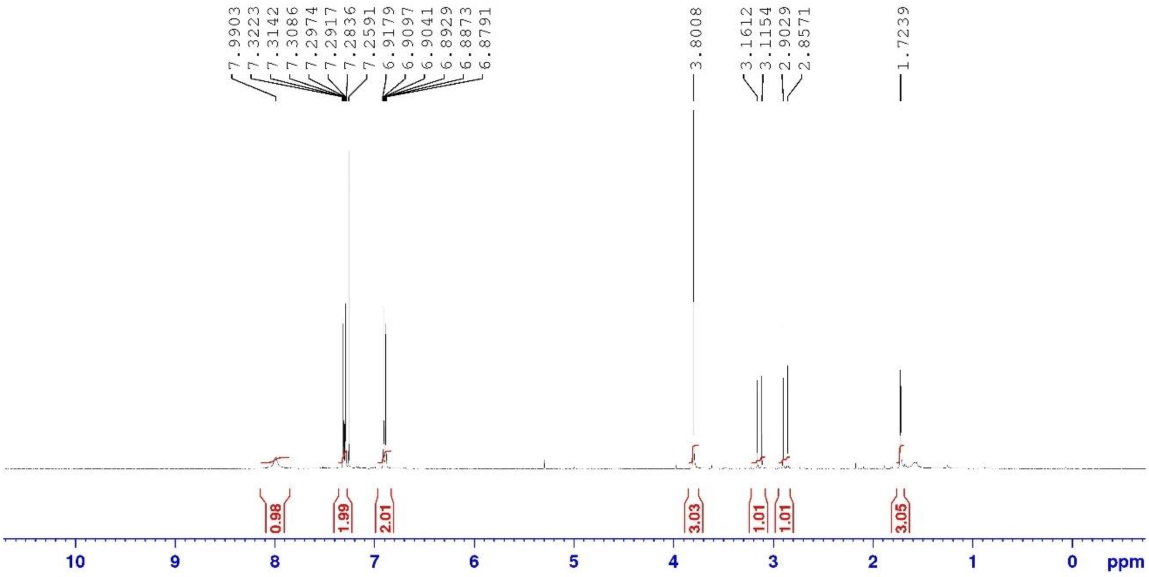
(S)-3-methyl-3-(4-methoxyphenyl)-succinimide (**79b**)



Chemical Formula: $C_{12}H_{13}NO_3$
Molecular Weight: 219.24

Crude (S)-3-methyl-3-(4-methoxyphenyl)-N-hydroxysuccinimide (0.461 g, 1 eq.) was dissolved in anhydrous CH_3CN (20 mL) and phenacyl bromide (0.398 g, 1eq.) and Et_3N (0.27 mL, 1eq.) were added before DMAP (0.0241 g, 0.1 eq.). The reaction mixture was then stirred at room temperature overnight before the solvent was removed in vacuo. The crude product (1.048 g) was purified by recrystallisation using 1:1 (hexane: diethyl ether). Pure product was a pale yellow/white solid (203 mg, 59% yield based on overall cyclisation and deprotection steps from Meldrum's acid adducts, as all crude products were carried on to each relevant next step once checked by NMR).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.99 (s, 1H), 7.32-7.28 (m, 2H), 6.92-6.88 (m, 2H), 3.80 (s, 3H), 3.14 (d, *J* 18.1 Hz, 1H), 2.88 (d, *J* 18.1 Hz, 1H), 1.72 (s, 3H).



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11. Appendix

Whilst completing my MRes I have also contributed to a Sweeney group paper which is currently still in progress before submission. This involved the synthesis and purification of a range of sulfinyl imines to be used in coupling reactions.