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Title:
Iridium-Catalysed Aryl CH Functionalisation with Alkenes

Branch-Selective Alkylation and Alkenylation

Iridium-Catalysed Aryl C–H Functionalisation with Alkenes: Branch-Selective Alkylation and Alkenylation

Phillippa Cooper

A thesis submitted to the University of Bristol in accordance with the requirements of the degree of Ph.D. in the Faculty of Science

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(**79,855** words)

Author's Declaration

I declare that the work described in this dissertation was carried out between September 2015 and November 2019, under the supervision of Professor John F. Bower in the School of Chemistry, University of Bristol. The work was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed:

Date:

Abstract

In Chapters 2 and 3 Ir(I)-catalysed methodology for the asymmetric hydroarylation of terminal alkenes is described. Initially an extensive screen of commercially available ligands was conducted to render a branch-selective alkene hydroarylation protocol previously developed at Bristol enantioselective. This study revealed ligand related reactivity trends, which enabled Dr. Simon Grélaud to design and synthesise a family of chiral bisphosphite ligands that promote highly enantioselective alkene hydroarylation with acetanilide substrates. Alongside Dr. Simon Grélaud, the protocol was expanded to thiophene substrates. Subsequently, investigations were directed towards the enantioselective alkylation of alternative heteroaromatic substrates. Excellent yields and highly promising levels of enantioselectivity have been achieved for styrene hydroarylation with pyrrole and furan moieties.

In Chapter 4 the scope of the Ir(I)-catalysed methodology is expanded to include 1,1-disubstituted alkenes. Challenging all-carbon quaternary centres have been generated in excellent yields and studies towards an enantioselective protocol have been undertaken. The mechanistic pathway has been investigated through deuterium labelling experiments and natural abundance ^{13}C KIE studies using the Singleton method. These results revealed a pathway unique to those previously determined at Bristol for Ir(I)-catalysed hydroarylation of mono-substituted alkenes.

In Chapter 5 an Ir(I)-catalysed method is presented for the α-selective C–H arylation of styrenes by dual C–H functionalisation. The chemistry relies upon an Ir(I)-catalyst modified with an electron-deficient ferrocene-based bisphosphine ligand. This reaction offers a regioisomeric alternative to the Pd-catalysed Heck and Fujiwara-Moritani reactions. The alkenylated products are useful moieties to rapidly build interesting *N*-containing heteroaromatics.

Publications arising from this work:

1. **P. Cooper**, G. E. M Crisenza, L. J. Feron and J. F. Bower; Iridium-Catalyzed α-Selective Arylation of Styrenes by Dual C–H Functionalization. *Angew. Chem. Int. Ed.* **2018**, *57*, 14198.

2. S. Grélaud, **P. Cooper**, L. J. Feron and J. F. Bower; Branch-Selective and Enantioselective Iridium-Catalyzed Alkene Hydroarylation via Anilide-Directed C–H Oxidative Addition. *J. Am. Chem. Soc.* **2018**, *140*, 9351.

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dazzling me with your fashion sense. I've forgiven you for that one time and I'm sure I'll continue to be 'a bit all over the place'. Tim, thank you for all the excellent coffees you eventually made me, and I feel very privileged to have been a part of your first ever BBQ. James, you were a great addition to the Lonely Bowass. I miss your honest responses and I'm glad me and Olivia softened your heart – you loved a hug in the end. Ian, you were a great character in the lab and gave me lots of topics to debate (even if you got too into them and your nose bled sometimes). Gangwei, thank you for being so lovely and it was a true pleasure to have you there throughout most of my PhD.

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Finally, I would like to thank my Mum and sisters, Charlotte and Harriette, for their unconditional love and support.

Table of Contents

Abbreviations

acac	acetylacetone
Ad	adamantyl
aq.	aqueous
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Boc	*tert*-butoxylcarbonyl
cod	1,4-cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
DABCO	1,4-diazabicyclooctane
dba	dibenzylideneacetone
1,2-DCB	1,2-dichlorobenzene
DCE	1,2-dichloroethane
DCT	3,4-dichlorotoluene
d^Fppb	1,4-bis(di(pentafluorophenyl)phosphino)butane
dppo	1,8-bid(diphenylphosphino)octane
DG	directing group
DMBP	bis(4-methoxyphenyl)methanone
DME	1,2-dimethoxyethane (glyme)
DMEDA	1,2-dimethylethylenediamine
DMPU	*N*,*N*′-dimethylpropyleneurea
dppb	1,4-bis(diphenylphosphino)butane
dppm	1,1-bis(diphenylphosphino)methane
dppf	1,1’-ferrocenediyl-bis(diphenylphosphine)
DFT	density functional theory
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.r.	enantiomeric ratio
e.s.	enantiomeric specificity
FCC	flash column chromatography
KIE	kinetic isotope effect
Mes	mesityl
PMP	*p*-methoxyphenyl

pin	pinacolato
rac	racemic
SFC	supercritical fluid chromatography
SPINOL	1,1′-spirobiindane-7,7′-diol
TBAB	*tetra*-*n*-butylammonium bromide
TBAF	*tetra*-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilyl
ZPE	zero-point energy

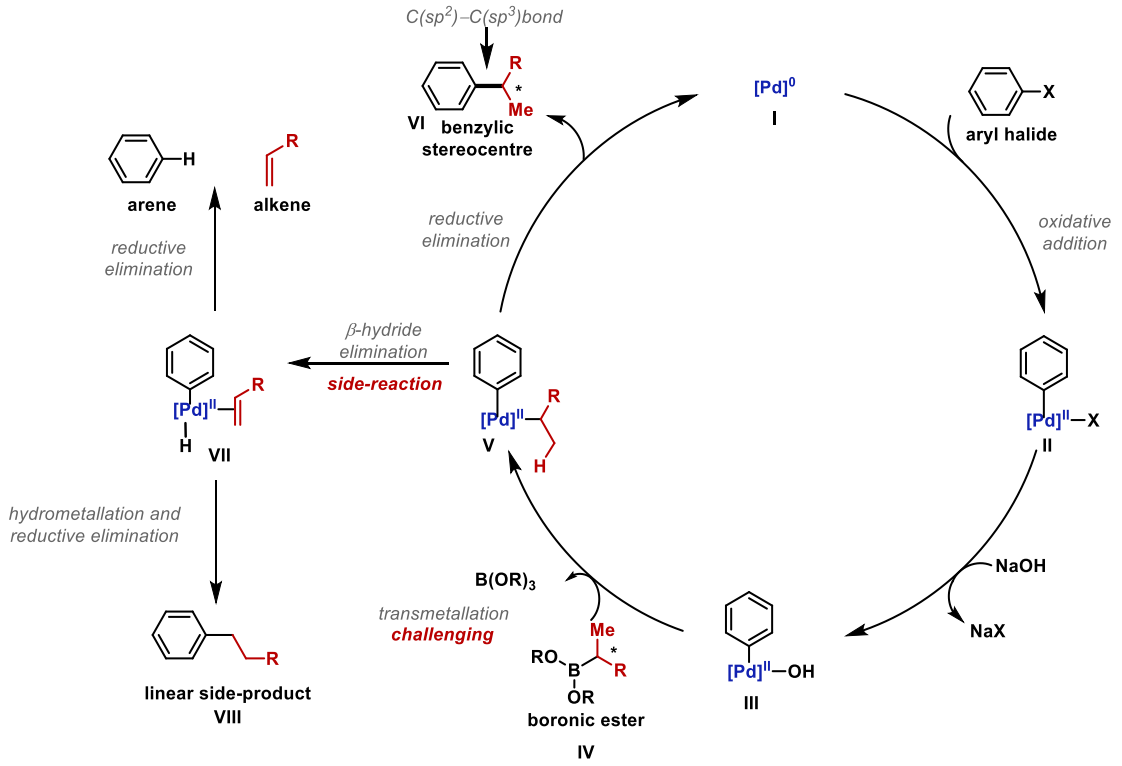
Standard abbreviations are not specified here.

Chapter 1 – Introduction

1.1 – The Importance of Tertiary Benzylic Stereocentres

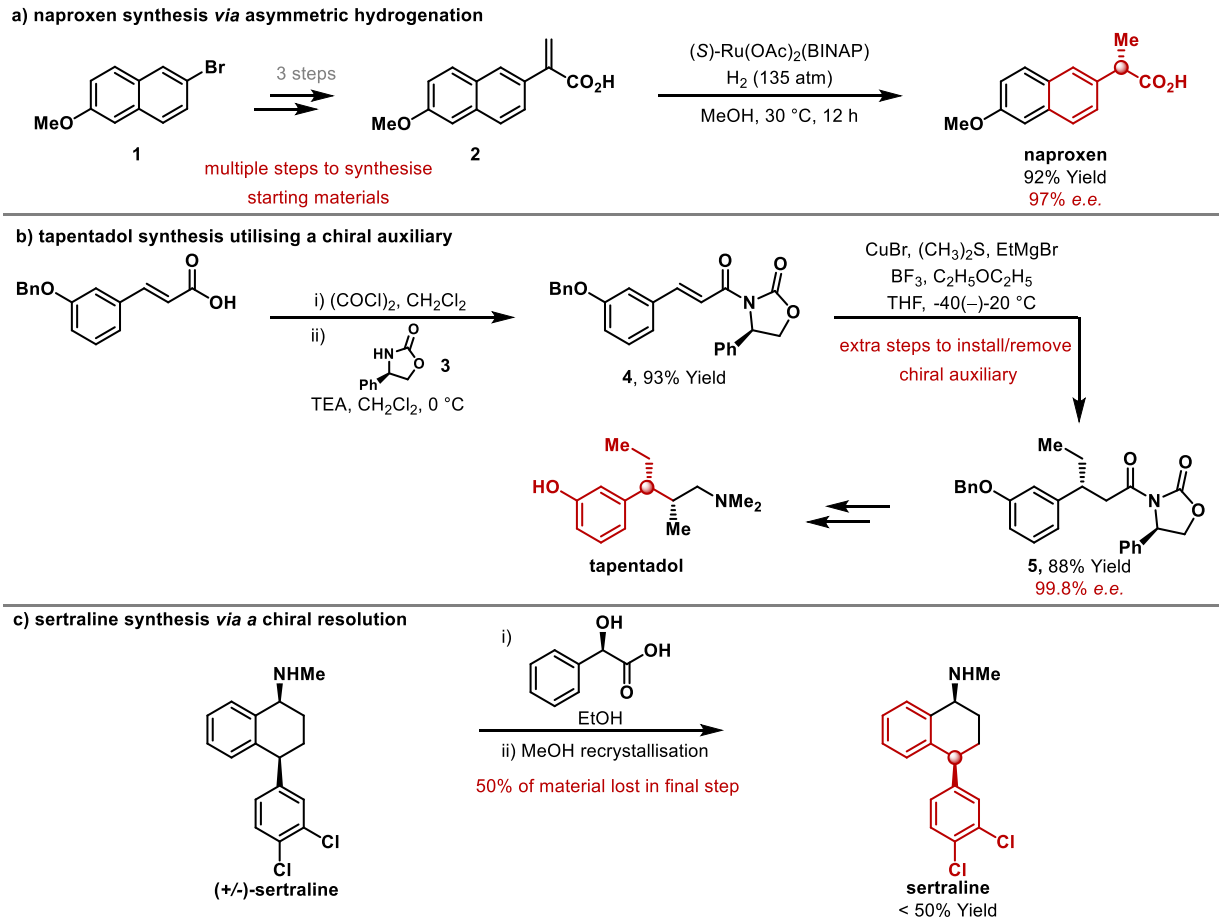
The development of new C–C bond forming reactions is of the upmost importance for the pharmaceutical, material and agrochemical industries, due to C–C bonds being ubiquitous in organic molecules. The way synthetic chemists form C–C bonds has been revolutionised by the advent of palladium-catalysed cross-coupling reactions, such as the Suzuki-Miyaura reaction, which is routinely used by synthetic chemists to construct $C(sp^2)–C(sp^2)$ bonds.[1] However, the success of the Suzuki reaction has led to drug candidates becoming increasingly sp^2-rich, which has been linked to declining success rates in the clinic.[2-3]

Despite the Suzuki reaction being commonly used for the formation of $C(sp^2)–C(sp^2)$ bonds, the construction of $C(sp^2)–C(sp^3)$ bonds by this method is often problematic because of challenges associated with several of the mechanistic steps (Scheme **1**).[4-8] For example, after oxidative addition of Pd(0)-catalyst **I** into an aryl halide, Pd(II)-intermediate **II** is formed, followed by ligand exchange in the presence of a base to generate Pd(II)-intermediate **III** (Scheme **1**). The subsequent transmetallation step with boronic ester **IV** is slow due to the highly sterically congested $C(sp^3)$–B bond, which restricts the formation of Pd(II)-intermediate **V**. Reductive elimination from **V** then affords target product **VI**. However, competing β-hydride elimination can occur from the alkyl Pd(II)-intermediate **V**, resulting in the formation of **VII**, which can either undergo hydrometallation and reductive elimination to form linear alkylated side-product **VIII** or reductive elimination to form an unfunctionalised arene and an alkene.



Scheme 1: *The mechanism of the Suzuki cross-coupling reaction for the formation of C(sp²)–C(sp³) bonds.*

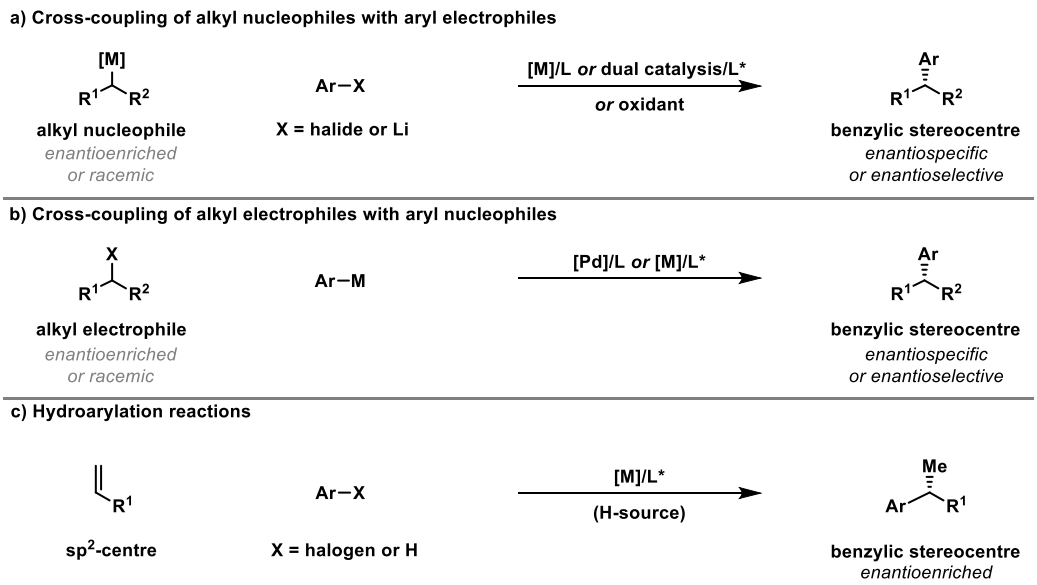
A general and robust cross-coupling reaction for the formation of C(sp^2)–C(sp^3) bonds would be extremely valuable. This would allow the streamlined formation of benzylic stereocentres, which are privileged motifs in bioactive molecules, such as naproxen,[9] an anti-inflammatory drug, tapentadol,[10] an analgesic, and sertraline,[11] an anti-depressant (Scheme **2**). Existing large-scale synthetic routes to these molecules clearly illustrate the difficulties in preparing enantiomerically pure benzylic stereocentres. In one example, the benzylic stereocentre in naproxen is installed by asymmetric hydrogenation of 1,1-disubstituted alkene **2**, which in turn is prepared in three steps from aryl bromide **1** (Scheme **2a**).[9] A more streamlined approach could be envisaged, whereby aryl bromide **1** could be directly coupled with a nucleophile to form the desired C(sp^2)–C(sp^3) bond. One synthesis of tapentadol utilises chiral auxiliary **3** in the asymmetric 1,4-conjugate addition of a Grignard reagent on to **4**, which generates moiety **5** bearing the desired tertiary benzylic stereocentre (Scheme **2b**).[10, 12] The extra steps required for the installation and removal of chiral auxiliary **3** results in low atom economy. Another common method to access enantioenriched benzylic stereocentres is to resolve the enantiomers by co-crystallisation with a second chiral molecule as is shown in the synthesis of sertraline in Scheme 2c.[13,14]



Scheme 2: *Pharmaceuticals which contain tertiary benzylic stereocentres and commercial synthetic routes to generate them.*

The synthetic routes to install benzylic stereocentres presented above (Scheme **2**) all involve multiple steps, which result in purification issues and large amounts of waste. Arguably, a much more efficient method to access these motifs would be to establish the stereocentre *via* a C–C bond forming fragment union step. This approach would provide a more direct route to benzylic stereocentres and would result in a more modular design, allowing each of the coupling components to be varied. In recent years a number of strategies have emerged for the synthesis of benzylic stereocentres *via* stereocontrolled C(sp^3)–C(sp^2) bond forming reactions and an overview of the current state of the art will be discussed in the proceeding pages. To aid the following discussion these methods have been broadly categorised based on whether the newly formed benzylic stereocentre is derived from an alkyl nucleophile (including radical species formed *in situ* from alkenes, alkanes etc.) (Scheme **3a**), an alkyl electrophile (Scheme **3b**), or an sp^2-centre which undergoes migratory insertion during the transformation (Scheme **3c**). Within these broad categories the methodologies can be divided further based on whether the transformation is enantiospecific or enantioselective. Furthermore, these transformations may proceed by a traditional two-electron process (similar to the Suzuki mechanism shown in Scheme **1**) or involve radical intermediates. However, this is often challenging to differentiate,

so each example will be commented on specifically. The discussion will begin with the cross-coupling of alkyl nucleophiles with aryl electrophiles, followed by alkyl electrophiles with aryl units. Hydroarylation of alkenes with organoboron reagents in the presence of external hydride sources will then be presented. The remainder of the introduction will focus on alkene hydroarylation reactions *via* metal-catalysed activation of C_{aryl}–H bonds. Previous work carried out at Bristol into the formation of benzylic stereocentres *via* Ir(I)-catalysed hydroarylation of styrenes and alkenes will then provide the basis for the research described in this thesis.



Scheme 3: *The current state of the art methods to synthesise tertiary benzylic stereocentres.*

1.2 – Cross-Coupling Strategies for the Formation of Tertiary Benzylic Stereocentres

For the cross-coupling reactions discussed in the following section, an important distinction to make is whether stereodefined alkyl components are used in a stereospecific reaction or racemic alkyl components are used in a stereoselective reaction. Examples of each of these possibilities are discussed below. These transformations can proceed *via* either concerted two electron transformations, as seen in Pd-catalysed cross-couplings, or *via* radical-based mechanisms. Furthermore, in some cases, such as those where two catalytic cycles are operative, both two electron and radical mechanisms might be occurring.

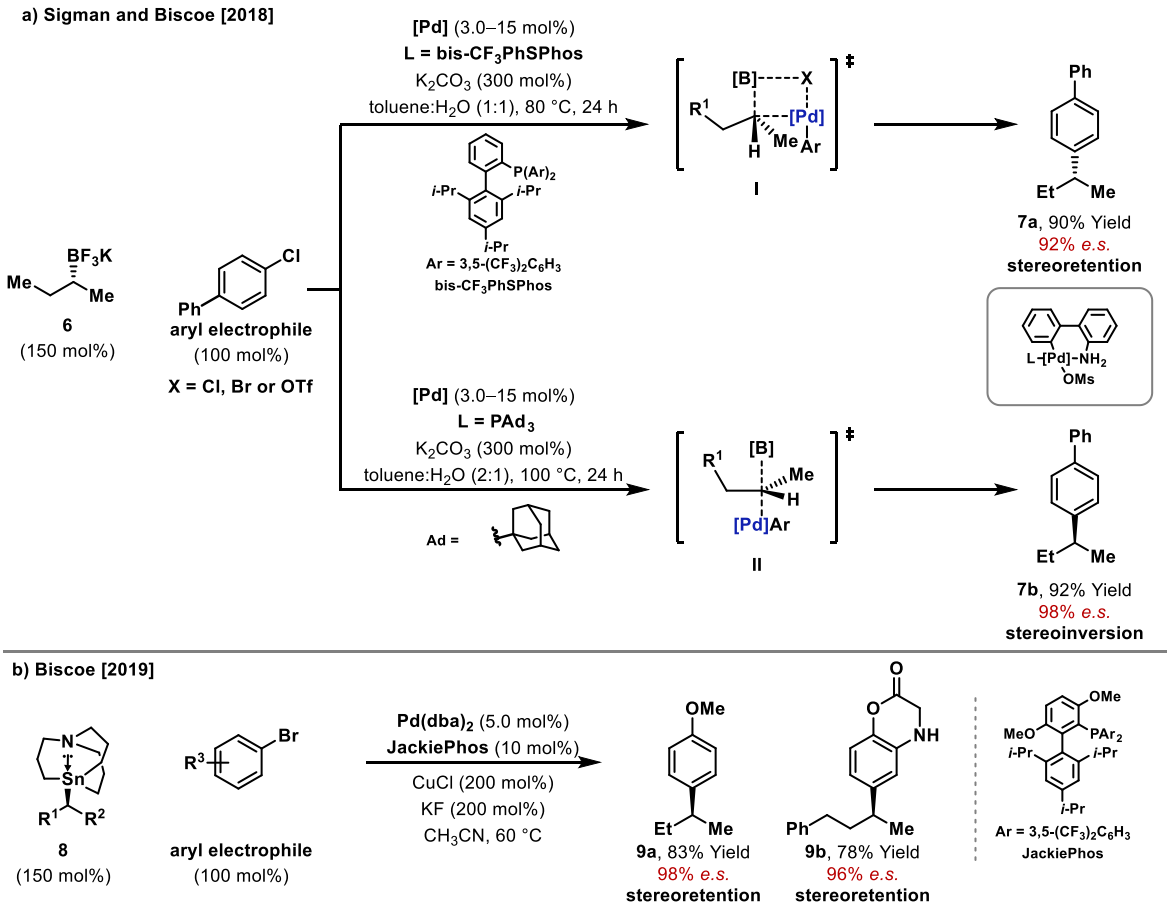
1.2.1 – Cross-Coupling Reactions of Alkyl Nucleophiles

1.2.1.1 – Enantioenriched Alkyl Nucleophiles in Cross-coupling Reactions

Scheme **1** illustrated some of the challenges associated with developing Pd-catalysed cross-couplings for the formation of $C(sp^2)$–$C(sp^3)$ bonds. Most notably, slow transmetallation between alkyl-nucleophiles and transition-metals restricts the use of typical nucleophiles in these transformations.

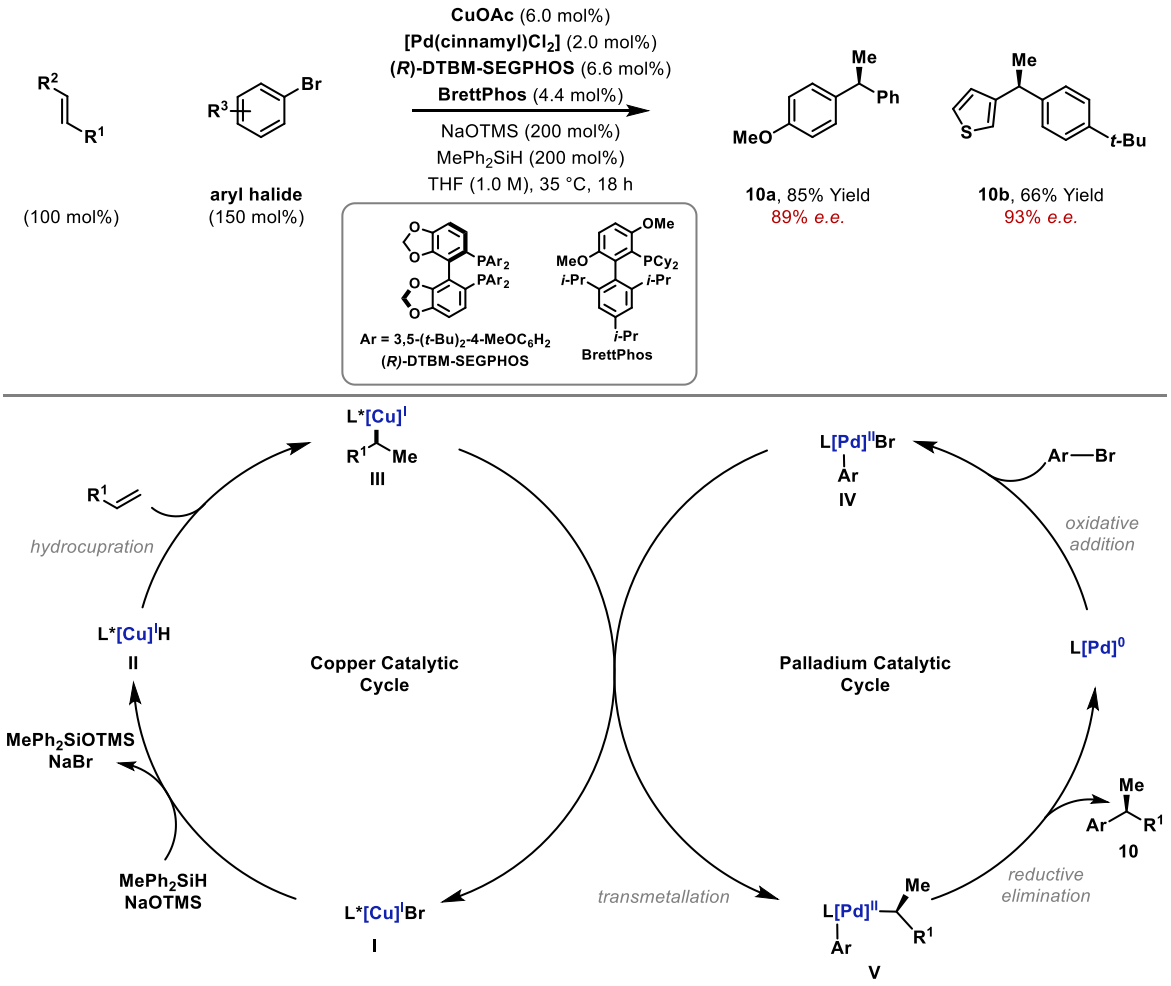
Significant efforts have been directed at overcoming these problems and one promising strategy is the development of chiral organoboron and organotin reagents, which balance configurational stability (to avoid decomposition pathways) with reactivity (to promote efficient transmetallation).[15-19] Another challenge is to avoid unwanted β-hydride elimination from alkyl Pd(II)-intermediates, such as **V** to **VII** (Scheme **1**). This has been achieved by developing new sterically demanding ligands, which either restrict β-hydride elimination and/or promote faster reductive elimination.[4, 6-7]

By combining both of these developments, the Sigman and Biscoe groups have developed a highly efficient and stereospecific Suzuki cross-coupling for the formation of benzylic stereocentres from enantioenriched alkyl trifluoroborates **6** and aryl electrophiles (Scheme **4a**).[20] The reaction begins as in the general catalytic cycle shown in Scheme 1. Initially, oxidative insertion of the Pd(0)-catalyst into the aryl halide forms a Pd(II)-intermediate, which proceeds *via* transition state **I** to form **7a** (92% yield) or **II** to form **7b**. (90% yield), depending on the ligand present. When electron-deficient ligand "bis-CF_3PhSPhos" is employed, transition state **I** is preferred and overall stereoretention is observed. However, when more electron-rich ligand PAd_3 is utilised, transition state **II** is accessed and the benzylic stereocentre forms with overall stereoinversion. Thus, Biscoe and Sigman access both enantiomers of the product from a single enantiomer of the starting material by judicious choice of the ligand. Additionally, both of these bulky, wide bite angle ligands (bis-CF_3PhSPhos and PAd_3) promote fast reductive elimination, which minimises the formation of isomeric side-products *via* β-hydride elimination. More recently, Biscoe and co-workers described a stereoretentive Pd(0)-catalysed Stille cross-coupling reaction of enantioenriched alkylcarbastannatranes **8** with aryl bromides to generate target products, such as **9a** and **9b**, with complete retention of stereochemistry (Scheme **4b**).[21-22] Here, the desired alkyl unit is selectively activated towards transmetallation through internal coordination of the nitrogen atom to the azastannatrane unit.



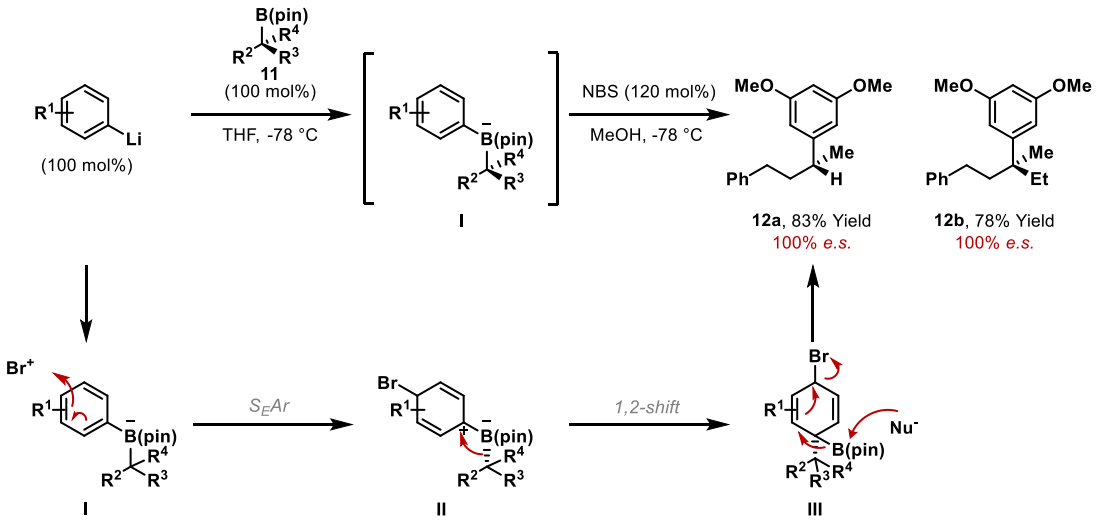
Scheme 4: *Ligand controlled stereospecific Pd(0)-catalysed cross-coupling reactions with stereodefined alkyl nucleophiles and aryl halides.*

A related approach avoids the need to preform chiral nucleophiles by forming them *in situ*. Building upon previously reported procedures,[23-25] Buchwald and co-workers developed an enantioselective Cu(I)/Pd(0)-dual-catalysed cross-coupling of alkenes with aryl halides to generate benzylic stereocentres (Scheme **5**).[26] Initially, chiral Cu(I)–H species **II** is formed *in situ* from CuBr precatalyst **I**, (*R*)-DTBM-SEGPHOS and methyldiphenylsilane. A styrene then undergoes enantioselective hydrocupration with **II** to afford chiral nucleophilic species **III**, which transmetallates with Pd(II)-species **IV**. Finally, stereoretentive reductive elimination from **V** is promoted by ligated BrettPhos to generate 1,1-diarylalkanes, such as **10a** and **10b**, in excellent yields (*up to* 99%) and enantiopurities (*up to* 98% *e.e.*). This methodology is noteworthy as the chiral nucleophile forms *in situ* from an alkene, avoiding prefunctionalisation steps.



Scheme 5: *Cross-coupling reaction of aryl halides with enantioenriched alkyl nucleophiles, which are formed in situ under Pd(0)/Cu(I) dual catalysis.*

Transition-metal free methods for the synthesis of benzylic stereocentres have begun to emerge, which provide a complementary approach to the methods described above (Scheme **4** and **5**).[27-29] Aggarwal and co-workers have been pioneers in this area, expanding their lithiation-borylation strategy to the cross-coupling of a broad range of electron-rich arenes (i.e. benzenes, furans, thiophenes, indoles and pyridines) and boronic esters (Scheme **6**).[27-29] The mechanism proceeds by the addition of an *in situ* generated aryl lithium to stereodefined alkyl boronic ester **11** to form boron-ate complex **I**. The electron-rich arene is then activated by electrophilic bromination with *N*-bromosuccinimide to generate intermediate **II**, which undergoes a 1,2-shift of the alkyl boron substituent to generate **III**. Finally, nucleophilic attack on boron triggers elimination of bromide and re-aromatisation to the arene, affording tertiary and more challenging quaternary benzylic stereocentres, such as **12a** and **12b**, with complete stereoretention. Additional studies have avoided the bromination step by introducing alternate leaving groups with phenol, aniline and pyridine reaction partners.[28, 30-32] One disadvantage of these methods is that the formation of stereo-defined alkyl boronic esters is often labour intensive.

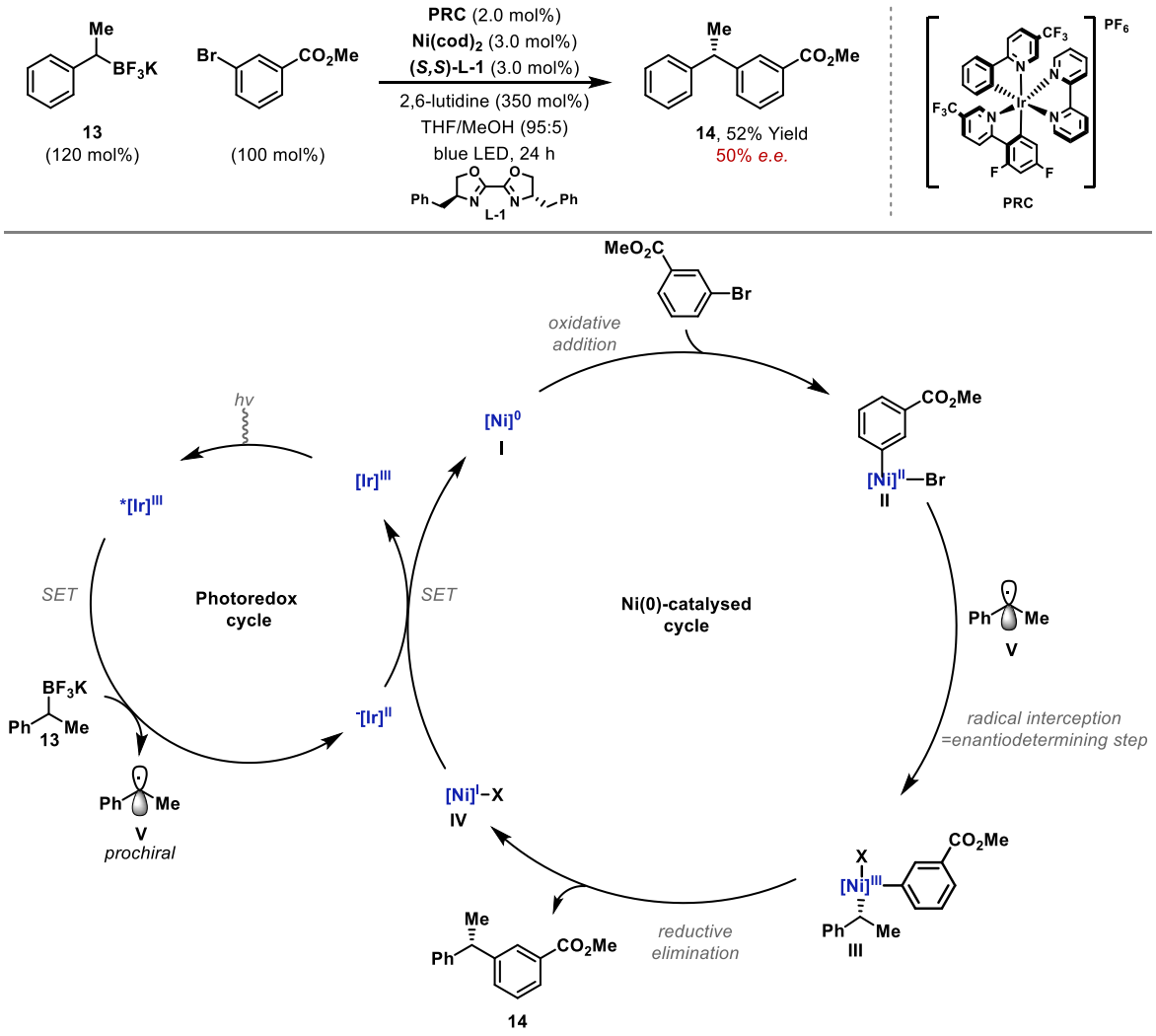


Scheme 6: *Stereospecific coupling of boronic esters and arene units to generate tertiary and quaternary benzylic stereocentres with retention of stereochemistry.*

1.2.1.2 – Enantioselective Processes Employing Racemic Alkyl Nucleophiles

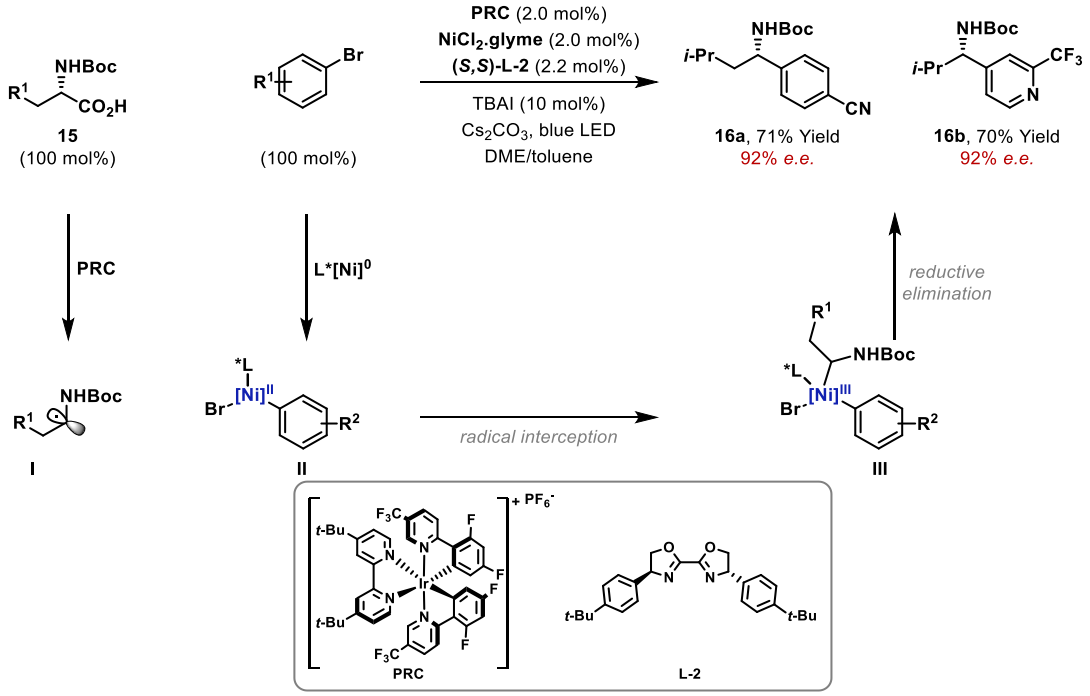
In the examples discussed so far (Section **1.2.1.1**), the stereochemistry is set in a process other than the C–C bond forming step. An alternative, often more step economical approach is the use of racemic reagents under chiral catalysed conditions, whereby the stereochemistry is determined during the C–C bond forming event. This approach is typically not possible *via* two-electron pathways employing alkyl nucleophiles because these processes are stereospecific. Therefore, several processes which proceed *via* configurationally unstable alkyl radicals in place of organoboron species have emerged. Photoredox catalysis is one method which has been used to generate alkyl radicals as intermediates in the formation of benzylic stereocentres. This approach uses mild conditions in comparison to traditional C–C bond forming cross-coupling reactions (ambient temperature, visible light and no strong bases) and it overcomes the slow transmetallation step often associated with organoboron reagents due to the highly reactive nature of the radical species. In 2014, Molander and co-workers merged an Ir(III)-photoredox cycle with a Ni(0)-catalytic cycle to promote an enantioselective cross-coupling reaction between benzylic trifluoroborates **13** and aryl bromides (Scheme **7**).[33] Trifluoroborate **13** undergoes single electron oxidation by the excited photoredox catalyst (PRC) to give prochiral alkyl radical **V**. Radical **V** is then intercepted by chiral **L-1** ligated Ni(II)-intermediate **II** to form Ni(III)-intermediate **III** in the enantiodetermining step. Subsequent reductive elimination generates desired product **14** and Ni(I)-complex **IV**, which is reduced back to active Ni(0)-catalyst **I** by the reduced Ir(II)-PRC *via* SET, thus completing the photoredox catalytic cycle. Despite the important contribution of this method towards the enantioselective synthesis of benzylic stereocentres, only one such example was disclosed, which achieved **14** with moderate levels of enantioselectivity (50% *e.e.*). Molander and Primer employed a related Ni(0)/Ir(I) catalyst system to

generate more challenging all-carbon benzylic quaternary centres; however, extension of this to generate quaternary stereocentres was not discussed.[34]



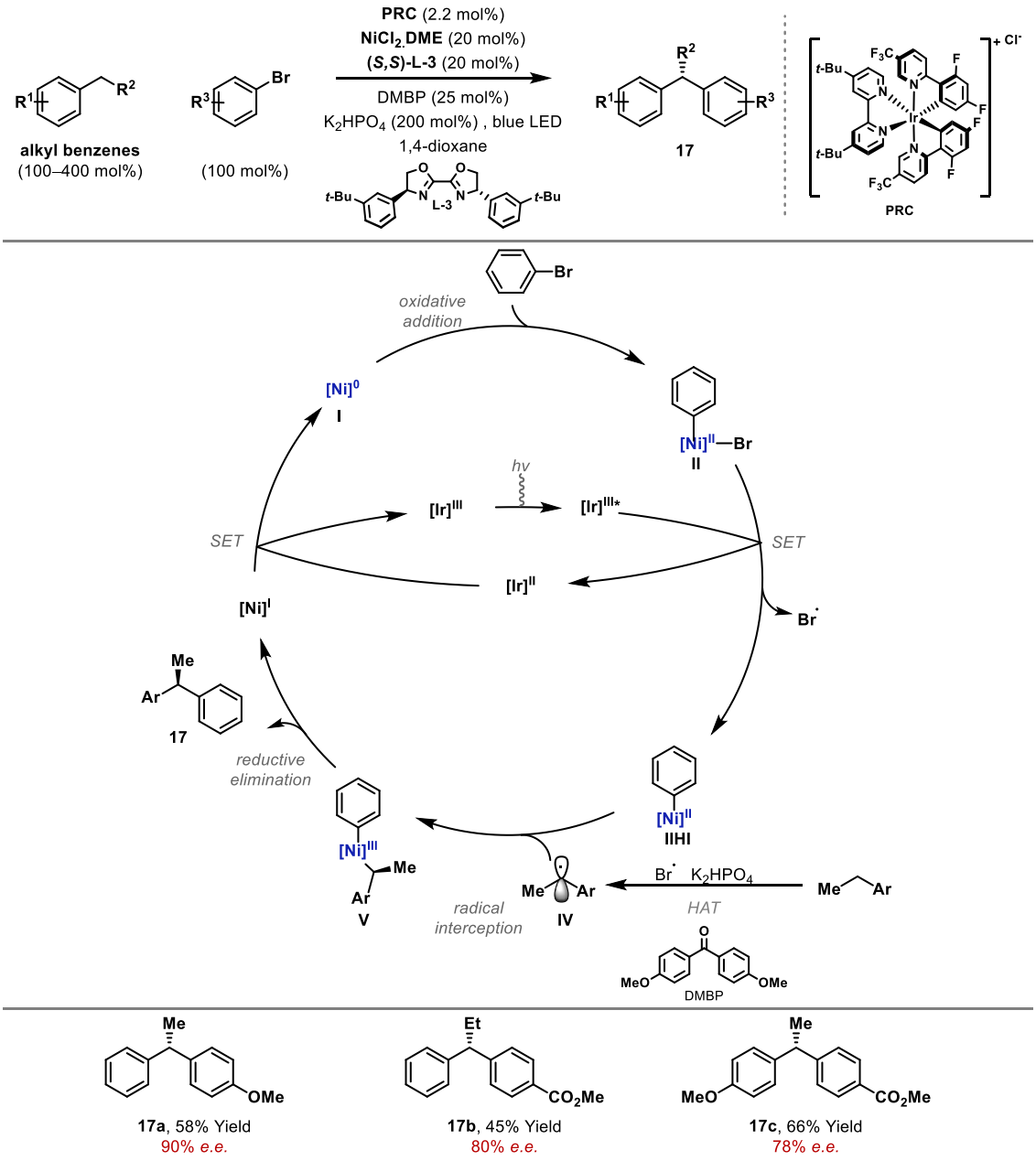
Scheme 7: *Dual photoredox and Ni(0)-catalysis to generate tertiary benzylic stereocentres from aryl halides and racemic trifluoroborates.*

In 2016, the MacMillan and Fu groups disclosed a strategy for the enantioselective arylation of α-amino acids **15** with aryl halides in a collaborative study using photoredox catalysis (Scheme **8**).[35] PRC promoted decarboxylation of enantioenriched α-amino acid **15** generates prochiral radical **I**. Stereoconvergent capture by Ni(II)-intermediate **II**, bearing chiral ligand **L-2**, followed by reductive elimination from ensuing Ni(II)-intermediate **III** affords enantioenriched benzylic amines, including **16a** and **16b**, in good yields and enantiopurities. In these processes, the enantioselectivity is determined by the chiral ligand during the combination of alkyl radical **I** and chiral Ni(II)-intermediate **II**. This method is notable in the fact that it uses amino acids, which are widely available and cheap, in place of alkyl boronic acids. However, the scope of the reaction is limited to groups that will stabilise the intermediate radical (i.e. arenes and amines).



Scheme 8: *Photoredox catalysed reaction of aryl halides and amino acids to generate tertiary benzylic amines with high enantiopurity.*

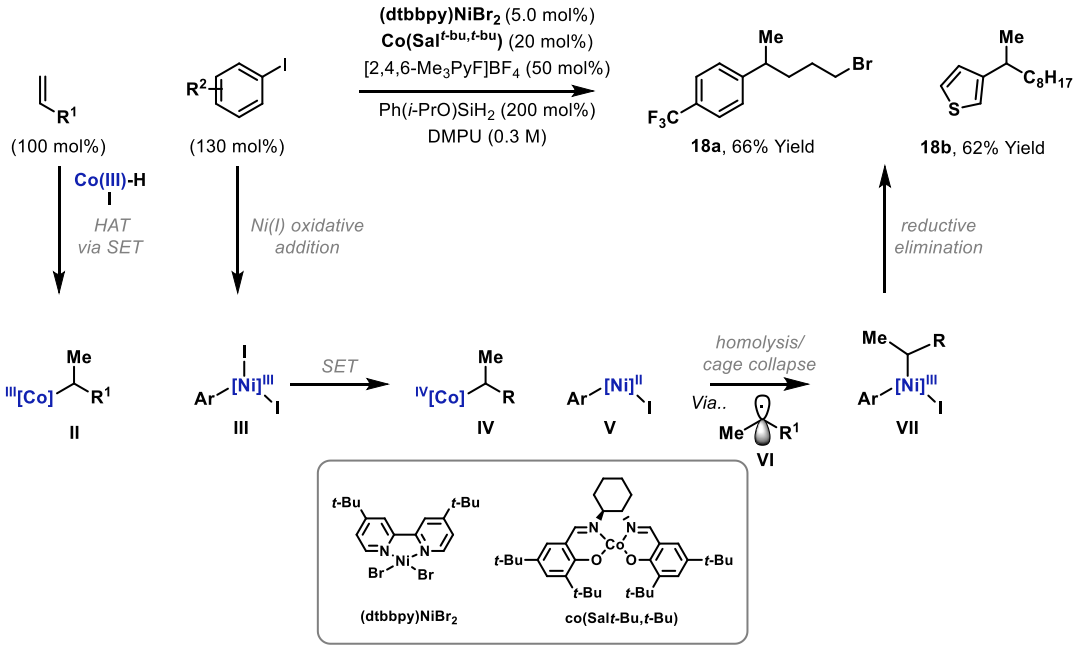
In the previous example, an alkyl radical coupling partner is generated through photoredox catalysis; however, these can also be generated through other methods, including hydrogen atom transfer (HAT). Lu and co-workers demonstrated the enantioselective C–H arylation of alkyl benzenes with aryl bromides to from 1,1-diarylalkanes (Scheme **9**).[36] They utilised an Ir(III)-PRC in combination with a Ni(0)-catalyst ligated with chiral bis-imidazoyl ligand **L-3** to access a SET dual-catalytic pathway. Oxidative addition of Ni(0)-catalyst **I** into the aryl bromide forms Ni(II)-intermediate **II**, from which a bromine radical is released during SET, forming Ni(II)-intermediate **III**. In this case, benzylic radical **IV** is formed *via* HAT from the alkyl benzene and 4,4'-dimethoxybenzophenone (DMPB), which acts a co-catalyst, in the presence of the bromine radical and a base. The resulting radical **IV** intercepts Ni(II)-species **III** to form Ni(III)-intermediate **V**, from which reductive elimination affords the 1,1-diarylated alkane **17**. The active Ni(0)-catalyst **I** is regenerated through SET, closing the catalytic cycle. This protocol provides facile access to tertiary benzylic stereocentres with high enantiopurity (e.g. **17a**–**c**) directly from unfunctionalised benzylic positions. The methodology tolerates electron-rich and -poor aryl bromides, including heteroaromatics. Additionally, various carbon substituents can be introduced at R^2.



Scheme 9: *Photoredox catalysed C–H arylation of aryl alkanes with aryl halides to form enantioenriched 1,1-diarylalkane species.*

The previous examples (Scheme **7**–**9**) all employ radicals that are stabilised by adjacent functionality (aryl and nitrogen groups), which limits the scope of these transformations. Shenvi and co-workers employed a Ni(I)/Co(II) dual catalytic approach to promote the hydroarylation of terminal alkenes with a range of electronically diverse aryl iodides (Scheme **10**).[37] This method allows aliphatic alkenes to be used in these types of reaction, most likely as a result of the tendency of Co-species to trap alkyl radicals. However, an enantioselective protocol is yet to be disclosed. Initially, the Co(II)-precatalyst is oxidised by [2,4,6-Me_3PyF]BF_4 to a Co(III)-species, which forms active Co(III)-hydride catalyst **I** in the presence of Ph(*i*-PrO)SiH_2. Co(III)-hydride **I** then undergoes Markovnikov hydrogen

atom transfer to an alkene to generate alkyl Co(III)-nucleophilic species **II** *in situ*.[38] Mechanistic studies suggest that the alkyl Co(III)-species **II** is oxidised to Co(IV)-species **IV** *via* SET in the presence of Ni(III)-species **III** (formed by oxidative addition of the Ni(I)-catalyst into an aryl iodide). Homolysis of the Co(IV)–C_{alkyl} bond of species **IV**, with resulting Ni(II)-species **V**, forms alkyl radical species **VI**, which is rapidly accepted by subsequent Ni(III) species **V**. This occurs within the solvent cage *via* a "cage-rebound" process. Ni(III)-intermediate **VII** then undergoes reductive elimination to form the cross-coupled products, such as **18a** and **18b**, and a Ni(I)-species, completing the catalytic cycle. Co(III)-species related to **II** have been used in Minisci-type reactions to generate racemic pyridines bearing quaternary centres.[39]



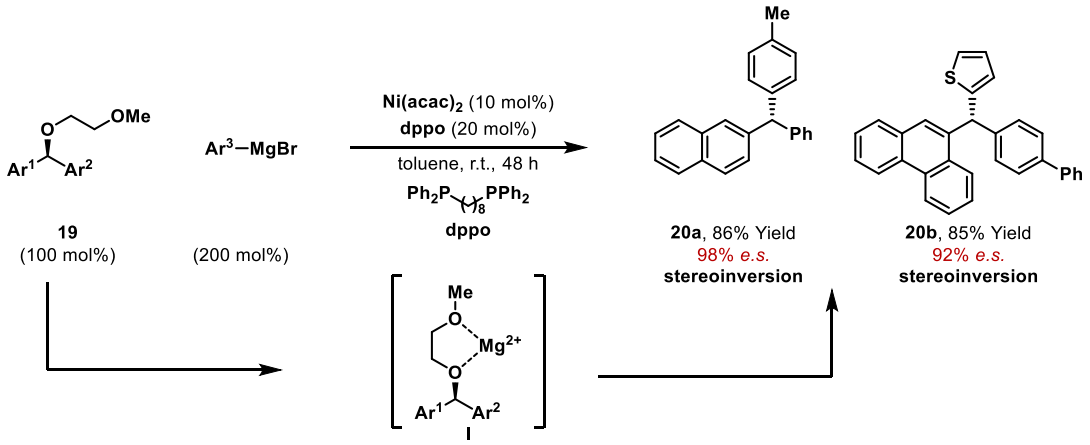
Scheme 10: *Synthesis of tertiary benzylic centres from aryl halides and alkenes by dual Ni(I)/Co(III) catalysis.*

1.2.2 – Cross-Coupling Reactions of Alkyl Electrophiles

1.2.2.1 – Enantioenriched Alkyl Electrophiles in Cross-coupling Reactions

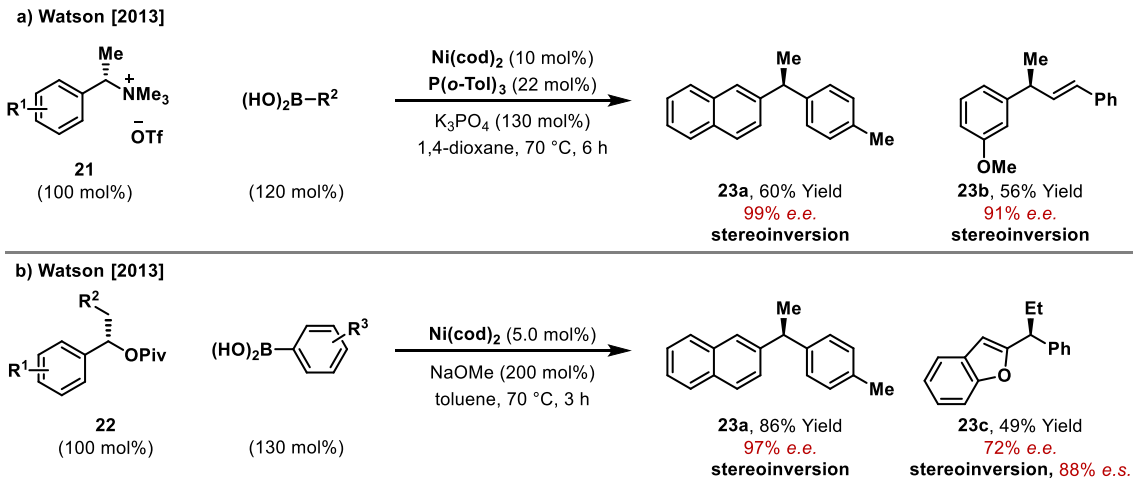
A complementary approach to the methods outlined in Section 1.2.1 is the employment of enantioenriched alkyl electrophiles with aryl nucleophiles. Similarly to alkyl nucleophiles, the cross-coupling of enantioenriched electrophiles can proceed with either retention or inversion of stereochemistry. One example reported in 2012 by Jarvo and co-workers described the Ni(0)-catalysed coupling of stereodefined benzyl ethers **19** with aryl Grignard reagents (Scheme **11**).[40] In this example, a chelating leaving group is attached to the benzyl ether, which upon chelation to magnesium activates the C–O bond towards stereoinvertive oxidative addition by the Ni(0)-catalyst (**I**). Subsequent transmetallation with Grignard reagents and reductive elimination forms the desired benzylic centres, such as **20a** and **20b**, with overall stereoinversion. The highly nucleophilic nature of Grignard reagents

restricts the functional group tolerance and the process is limited to bisbenzylic electrophiles, presumably to facilitate oxidative addition of the Ni(0)-catalyst.



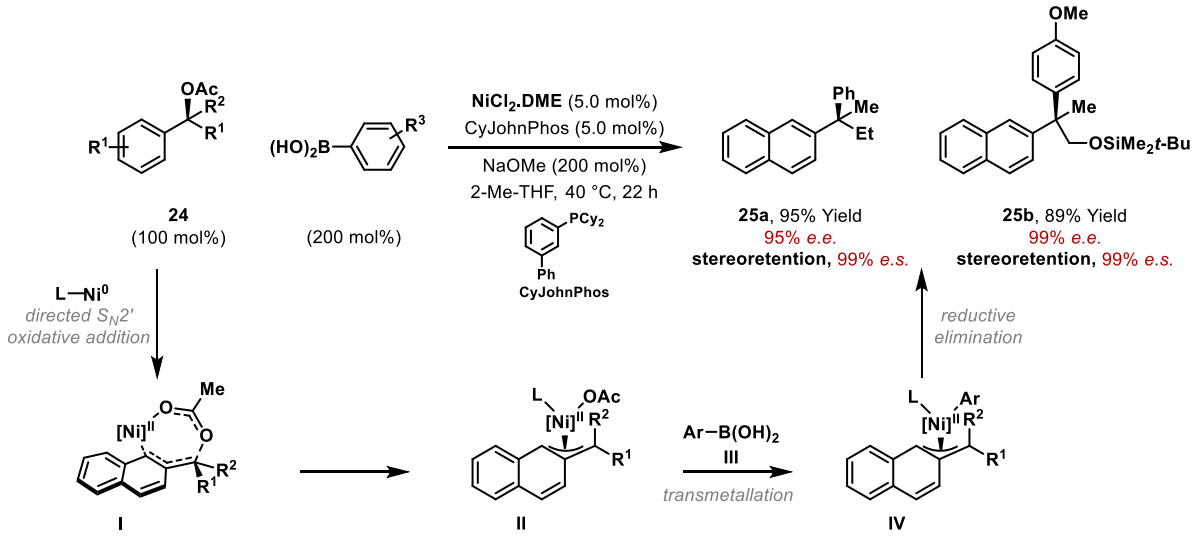
Scheme 11: *Ni(0)-catalysed cross-coupling of Grignard reagents with enantioenriched ethers*.

Towards a more versatile protocol, Watson and co-workers disclosed the Ni(0)-catalysed cross-coupling of benzylic ammonium triflates **21** with aryl boronic acids (Scheme **12a**).[41] Additional studies by the Watson group subjected stereodefined benzylic pivalates **22** and boronic acids to a Ni(0)-catalyst in the absence of a phosphorus ligand (Scheme **12b**).[42] Both transformations are proposed to occur by S_N2 oxidative addition of the Ni(0)-catalyst into the C–X bond (X = N or O) of the stereodefined substrate, which results in the inversion of configuration that is observed.[41-42] Transmetallation with the boronic acid, is followed by reductive elimination to afford the target products. In both protocols 1,1-diarylalkanes, such as **23a**–**c**, were generated in excellent yields (Scheme **12a** and **12b**). In these examples the use of a Ni(0)-catalyst suppresses β-hydride elimination.[43] The processes discussed in Scheme 12 are limited to the generation of bisbenzylic or benzylic-vinylic stereocentres.[41-42] This is presumably due to hyperconjugation of the aryl π-system with the σ^*–orbital of the C–X bond promoting more facile oxidative addition. Processes which start from alkyl triflates or alkyl halides have been reported; however, these are often limited by specific functional group requirements.[44-45]



Scheme 12: *Stereodefined electrophiles in Ni(0)-catalysed Suzuki-type cross-coupling reactions to generate tertiary benzylic stereocentres.*

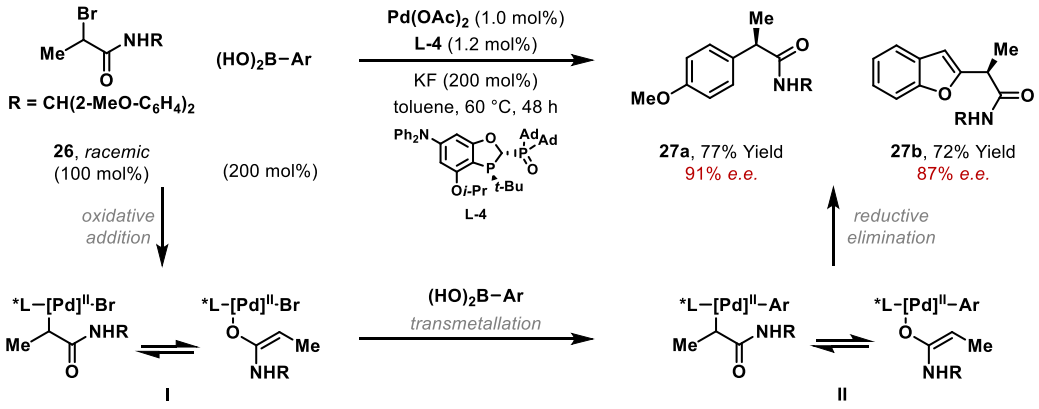
Watson and co-workers expanded the methodology in Scheme 12 to couple sterically demanding enantioenriched tertiary alcohol derivatives **24** with aryl boronic acids, thereby generating all-carbon quaternary centres with retention of stereochemistry (Scheme **13**).[46] It is proposed that the acetate of the electrophile binds to the Ni(0)-catalyst to direct S_N2'-like oxidative addition (**24** to **II**). Transmetallation with boronic acid **III**, followed by reductive elimination from **IV** then affords the 1,1-diaryl quaternary stereocentres (e.g. **25a** and **25b**). A Ni(0) catalyst ligated with bulky biaryl phosphine ligand CyJohnPhos was used to prevent undesirable β-hydride elimination from **IV**. This transformation requires a naphthyl substituent, which is consistent with the proposed directed oxidative addition step. Despite forming a range of benzylic quaternary centres in high yields and enantiopurities, the starting chiral alcohols are synthesised in two steps from acetophenones, resulting in increased workload and waste.



Scheme 13: *Stereodefined electrophiles in Ni(0)-catalysed cross-coupling reactions to generate all-carbon quaternary stereocentres.*

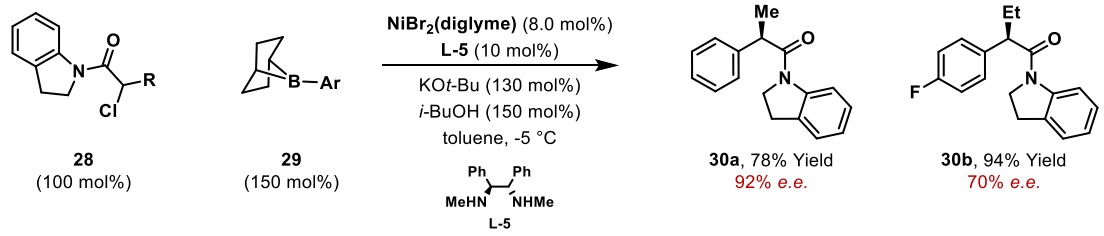
1.2.2.2 – Enantioselective Processes Employing Racemic Alkyl Electrophiles

Similar to the processes discussed in Section 1.2.1.2 employing racemic alkyl nucleophiles, enantioselective processes have begun to emerge which utilise racemic alkyl electrophiles. For example, in 2019, Tang and co-workers reported the enantioconvergent Pd(0)-catalysed cross-coupling of aryl boronic acids with racemic α-bromo carboxamides **26** (Scheme **14**).[47] Here, oxidative addition of a Pd(0)-catalyst into the alkyl-bromine bond (to give **I**) is followed by transmetallation to generate Pd(II)-species **II**. Subsequent reductive elimination generates a range of electron-rich and -deficient α-aryl carboxamides (e.g. **27a** and **27b**). The enolisation of the starting material is critical to achieve the high enantioselectivities observed. The chemistry is reliant upon bulky phosphine oxide ligand **L-4**, which prevents Pd(II)-intermediate **II** from undergoing a second transmetallation event and subsequent reductive elimination to form unwanted biaryl-species.



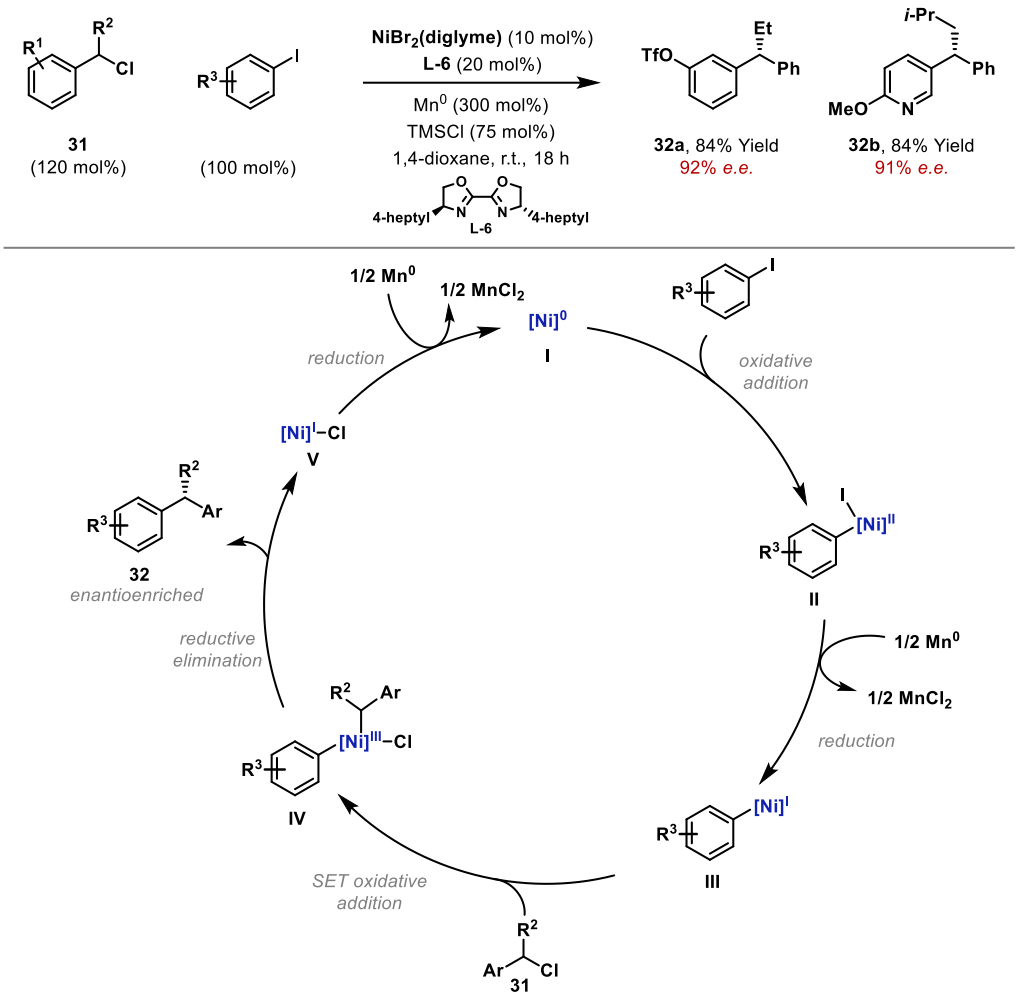
Scheme 14: *Enantioselective Pd(0)-catalysed cross-coupling of racemic α-bromo carboxamides with aryl boronic acids to generate tertiary benzylic stereocentres.*

The enantioselective cross-coupling of racemic alkyl electrophiles with organoboranes can also be conducted under Ni(0)-catalysed conditions; however, these protocols proceed *via* a radical-based pathway.[48] In 2010, Fu and Lundin reported the enantioselective Ni(0)-catalysed cross-coupling of racemic amide activated alkyl halides **28** with aryl organoboranes **29** to generate benzylic stereocentres, such as **30a** and **30b** (Scheme **15**).[48] This process is stereoconvergent, whereby both enantiomers of racemic starting material **28** are catalytically converted to a single enantiomer of product **30**. This transformation is reliant on the amide activating group on the electrophile to stabilise the intermediate radical formed upon oxidative addition, limiting the scope of the reaction.



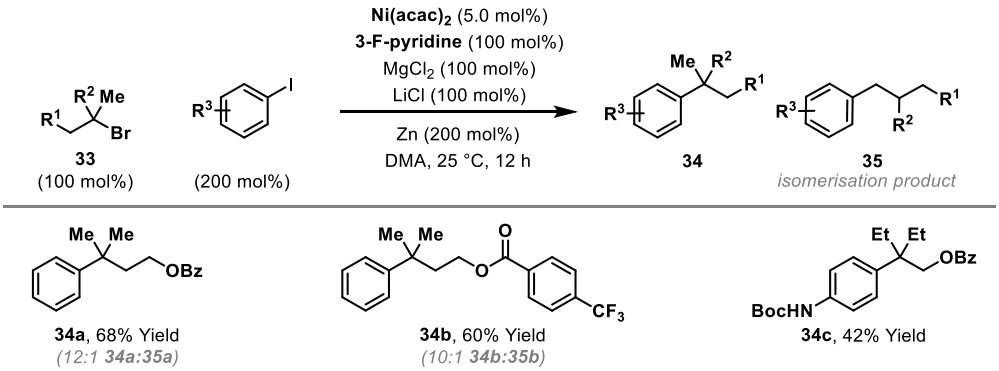
Scheme 15: *Enantioselective cross-coupling of racemic alkyl electrophiles and aryl organoboranes via a Ni(0)-catalysed radical-based mechanism.*

Reductive cross-coupling of two electrophilic components *via* asymmetric metal catalysis is another strategy that has been employed to generate enantioenriched benzylic stereocentres.[49-52] One example relevant to this thesis is the enantioselective Ni(0)-catalysed reductive cross-coupling of (hetero)aryl iodides with racemic benzyl chlorides **31** to generate 1,1-diarylalkanes (e.g. **32a** and **32b**) (Scheme **16**).[52] It is proposed that following oxidative addition of the Ni(0)-catalyst into the aryl iodide bond to form Ni(II)-intermediate **II**, **II** is reduced to Ni(I)-intermediate **III** by manganese.[49] This facilitates stereoconvergent single electron oxidative addition of benzyl chloride **31**. Subsequent reductive elimination from Ni(III)-species **IV** generates enantioenriched coupled product **32** and Ni(I)-species **V**, which is reduced by manganese to active Ni(0)-catalyst **I**. Notably, this protocol avoids stereodefined electrophiles and organometallic reagents, thereby minimising the number of steps needed to reach the target product. All of the enantioselective examples described here employ electrophilic radical species, which require radical stabilising functionality (e.g. aryl and amide groups) and limit the generality of the approach towards the synthesis of benzylic stereocentres (Scheme **7–10**, **15**).



Scheme 16: *Synthesis of 1,1-diarylalkanes via a reductive Ni(0)-catalysed cross-coupling reaction.*

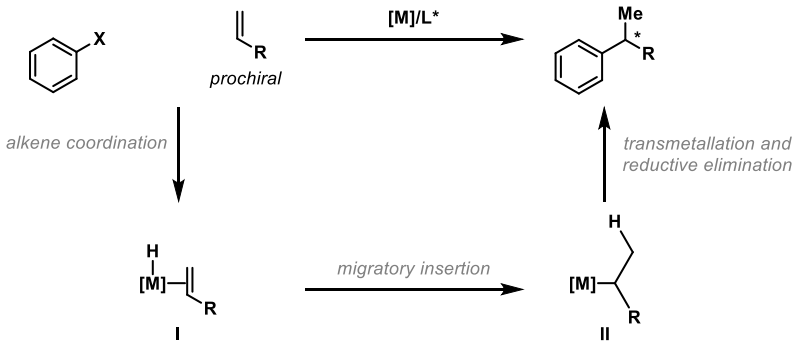
In 2018, a related approach was reported by Gong and Wang and co-workers, who described the non-enantioselective 3-fluoropyridine ligated Ni(0)-catalysed reductive cross-coupling of aryl iodides with tertiary alkyl halides **33** to afford demanding all-carbon quaternary centres, such as **34a–c** (Scheme **17**).[53] In this example, mechanistic experiments revealed two possible catalytic cycles; a radical chain mechanism or a double oxidative addition pathway. In both cases, zinc acts a reductant to regenerate the Ni(0)-catalyst. For some transformations, isomeric side product **35** was also observed, which presumably forms *via* a β-hydride elimination/migratory insertion pathway.



Scheme 17: *Synthesis of all-carbon quaternary centres via a reductive Ni(0)-catalysed cross-coupling reaction.*

1.2.3 – Enantioselective Hydroarylation Reactions

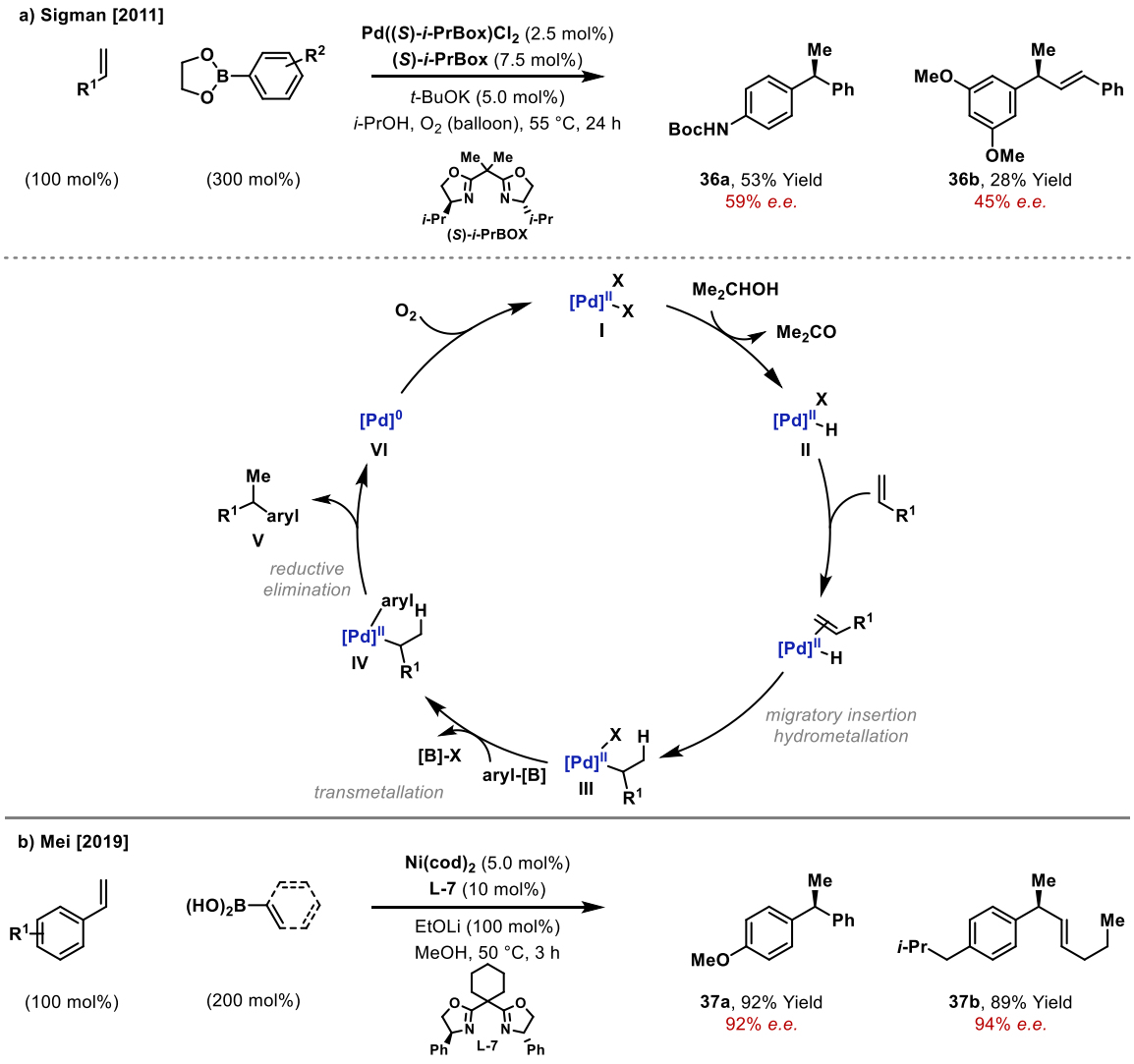
The final category of $C(sp^2)$–$C(sp^3)$ bond forming reactions that will be outlined are those where the stereocentre is formed during a migratory insertion step in the catalytic cycle (**I** to **II**) (Scheme **18**). This is advantageous because it uses simple alkenes as prochiral substrates and does not require specific stabilising groups. Furthermore, this method is innately highly atom economical and fits the ideals of a green process, where a stock chemical (alkene) is coupled directly without prefunctionalisation.



Scheme 18: *Migratory insertion as a route to tertiary benzylic stereocentres.*

The hydroarylation of unfunctionalised alkenes (rather than the cross-coupling of alkyl halides), where the hydride comes from an external source, is a powerful method to install benzylic stereocentres. Here, chiral Pd(II)- and Ni(0)-catalysts can be utilised for the enantioselective cross-coupling of alkenes with aryl boronic esters.[54-55] In 2011, Sigman and co-workers developed a moderately enantioselective Pd(II)-catalysed alkene hydroarylation with aryl boronic esters (Scheme **19a**).[54] Pd(II)-hydride **II** forms *via* oxidation of iso-propanol by **I**. Enantio-determining alkene insertion into Pd(II)-hydride **II** is then followed by transmetallation of the aryl boronic ester (**III** to **IV**) and reductive elimination (**IV** to **V**). Oxygen acts as an external oxidant to regenerate active Pd(II)-catalyst **I** from Pd(0)-species **VI**. The target bisbenzylic or benzylic-vinylic stereocentres, such as **36a** and **36b**, were produced in moderate yield (*up to* 53%) and with promising levels of enantioselectivity (*up to* 59% *e.e.*). Building upon

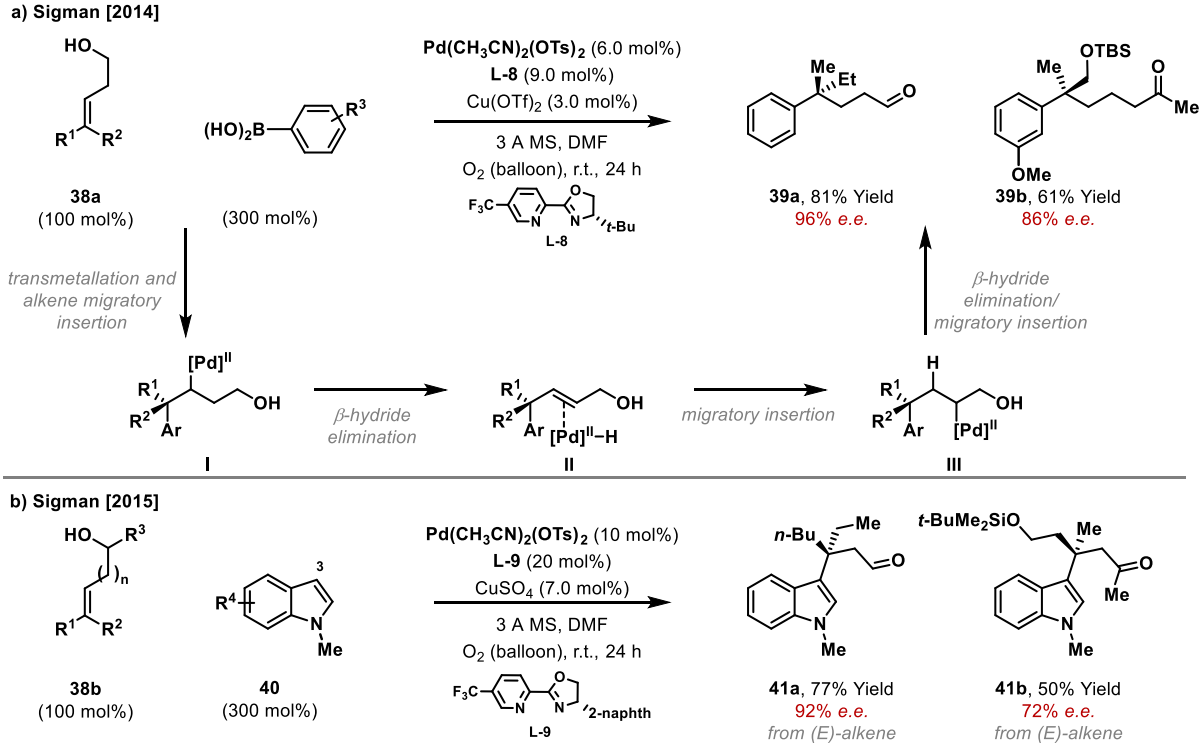
Sigman's seminal work,[54] Mei developed a highly enantioselective Ni(0)-catalysed protocol for the hydroarylation of styrenes with aryl boronic acids (Scheme **19b**).[55] In this example, MeOH acts as the hydride source and chiral bis-oxazoline ligand **L-7** provides high levels of enantioselectivity (*up to* 96% *e.e.*) for alkene hydroarylation with both aryl and vinyl boronic acids, generating benzylic stereocentres in high yields (e.g. **37a** and **37b**). This work is a significant contribution to the field as it provides access to benzylic stereocentres enantioselectively, directly from feedstock alkenes.



Scheme 19: *Enantioselective Pd(II)- and Ni(0)-catalysed hydroarylation of styrenes with boronic acids to generate tertiary benzylic stereocentres.*

Sigman and co-workers developed a similar Pd(II)-catalysed methodology for the enantioselective construction of sterically demanding all-carbon quaternary centres from secondary alkyl alcohols **38a** and boronic acids (Scheme **20a**).[56] Here, a Cu-source was added to aid reoxidation of the Pd(0)-catalyst to active Pd(II)-species. The mechanistic pathway begins with transmetallation of the aryl boronic acid, followed by migratory insertion of the alkene to generate the desired quaternary stereocentres. Subsequent relay β-hydride elimination/migratory insertion affords the carbonyl

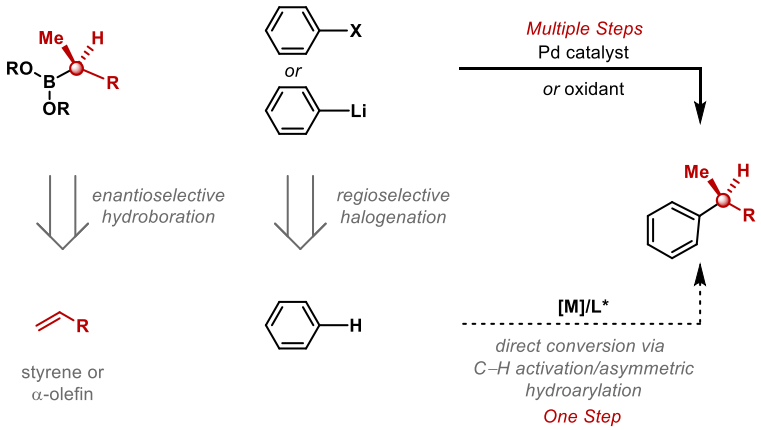
compounds bearing all-carbon stereocentres enantioselectively (e.g. **39a** and **39b**). Through modification of the chiral pyridine oxazoline ligand (**L-8** to **L-9)**, Sigman and co-workers expanded the enantioselective dehydrogenative Heck arylation of trisubstituted alkenes **38b** to electron-rich indoles **40** (Scheme **20b**).[57] Here, the C3 C–H bond of indole **40** is functionalised directly to form indoles bearing quaternary centres (e.g. **41a** and **41b**). However, this protocol is only applicable for electron-rich arenes and multiple synthetic steps are required for the synthesis of the alkenes **38**.[56-57]



Scheme 20: *Enantioselective Pd(II)-catalysed hydroarylation of styrenes with boronic acids to form all-carbon quaternary stereocentres.*

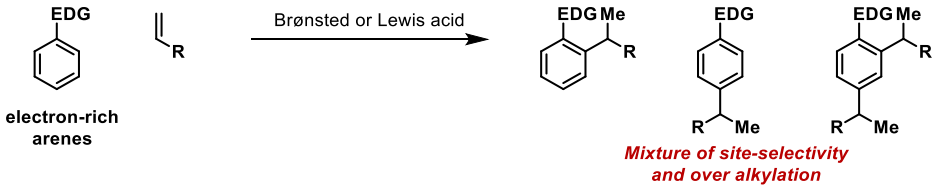
1.3 – Metal-Catalysed C–H Activation and Asymmetric Hydroarylation

The methodology discussed in section **1.2** has been utilised to afford benzylic stereocentres with excellent levels of enantioselectivity. All of the protocols presented require prefunctionalised starting materials, which results in extra synthetic steps, increased workload and large amounts of waste. For example, stereo-defined alkyl boronic esters are often synthesised *via* enantioselective hydroboration of alkene precursors[58-60] and aryl halides are frequently prepared by regioselective halogenation of aryl C–H bonds.[61-62] An ideal strategy to generate tertiary benzylic stereocentres would directly couple an alkene and an aryl C–H bond *via* directed C–H activation (Scheme **21**). This desirable approach would generate benzylic stereocentres in an atom and step economical manner.



Scheme 21: *Asymmetric hydroarylation of alkenes via C–H activation as an ideal approach to generate benzylic stereocentres.*

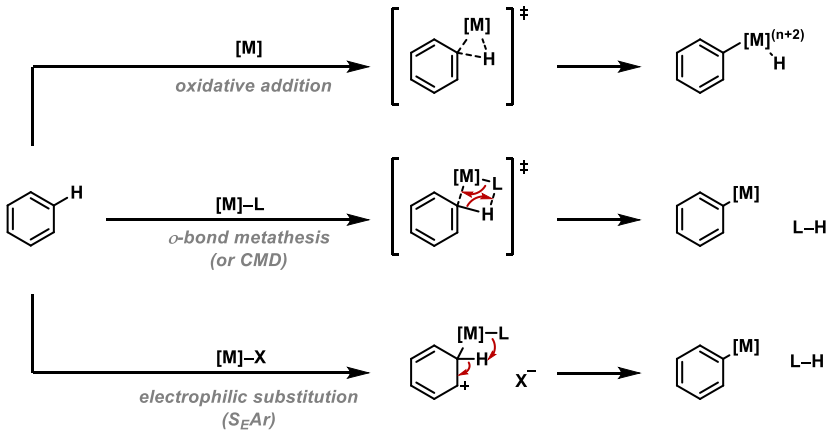
The ability to take 'feedstock' materials and directly transform them into valuable products is highly desirable. One approach towards the direct functionalisation of C–H bonds is the well-established Friedel-Crafts reaction, which achieves branch-selective hydroarylation of styrenes with unfunctionalised arenes in the presence of an acid (Scheme **22**).[63-66] However, this method requires electron-rich arenes and suffers from poor site-selectivity (*ortho vs para*) as well as over alkylation. Additionally, enantioselective alkylation by this method is challenging. Therefore, the development of strategies that allow the selective activation and subsequent functionalisation of the desired C–H bond is key to the development of this ideal.



Scheme 22: *Hydroarylation of alkenes via a Friedel-Crafts reaction.*

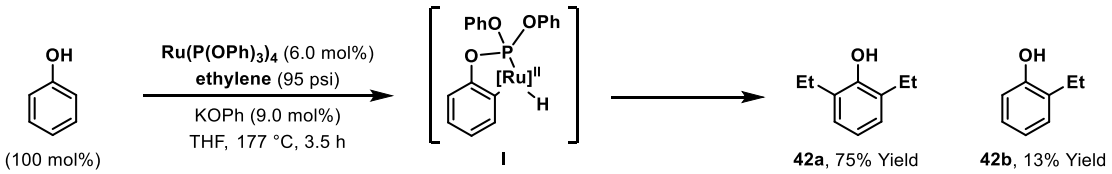
The selective functionalisation of 'inert' C–H bonds (~110 kcal/mol C_{aryl}–H bond) using metal catalysis has gained significant attention in recent years, owing to these more direct methods being both environmentally and economically attractive.[67-76] Organometallic C–H activation involves the direct insertion of a metal complex into a C–H bond with concomitant two-electron oxidation of the metal centre, to generate a metal-hydride (Scheme **23**).[77] Functionalisation of the organometallic intermediate can then proceed. Additionally, alternative C_{aryl}–H metalation pathways exist, but strictly speaking these are not examples of C–H activation. For example, σ-bond metathesis (also known as concerted metalation deprotonation (CMD)) between a metal-ligand bond and an aryl C–H bond proceeds through a concerted transition state to form a C–M bond and L–H bond (Scheme **23**). Alternatively, an electrophilic substitution pathway (S_EAr) involves an initial electrophilic interaction with the electron-

rich arene π-system and an electron-deficient metal. The [M]–L bond interacts with the C–H bond of the resulting intermediate to form a M–C bond, whilst also re-establishing the aromaticity.



Scheme 23: *The various mechanisms for transition metal catalysed activation and metallation of aryl C–H bonds.*

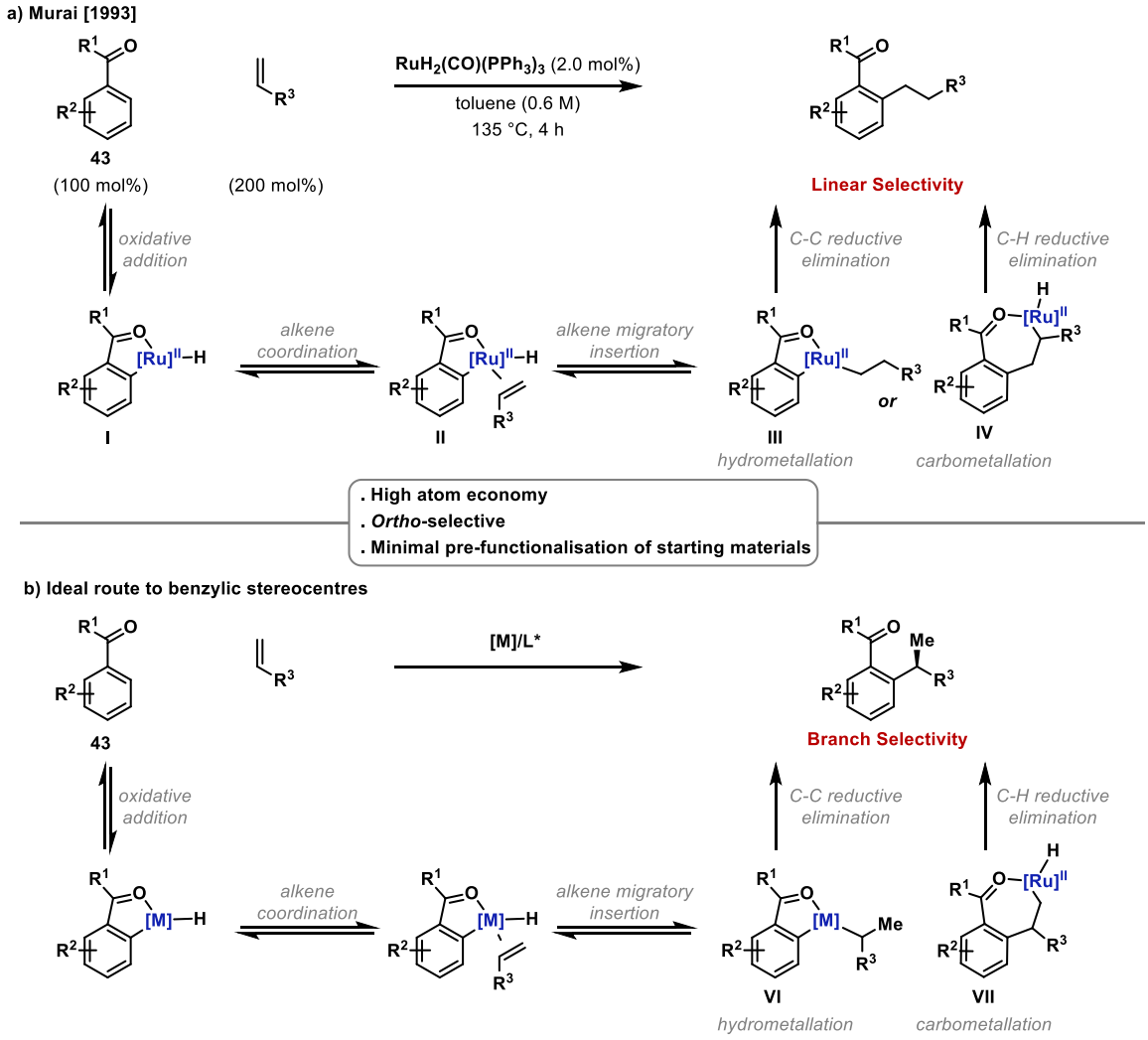
C–H bonds are ubiquitous in organic molecules, so selectively targeting the bond of interest poses a considerable challenge. One approach to selectively activate C–H bonds is the use of directing groups, which can coordinate to the metal catalyst and hold it in the correct position for oxidative addition into the desired bond. This directing group strategy has been applied in hydroarylation reactions to generate C(sp^3)–C(sp^2) bonds. The first protocol for selective *ortho*-alkylation of arenes *via* directed metal-catalysed C–H activation was reported in 1986 by Lewis and Smith (Scheme **24**).[78] Their hydroarylation methodology utilises a Ru(0)-catalyst and a catalytic phosphorus-based directing group, to achieve *ortho*-ethylation of aryl phenols. Despite the relatively harsh conditions employed (177 °C, 95 psi), *ortho*-alkylated phenols were generated exclusively as a mixture of mono- and bis-alkylated moieties (**42a** and **42b**).



Scheme 24: *The first reported example of directed metal-catalysed ortho-alkylation of arenes.*

Following Lewis and Smiths' pioneering work (Scheme **24**), Murai and co-workers described a Ru(0)-catalysed protocol for *ortho*-alkylation of aryl ketones **43** with mono-substituted alkenes to generate linear hydroarylation products (Scheme **25a**).[79] This catalytic process is significant, as it employs a weakly coordinating carbonyl directing group and provides the desired products atom economically, with alkylation occurring with complete *ortho*- and linear selectivity. The protocol was suggested to proceed by reversible carbonyl-directed oxidative addition of the Ru(0)-catalyst into the *ortho* C–H bond of the arene to give **I**, followed by alkene coordination (**I** to **II**). Hydrometallation

(insertion of the alkene into the [Ru]–H bond) (**II** to **III**) is then followed by the first irreversible step, C–C bond forming reductive elimination. Evidence for a hydrometallation pathway instead of a carbometallation pathway (insertion of the metal into the [Ru]–C bond) was provided by DFT calculations.[80-81] The linear selectivity is most likely a product of an equilibrium preference for linear intermediate **III** (Scheme **25a**) over branched intermediate **VI** (Scheme **25b**). The Murai methodology has inspired the development of other transformations promoted by metal-catalysed *ortho* C–H activation. Protocols which override the usual linear selectivity to generate branched hydroarylation products are of particular interest as they are atom economical ways to access privileged structures bearing benzylic stereocentres (Scheme **25b**).[82]

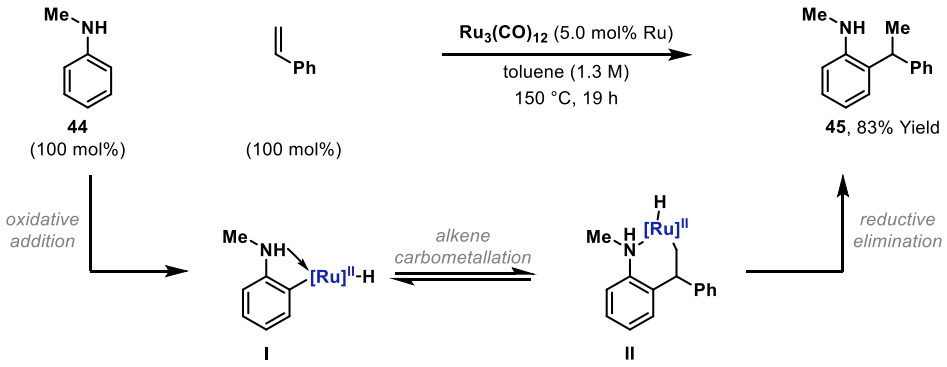


Scheme 25: *An ideal approach to generate benzylic stereocentres based on Murai's pioneering work.*

1.3.1 – Directed Branch-Selective Alkene Hydroarylation

In 1999, Uchimaru disclosed the first example of directed branch-selective alkene hydroarylation (Scheme **26**).[83] *N*-Methylaniline **44** and styrene were subjected to a Ru(0)-catalyst to generate *ortho*-alkylated arene **45** in 85% yield and with complete branch selectivity. The

transformation is suggested to proceed *via* amine-directed oxidative addition of the Ru(0)-catalyst into the *ortho* C–H bond, giving 4-membered chelate **I**. Subsequent alkene carbometallation forms **II**, from which C–H reductive elimination generates branched product **45**. In contrast to Murai's pioneering work, a carbometallation pathway was proposed rather than a hydrometallation pathway, due to insertion of the alkene into the Ru(II)–C bond relieving the strain associated with 4-membered chelate **I**. Exemplification of this protocol was not disclosed.

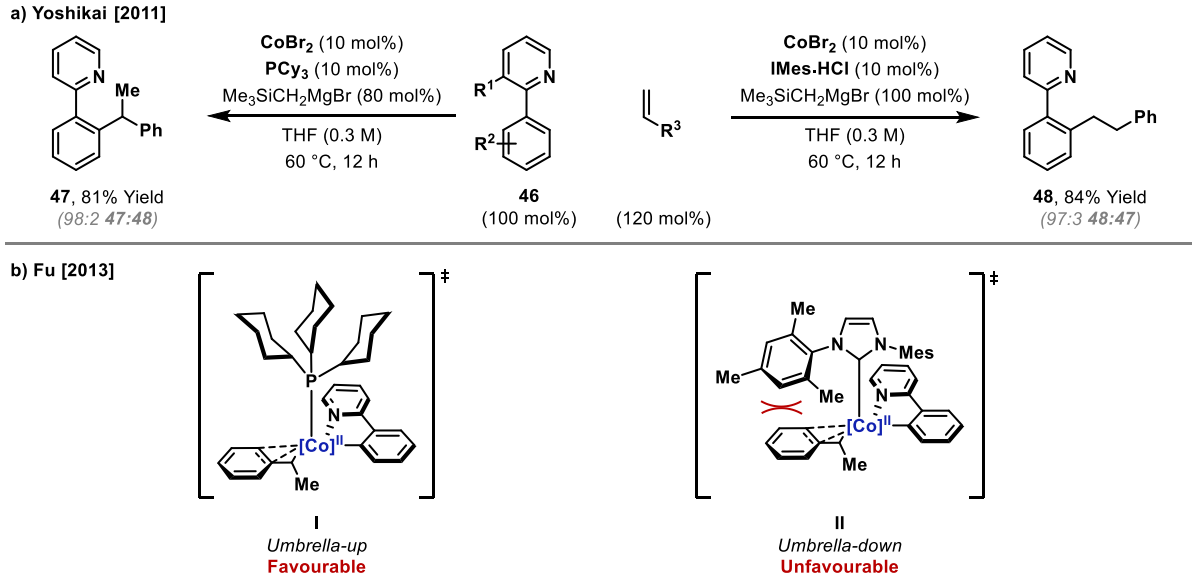


Scheme 26: *The first example of branch-selective alkene hydroarylation.*

In 2011, Yoshikai and Gao utilised a PCy_3-ligated Co(0)-catalyst to promote branch-selective styrene hydroarylation with 2-phenylpyridine **46**, generating hydroarylation products with complete branch selectivity (e.g. **47** in 81% yield) (Scheme **27a**).[84] The active Co(0)-catalyst forms *in situ* by Grignard-promoted reduction of the Co(II)-precatalyst. The ligand was found to be crucial to the regioselectivity of the hydroarylation reaction, with a complete switch to linear hydroarylation product, such as **48**, observed when using IMes·HCl as the ligand. The hydroarylation of electronically varied styrenes with a variety of arylpyridines proceeded to give the desired products branch-selectively and in good yields. However, when aliphatic alkenes were utilised only linear hydroarylation products were isolated. Deuterium-labelling reactions resulted in scrambling of the deuterium signals, leading to a Murai-type mechanism being proposed. Here, reversible pyridyl directed oxidative addition and insertion of the alkene into the Co(II)–H bond is followed by irreversible and regioselectivity determining C–C reductive elimination. Hence, this is strictly the first reported example of a branch-selective Murai-type hydroarylation (hydrometallation is operative as opposed to carbometallation).[84]

Subsequent mechanistic studies by Fu and co-workers supported the mechanism proposed above, with DFT calculations revealing hydrometallation as the most probable pathway (Scheme **27b**).[85] These studies also gave insight into the ligand controlled regioselectivity of the reaction. It was proposed that both the ligand shape and the steric interactions between the ligand and the arene were the regiocontrol factors. For example, it was suggested that the cyclohexyl substituents on PCy_3 sit away from the Co(II)-centre (umbrella-up) in intermediate **I**. However, in intermediate **II**, the mesityl unit of the IMes ligand points towards the Co(II)-centre (umbrella-down), creating a more sterically crowded

conformation, whereby there is an interaction between the mesityl unit of the ligand and the arene. **II** is therefore disfavoured and a less sterically crowded conformation is adopted to afford linear regioisomer **48**.

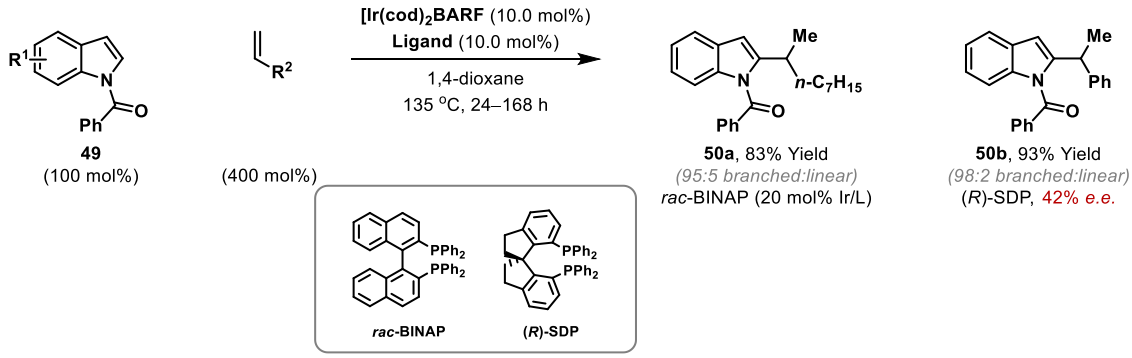


Scheme 27: *Ligand-controlled regioselectivity of Co(0)-catalysed styrene hydroarylation with arylpyridines.*

1.3.2 – Recent Developments in Enantio- and Branch-Selective Alkene Hydroarylation

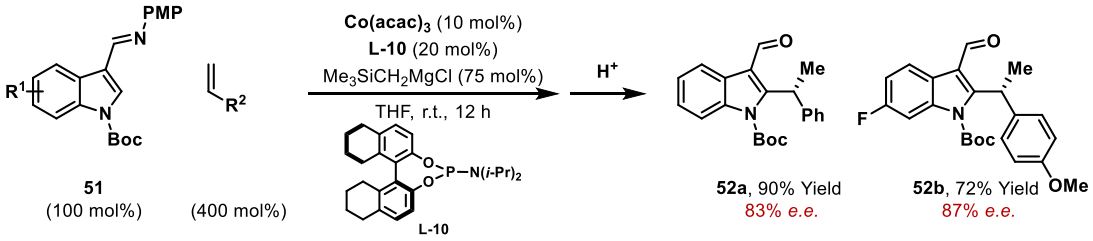
Since this first general example (Scheme **27a**), a wealth of research into the branch-selective hydro(hetero)arylation of a range of alkenes (styrenes, aliphatic alkenes, enol ethers, acrylates) has emerged[82] with significant contributions made by the groups of Yoshikai,[84, 86-90] Shibata,[91-93] Ackermann[94-95] and Nishimura.[96-101] Significantly, enantioselective protocols have begun to take precedence, providing atom and step economical routes to benzylic stereocentres.

In 2012, Shibata and co-workers developed an Ir(I)-catalysed method for alkene hydroheteroarylation at the C2-positions of indoles (Scheme **28**).[92] The use of a simple *N*-benzoyl directing group, promoted the alkylation of indoles **49** with a range of styrenes to afford the desired products branch-selectively and in excellent yields (*up to* 93%). Significantly, the process was effective with non-1-ene, an alkyl alkene, to afford **50a**; here, 20 mol% of Ir(I)-catalyst and a reaction time of seven days was required. Additionally, promising levels of enantioselectivity were achieved for the enantioselective hydroarylation of styrene (42% *e.e.*), when using (*R*)-SDP as the ligand (**50b**). Interestingly, when an *N*-acetyl directing group was employed alongside *rac*-BINAP as the ligand, linear hydroarylation was promoted. No studies into this switch in selectivity were disclosed.



Scheme 28: *Ir(I)-catalysed alkene hydroheteroarylation with indoles and studies towards an enantioselective protocol.*

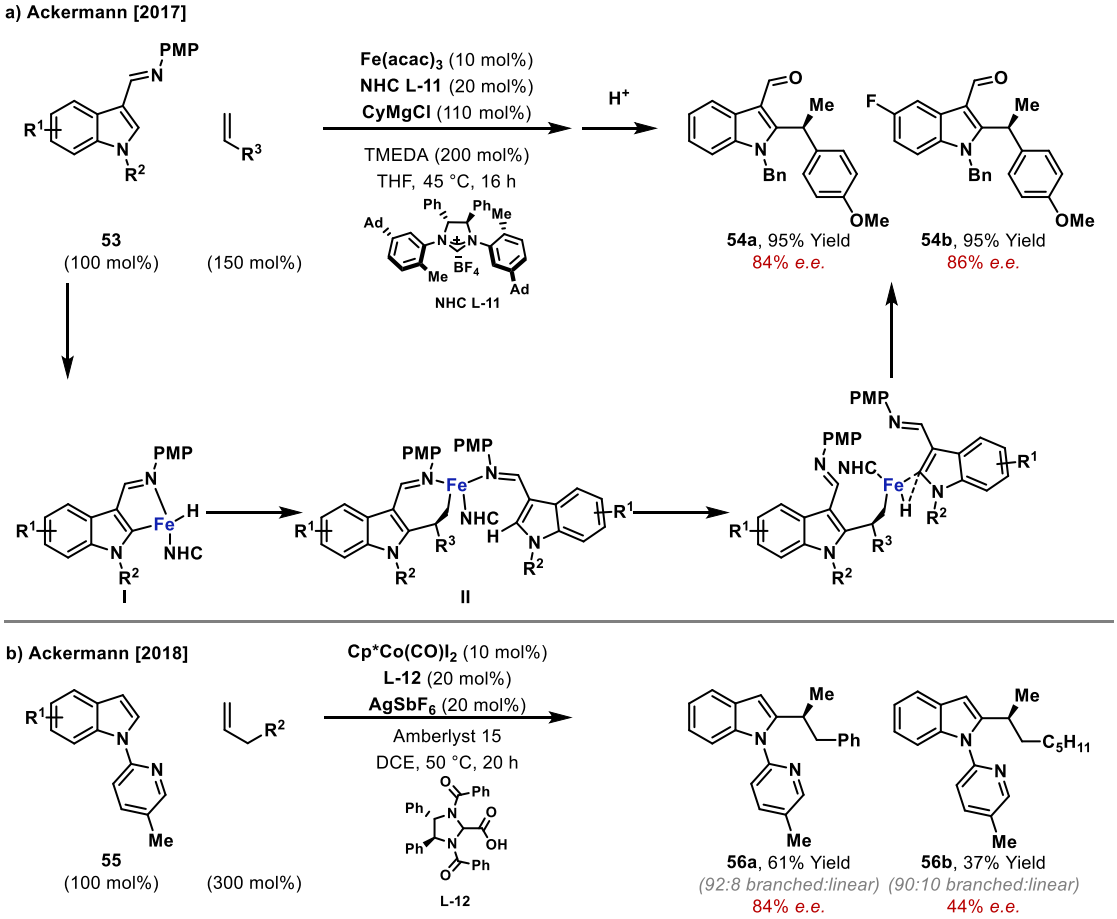
Following Shibata's initial studies towards enantioselective alkene hydroarylation with indole derivatives (Scheme **28**), Yoshikai and Lee reported a Co(I)-catalysed enantioselective protocol (Scheme **29**).[89] They utilised an imine moiety as a transient directing group (**51**), which they had previously demonstrated to promote branch-selective hydroarylation of aryl aldehydes and ketones with a range of styrenes.[84, 87] The active Co(I)-catalyst forms *in situ* from $Co(acac)_3$, chiral phosphoramidite ligand **L-10** and Grignard reagent. The desired alkylated indoles (e.g. **52a** and **52b**) were generated in good yields (*up to* 90%) and enantiopurities (*up to* 87% *e.e.*). However, unlike Shibata's methodology, the hydroarylation of aliphatic alkenes was not described.



Scheme 29: *Co(I)-catalysed methodology for the enantioselective styrene hydroheteroarylation with indoles.*

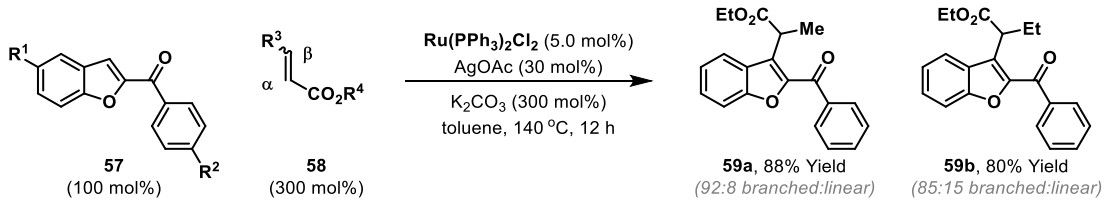
Two years later, Ackermann and co-workers reported a chiral NHC ligated Fe(I)-catalyst that selectively alkylates *N*-protected indoles **53** bearing the same transient imine directing group as Yoshikai and Lee (Scheme **30a**).[94] The protocol was applicable for the hydroarylation of a range of alkenyl metallocenes and styrenes with indoles equipped with carbon-based *N*-protecting groups. The active Fe(I)-catalyst forms *in situ*, *via* reduction of the Fe(III)-precatalyst in the presence of a Grignard reagent. Oxidative addition of the Fe(I)-catalyst into the relevant C–H bond gives intermediate **I**. Alkene coordination and subsequent coordination of a second equivalent of indole substrate promotes migratory insertion of the alkene into the C–Fe bond to give intermediate **II**. Subsequent reductive elimination generates the benzylic stereocentres, such as **54a** and **54b**, in excellent yields and enantiopurities. More recently, Ackermann and co-workers detailed methodology for Co(I)-catalysed enantioselective hydroarylation of alkenes with indoles equipped with *N*-methylpyridine directing

groups **55**, to generate benzylic stereocentres, including **56a** (Scheme **30b**).[95] Here, one example of an aliphatic alkene was detailed; however, desired alkylated indole **56b** was produced in moderate yield (37%) and enantiopurity (44% *e.e.*). A related protocol was reported by Meek and co-workers who achieved enantioselective Rh(I)-catalysed alkylation of the C3-position of indoles with 1,3-dienes.[102] However, this transformation proceeds *via* nucleophilic attack of indole onto an allyl-rhodium intermediate instead of *via* an aryl-Rh intermediate.



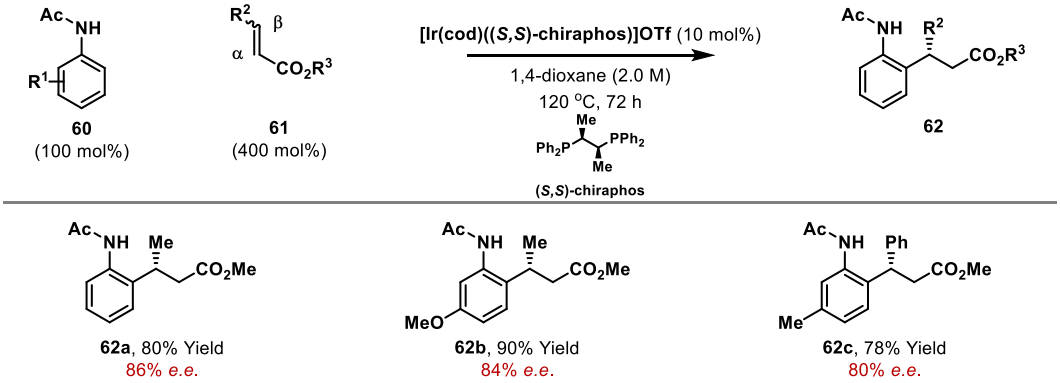
Scheme 30: *Methodologies for the enantioselective hydroheteroarylation of alkenes with indoles.*

In 2014, Ramana and co-workers made a substantial contribution towards utilising coupling partners other than styrenes for branch-selective hydroarylation reactions (Scheme **31**).[103] They employed a ketone directing group for Ru(0)-catalysed branch-selective hydroheteroarylation of acrylates **58** with benzofurans **57**. A range of terminal and β-substituted acrylates generated C3-alkylated 2-aroylbenzofurans in excellent yields (e.g. **59a** and **59b**). Interestingly, a linear selective protocol was developed by employing additional triphenylphosphine, omitting AgOAc and changing the base and solvent.[103]



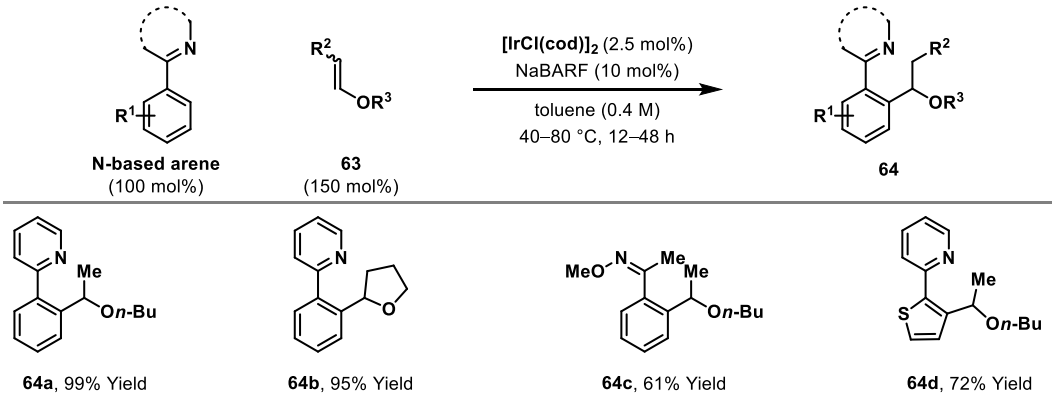
Scheme 31: *Ru(0)-catalysed hydroarylation of acrylates with benzofuran substrates.*

More recently, Shibata and co-workers developed methodology for the enantioselective hydroarylation of acrylates **61** with a range of arenes bearing acetanilide directing groups **60** (Scheme **32**).[91] They employed an Ir(I)-catalyst equipped with a commercially available chiral ligand to afford 3,3-disubstituted propanoates in excellent yields and enantiopurities (e.g. **62a**–**c**). Notably, in contrast to Ramana's methodology, the benzylic bond is formed to the β-position of the acrylate. This transformation is proposed to proceed *via* carbonyl-directed oxidative addition and hydrometallation, followed by irreversible C–C reductive elimination.



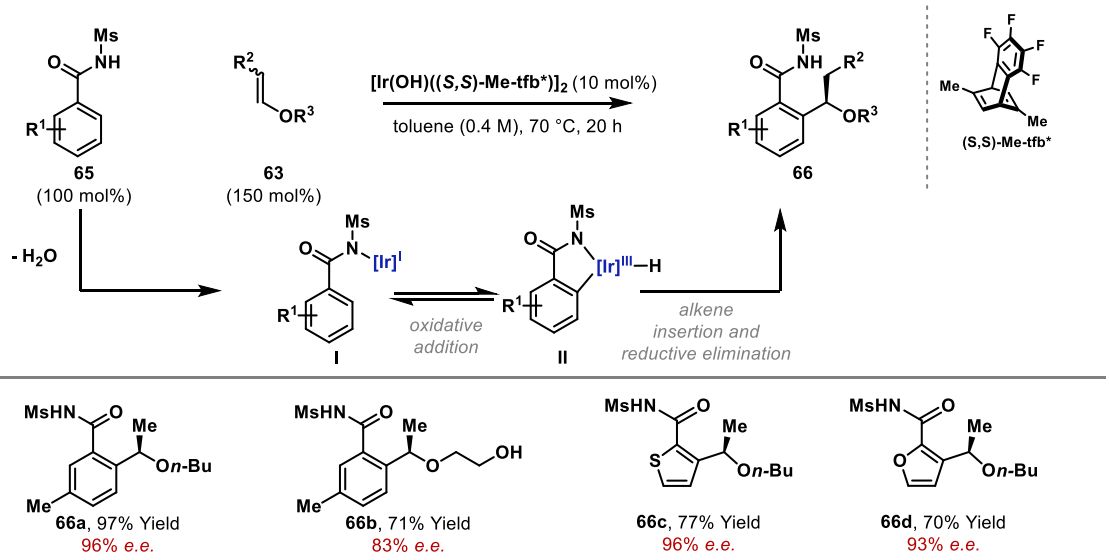
Scheme 32: *Enantioselective Ir(I)-catalysed hydroarylation of acrylates with acetanilides.*

In 2015, Nishimura and Ebe demonstrated that enol ethers **63** could undergo Ir(I)-catalysed branch-selective hydroarylation (Scheme **33**).[99] A range of arenes with *N*-based directing groups, including pyridines, oxazolines and oxime ethers were employed to afford benzylic ether products, such as **64a**–**d**, in good yields and with complete branch selectivity. Alkyl, aryl and cyclic enol ethers all underwent efficient hydroarylation; however, styrenes and alkyl alkenes were unsuitable. Notably, by utilising a pyridine directing group, the process was expanded to the hydroheteroarylation of an enol ether with a thiophene derivative to give **64d**. Here, 1,5-cyclooctadiene acts as a chelating ligand, with no external phosphine ligand required. It is proposed that both oxidative addition and alkene migratory insertion occur reversibly, with reductive elimination being the first irreversible and regioselectivity determining step.



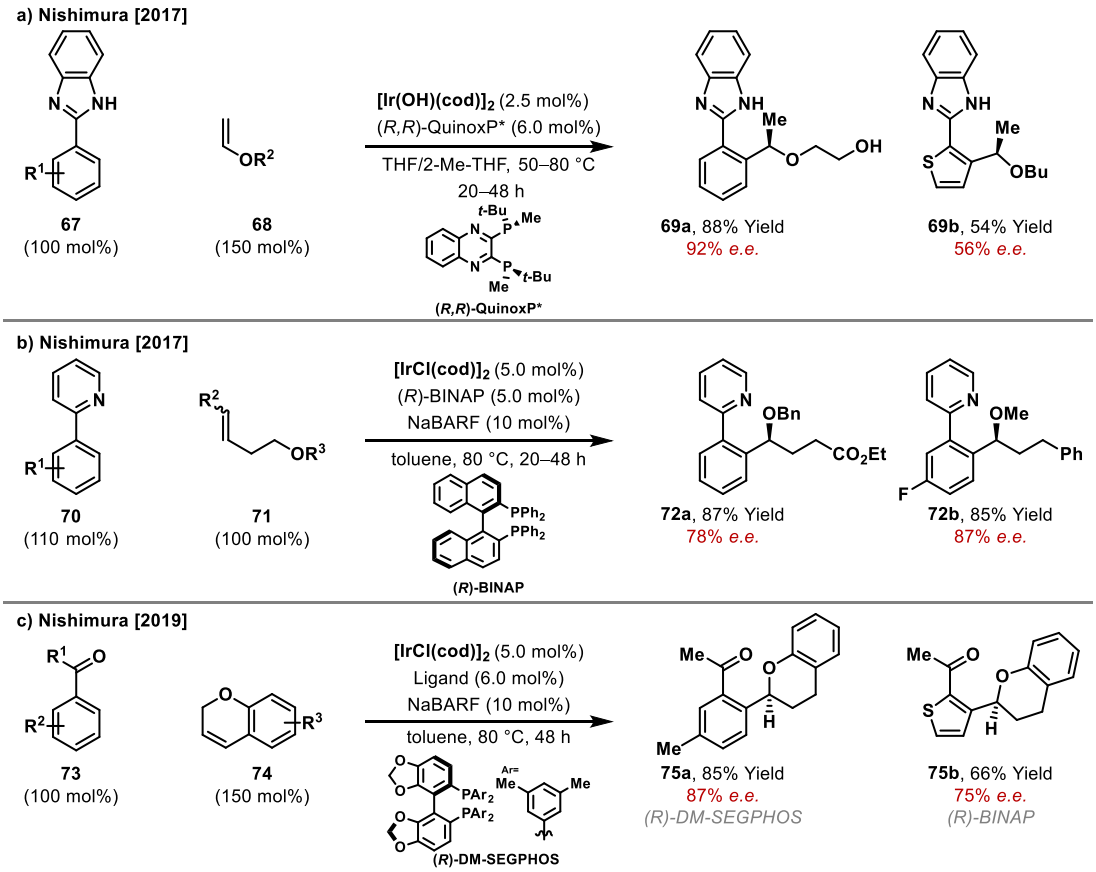
Scheme 33: *Pyridine-directed hydroarylation of enol ethers with (hetero)arenes under Ir(I)-catalysed conditions.*

Through modification of the Ir(I)-catalyst system with chiral diene ligand (*S*,*S*)-Me-tfb*, Nishimura and co-workers developed an enantioselective protocol for the hydroarylation of enol ethers **63** (Scheme **34**).[96] The methodology was applicable to a range of arenes **65** bearing amide-based directing groups, which gave benzylic ether products **66a**–**d**, in good yields and enantiopurities (*up to* 99% *e.e.*). The protocol tolerates the hydroarylation of both cyclic and acyclic enol ethers with a broad range of substituted arenes. Additionally, the alkylation of heteroaromatics proceeded to generate the desired products, such as **66c** and **66d**, in excellent yields and enantiopurity (*up to* 96% *e.e.*). Here, the nitrogen atom of the amide moiety (rather than the carbonyl unit as previously seen) coordinates and directs the Ir(I)-catalyst. Deuterium exchange experiments showed reversible hydrometallation but irreversible carbometallation. This method accesses benzylic alcohols enantioselectively, *via* an alternative route to traditional protocols (Grignard addition to aldehyde). It is notable for the high enantioselectivity achieved; however, the process requires a directing group with an acidic N–H bond to successfully establish 5-membered aminoiridacycle **(I** to **II)**. Additionally, enol ethers are electronically predisposed to undergo branch-selective hydroarylation.



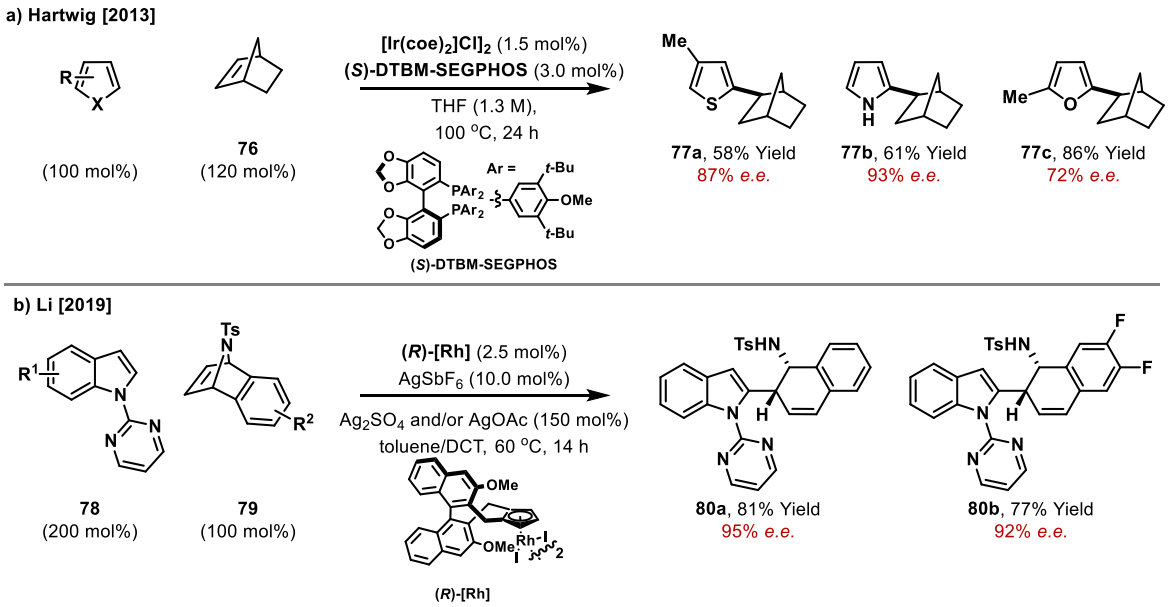
Scheme 34: *Enantioselective Ir(I)-catalysed hydroarylation of enol ethers with (hetero)arenes.*

Through modification of Ir(I)-pre-catalysts with chiral bisphosphine ligands, Nishimura and co-workers expanded their asymmetric hydroarylation methodology. For example, they reported the hydroarylation of vinyl ethers **68** with arenes bearing 2-aryl-substituted azole directing groups **67**, which generated hydroarylation products, such as **69a** and **69b** (Scheme **35a**, (*R*,*R*)-QinoxP*).[97] Long chain alkenyl ethers **71** were isomerised by the Ir(I)-catalyst, before undergoing enantioselective hydroarylation with 2-phenylpyridines **70**, generating hydroarylation products, such as **72a** and **72b** (Scheme **35b**, (*R*)-BINAP).[101] Additionally, cyclic tertiary benzylic stereocentres were generated enantioselectively *via* asymmetric hydroarylation of cyclic enol ethers **74** with arenes equipped with ketone directing groups **73** to give products, including **75a** and **75b** (Scheme **35c**, (*R*)-DM-SEGPHOS).[98]



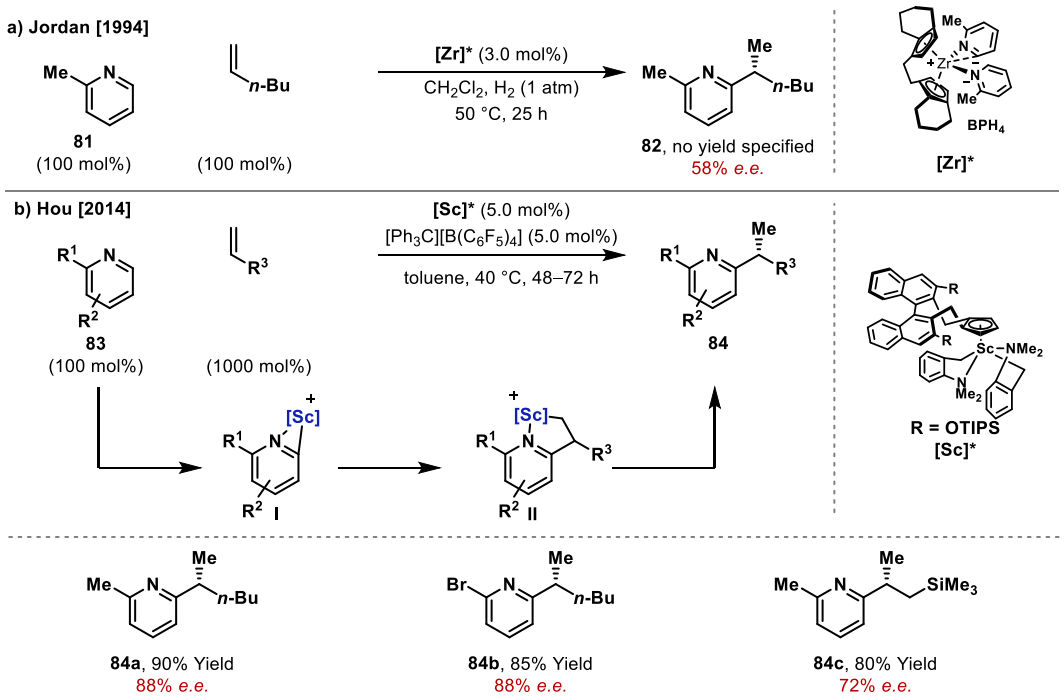
Scheme 35: *Ir(I)-catalysed enantioselective hydroarylation of various enol ethers.*

In addition to the above examples (Scheme **29**–**30**, **32** and **34**–**35**), asymmetric Murai-type hydroarylation reactions have also been reported with strained bicyclic alkene coupling partners.[104-108] For example, in 2013 Hartwig and co-workers demonstrated the Ir(I)-catalysed asymmetric hydroheteroarylation of norbornene **76** to give the target products, including **77a–c**, in moderate to excellent yields and good levels of enantiopurity when using DTBM-SEGPHOS as the chiral ligand (*up to* 98% *e.e.*) (Scheme **36a**).[106] More recently, Li and co-workers reported the hydroarylation of azabenzonorbornadienes **79** with indoles bearing pyrimidyl directing groups **78** (Scheme **36b**).[109] They utilised a chiral Rh(III)-precatalyst, with Ag_2SO_4/AgOAc as an additive to generate the desired cyclic benzylic stereocentres, such as **80a** and **80b**, in excellent yields and enantiopurities. These methodologies are significant for the high atom economy achieved and the broad range of heteroaromatics applicable. Despite this, the protocols are limited to highly reactive norbornene derivatives as the alkene coupling partner and, because this system is symmetrical, the requirement to control branched *vs* linear selectivity is obviated.



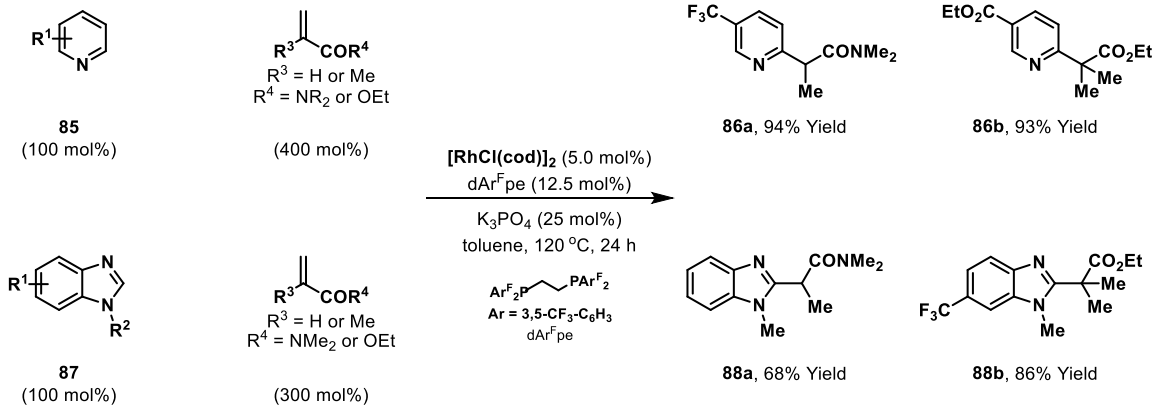
Scheme 36: *Transition-metal catalysed enantioselective hydroheteroarylation of strained bicyclic alkenes.*

The enantioselective alkene hydroarylation processes discussed so far all rely on additional directing groups for *ortho*-selective C–H functionalisation. However, it has been demonstrated in a few cases that hydroarylation can occur under directing group free conditions. For example, in 1994 Jordan and co-workers reported that a chiral Zr(III)-catalyst promoted the hydroarylation of hex-1-ene with 2-methylpyridine **81** to generate motif **82** bearing a benzylic stereocentre with promising levels of enantiopurity (58% *e.e.*).[110-111] Building upon these seminal studies (Scheme **37a**), Hou and co-workers developed a highly enantioselective protocol (Scheme **37b**).[112] They employed a Sc(III)-catalyst, which coordinates to the pyridine *N*-atom, facilitating oxidative addition into the *ortho* C–H bond of **83**. Subsequent alkene coordination and migratory insertion into the [Sc]–C bond, generates the alkylated pyridines, including **84a**–**c**, with excellent enantiopurity (*up to* 96% *e.e.*). This significant advance towards directing group free branch- and enantioselective alkene hydroarylation requires substituents in the *ortho*-position of pyridine, presumably to prevent bis-alkylation from occurring. Additionally, this methodology is substrate specific as the C–H activation step is dependent upon the nitrogen atom of pyridine coordinating to the metal catalyst.



Scheme 37: *Directing group free enantioselective alkene hydroarylation with pyridine moieties.*

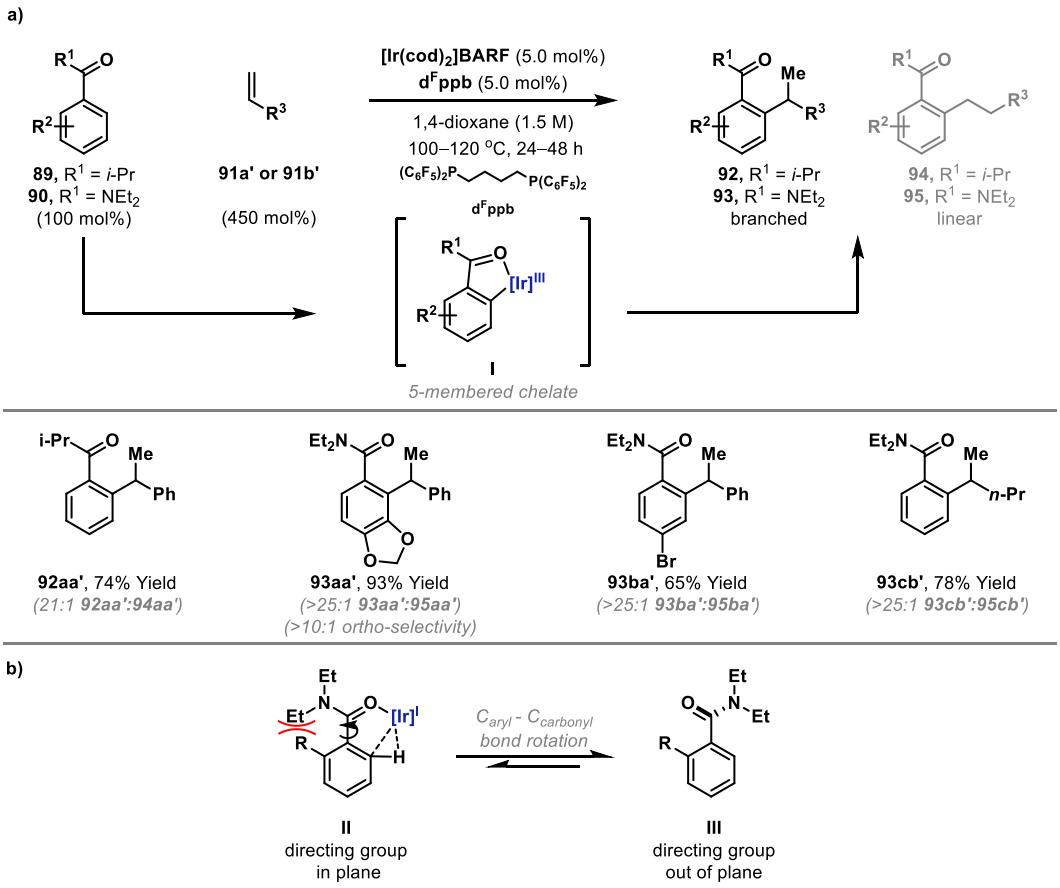
Another directing group free approach was reported by Ellman and co-workers, who employed a Rh(I)-catalyst ligated with an electron-deficient bisphosphine ligand for the branch-selective hydroarylation of acrylates and acrylamides with pyridines **85** and benzimidazoles **87** (Scheme **38**).[113-114] Significantly, ethyl methacrylate was applicable, affording challenging all-carbon quaternary centres, such as **86b** and **88b**. Interestingly, this method offers alternate regioselectivity *vs* Rh-catalysed conjugate addition strategies.[115]



Scheme 38: *Access to all-carbon quaternary centres via non-directed alkene hydroarylation of acrylates with N-heteroaromatics.*

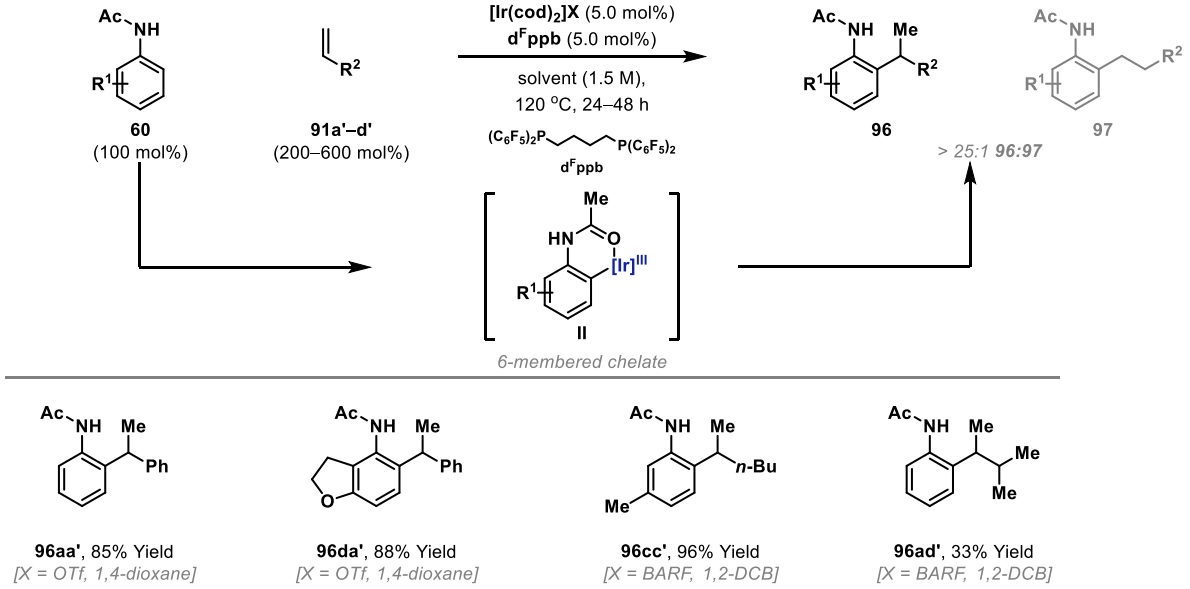
1.4 – Versatile Methodology for Ir(I)-Catalysed Branch-Selective Alkene Hydroarylation

In 2014, building upon the pivotal Ir(I)-catalysed conditions developed by Shibata (Scheme **28**), former PhD student, Dr. Giacomo Crisenza developed a protocol for branch-selective Murai-type alkene hydroarylation with aryl ketones **89** and amides **90** (Scheme **39a**).[116] A range of weakly-coordinating carbonyl-based directing groups (*e.g.* ketones and amides) were employed to direct oxidative addition of an Ir(I)-catalyst ligated with the wide bite angle, electron-deficient bisphosphine ligand, d^Fppb (1,4-bis(di(pentafluorophenyl)phosphino)butane) (*via* 5-membered chelate **I**). The desired products (e.g. **92** and **93**) were produced in excellent yield and with complete branch selectivity for the hydroarylation of a range of styrenes and aliphatic alkenes with electron-rich and -poor benzamides. For substrates bearing substituents in the *meta*-position, the *ortho*-regioselectivity was a result of both electronic and steric effects, with high selectivity often observed (e.g. **93aa'**). However, *ortho*-substituents on the arene partner were not tolerated, most likely due to a steric interactions with the directing group, forcing it to twist out of the plane of the arene, and hence inhibiting oxidative addition (**II** to **III**) (Scheme **39b**).[116]



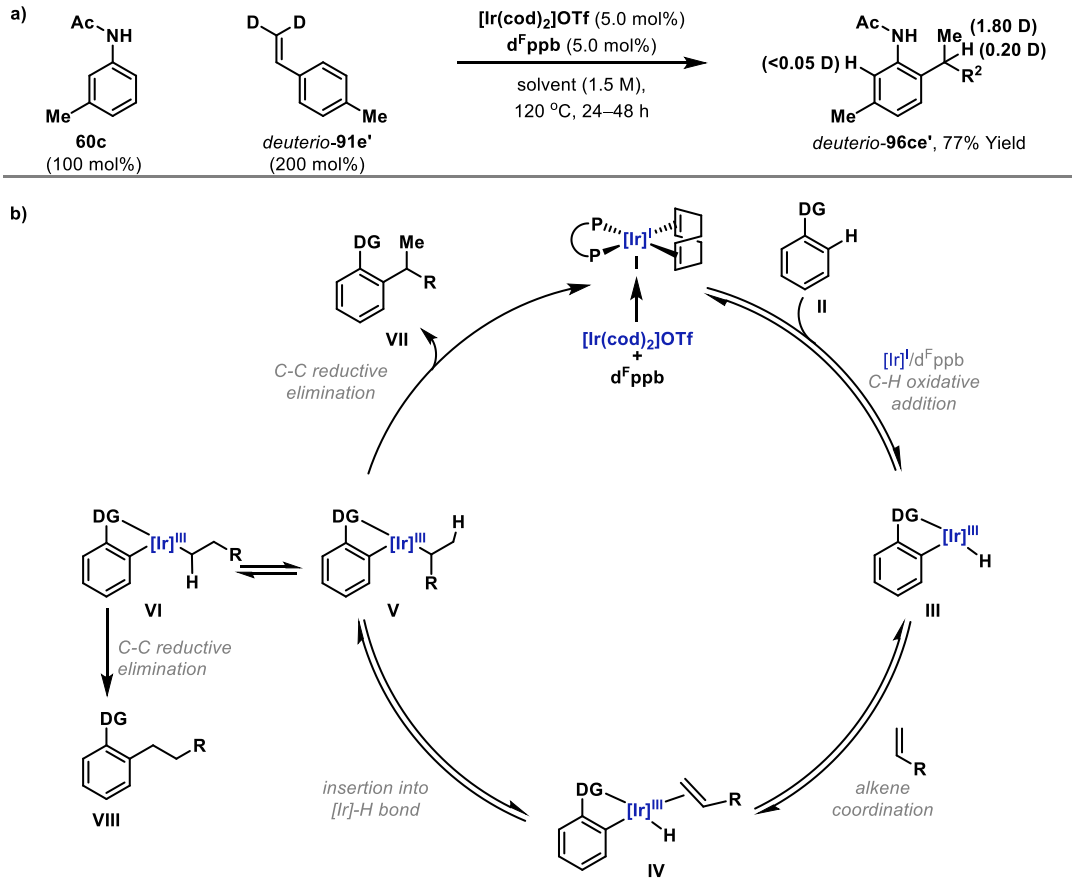
Scheme 39: *Ir(I)-catalysed hydroarylation of alkenes with benzamide derivatives.*

Similar Ir(I)-catalysed conditions were also applicable to alkene hydroarylation with electron-rich acetanilide substrates **60** (Scheme **40**).[117] Here, the mechanistic pathway proceeds *via* more challenging 6-membered chelate **II**. *Ortho*-alkylated products, such as **96**, were generated in excellent yields and with complete branch selectivity for the hydroarylation of styrenes or aliphatic alkenes. Significantly, by proceeding through more flexible 6-membered chelate **II**, *ortho*-substituents on the anilide coupling partner were tolerated (e.g, **96da'**).



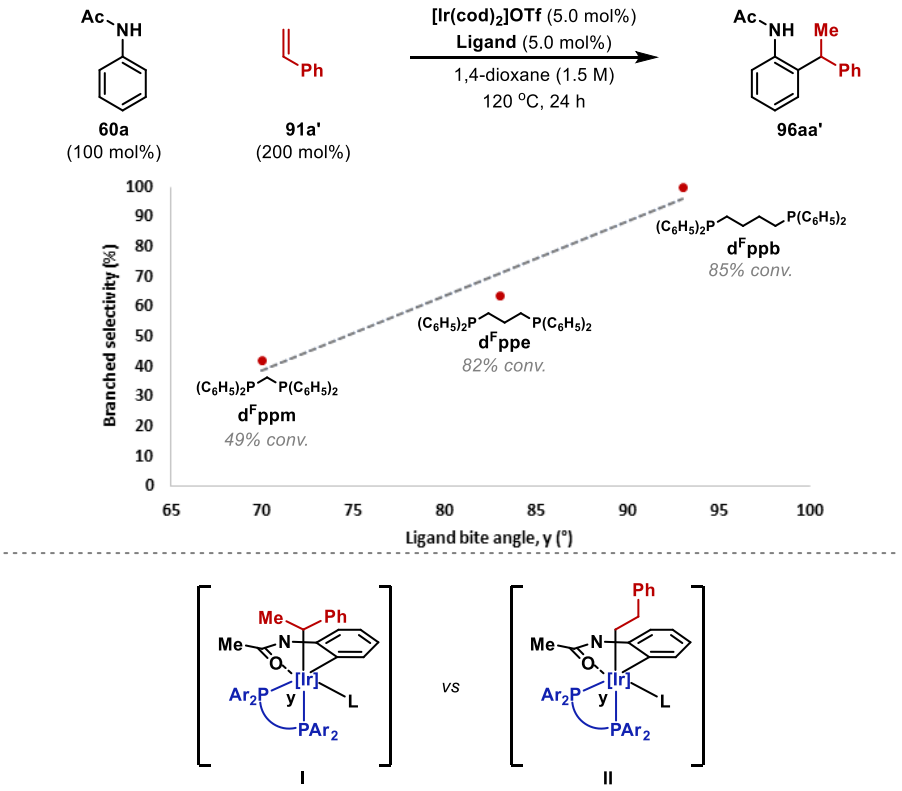
Scheme 40: *Ir(I)-catalysed hydroarylation of alkenes with acetanilide derivatives.*

Crisenza carried out experiments to elucidate the mechanistic pathways for these processes. Initially, the hydroarylation of deuterated alkene *deuterio*-**91e'** with acetanilide **60c** was performed and deuterium incorporation was observed at both the benzylic position (0.20 D, 20% deuteration) and in the methyl unit (1.80 D, 60% deuteration) of product *deuterio*-**96ce'** (Scheme **41a**).[116-117] The observed scrambling supports reversible C–H oxidative addition (**I** to **III)**, and reversible alkene hydrometallation to generate intermediates **V** or **VI** (Scheme **41b**). Reductive elimination then forms branched product **VII** or linear product **VIII**. Crisenza determined natural abundance ^{13}C kinetic isotope effects (KIE's) using the Singleton method (*see* Section **4.4**) and this supported a reversible hydrometallation pathway, followed by irreversible C–C reductive elimination.[118] This mechanistic pathway was also found to be operative for benzamide substrates (Scheme **39**).



Scheme 41: *Proposed mechanism for the carbonyl directed Ir(I)-catalysed hydroarylation of alkenes.*

For both benzamide **90** (Scheme **39**) and acetanilide **60** substrates (Scheme **40**), the ligand d^{F}ppb was crucial for achieving the high levels of branch selectivity observed.[117] Indeed, when changing the ligand from d^{F}ppm to d^{F}ppb in the hydroarylation of styrene **91a'** with acetanilide **60a**, increased branch selectivity was achieved (40% to 100%) (Scheme **42**). This is due to the significant change in the bite angle of the ligand (70º to 94º). Additionally, a corresponding increase in yield of **96aa'** was observed (49 to 85% yield). The wide bite angle bisphosphine ligand increases the bond angle (y), which in turn, positions the alkyl substituent closer to the Ir–C_{aryl} bond. This may increase the rate of C–C reductive elimination. Steric destabilisation of branched intermediate **I** would be greater than for linear regioisomer **II**, potentially explaining the branch selectivity observed. Specifically, intermediate **I** is less favourable than intermediate **II** and therefore, reductive elimination from **I** is faster than from **II**.

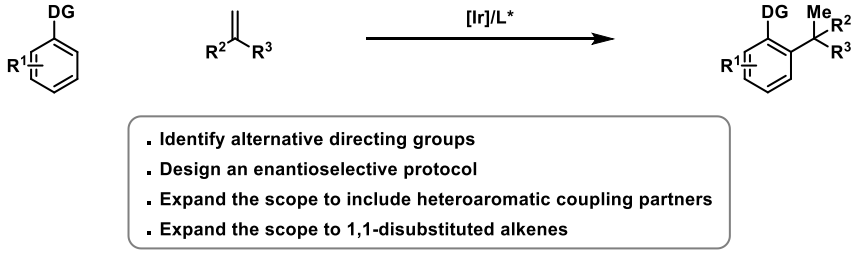


Scheme 42: *The effect of the ligand bite angle on conversion and branch selectivity.*

The protocols outlined above (Scheme **39** and **40**) offer a facile and atom economical approach to generating tertiary benzylic centres with a broad range of simple styrenes and aliphatic alkenes. The development of an asymmetric protocol would provide a direct and waste-free alternative to cross-coupling reactions for the enantioselective synthesis of benzylic stereocentres.

1.5 – Outlook and Project Aims

Since the advent of C–H activation/hydroarylation protocols, many methods for branch-selective alkene hydroarylation have emerged. The processes outlined in Section 1.3 represent significant developments towards a comprehensive protocol for a range of arenes and alkenes (i.e. styrenes, vinyl ethers and acrylates), with examples of enantioselective hydroarylation beginning to emerge. Despite these recent developments, at the outset of this project a general protocol for the carbonyl-directed enantioselective hydro(hetero)arylation of nonpolarized acyclic alkenes, such as α-olefins, was yet to be reported. The methodologies developed by Crisenza for the carbonyl-directed branch-selective hydroarylation of simple styrenes and aliphatic alkenes were described, and this has provided the basis for this research project. This atom economical strategy holds great promise for generating valuable benzylic stereocentres enantioselectively. Additionally, no examples currently exist which generate more challenging quaternary benzylic stereocentres enantioselectively *via* a C–H activation/alkene hydroarylation route.



Scheme 43: *The aims of this research project.*

The research described in this thesis is split into four chapters. Chapter 2 and 3 detail developments into enantioselective alkene hydroarylation and hydroheteroarylation respectively. The main aim of these chapters was to identify a catalytic system that would allow a general enantioselective approach for a wide range of aromatics and heteroaromatics and to exemplify the developed protocol.

Chapter 4 details methodology developed for the generation of all-carbon quaternary centres and studies undertaken into the development of an enantioselective protocol. The main goal of this project was to expand the Ir(I)-catalysed methodology to include 1,1-disubstituted alkenes. The scope was investigated, and mechanistic experiments were carried out to elucidate the catalytic cycle.

Finally, the aim of Chapter 5 was to design and synthesise ligands that would promote a β-hydride elimination step rather than the usual C–C reductive elimination pathway. Using this approach 1,1-disubstituted alkenes were generated *via* Ir(I)-catalysed dual C–H activation and the scope of the reaction was investigated. The target products are useful moieties to build a range of *N*-containing heteroaromatics.

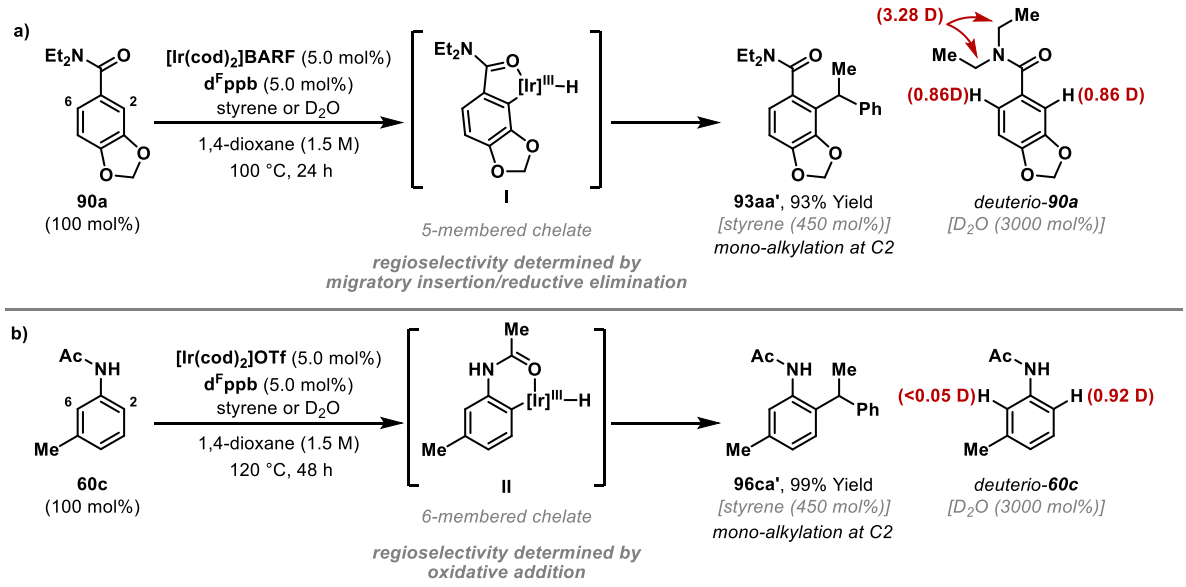
Chapter 2 – Branch- and Enantioselective Iridium Catalysed Alkene Hydroarylation

Parts of this chapter have been adapted from a publication by Grélaud et al.

*(J. Am. Chem. Soc. **2018**, 140, 9351–9356)*

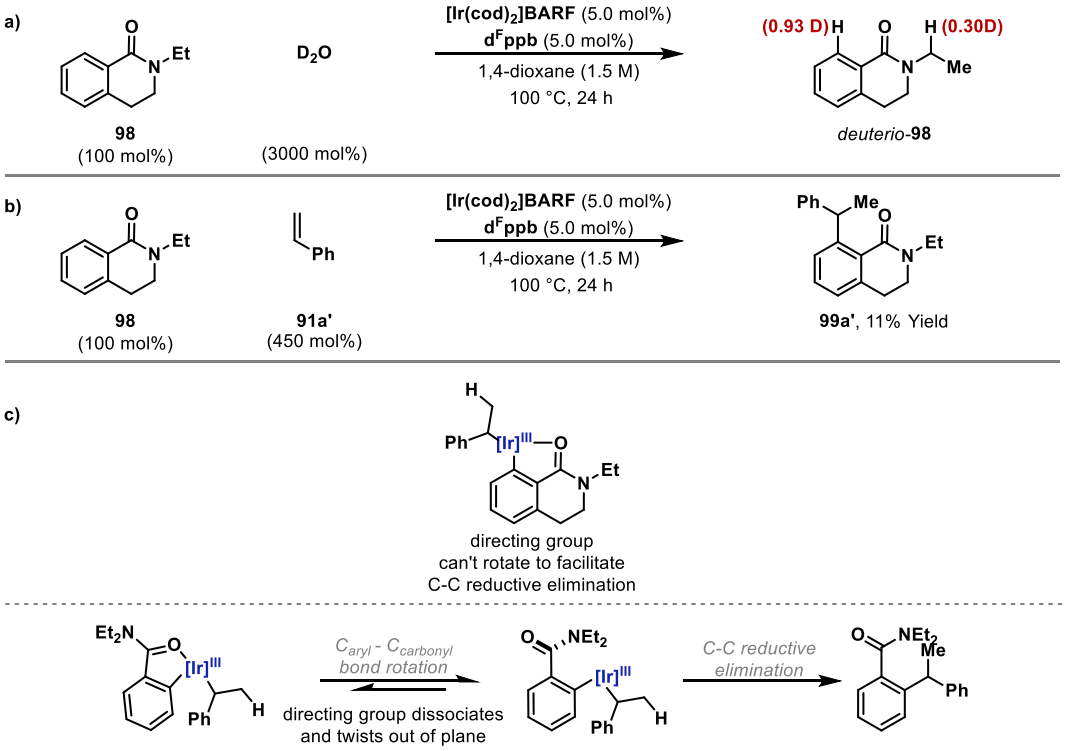
2.1 – Investigating Alternative Directing Groups for Branch-Selective Alkene Hydroarylation

The initial studies of this project focused on identifying a suitable directing group for an enantioselective alkene hydroarylation. As described in Section 1.4, Dr. Giacomo Crisenza demonstrated that weakly coordinating carbonyl groups, including benzamide **90a** (5-membered chelate) and acetanilide **60c** (6-membered chelate), were suitable directing groups to promote Ir(I)-catalysed branch-selective alkene hydroarylations (Scheme **44**).[116-117] The resulting products, such as **93aa'** and **96ca'**, were generated with complete regioselectivity and in excellent yields (93% of **93aa'** and 99% of **96ca'**). In addition to the mechanistic experiments described in Section 1.4 (Scheme **41**), Crisenza subjected benzamide **90a** to [Ir(cod)$_2$]BARF/d^{F}ppb in the absence of styrene, but in the presence of deuterium oxide, to determine the directing ability of the acetanilide unit (Scheme **44a**). High deuterium incorporation was observed at both the *ortho*-positions of *deuterio*-**90a** (C2, and C6, 0.86 D, 86% *deuteration)* and at the methylene units of the directing group (3.28 D, *82% deuteration*).[116] However, in the absence of deuterium oxide, alkylation with styrene **91a'** occurred mono-selectively at the more hindered *ortho*-position C2 of **90a**, indicating that the regioselectivity (C2 *vs* C6) of the hydroarylation is determined at the stage of C–C bond formation and not by the initial C–H activation event (*see* Section **1.4**, Scheme **41**). Additionally, no alkylation is observed at the directing group due to C(sp^2)–C(sp^3) bond formation being more facile than C(sp^3)–C(sp^3). In contrast, when acetanilide **60c** was subjected to deuterium oxide under Ir(I)-catalysed conditions,[117] deuterium incorporation was observed selectively at the less hindered *ortho*-position of *deuterio*-**60c** (C2, 0.92 D, *92% deuteration*), showing that, in this case, oxidative addition is the regioselectivity determining factor (Scheme **44b**). These deuterium exchange experiments highlight the ability of acetanilide and benzamide substrates to direct oxidative addition of an Ir(I)-species, which provides the basis for alternative directing groups to be compared.



Scheme 44: *Deuterium exchange reactions with benzamide **90a** and acetanilide **60c**, carried out by Dr. Giacomo Crisenza.*

The initial aim of the studies detailed in this thesis was to identify alternative directing groups to benzamide and acetanilide moieties, as in **90a** and **60c** (Scheme **44**), that would successfully direct Ir(I) oxidative addition, and therefore promote branch-selective alkene hydroarylation. Electronically differentiated directing groups were investigated, alongside alternative benzamide derivatives. Initially, cyclic benzamide **98**, where the rotation of the directing group is inhibited, was exposed to D_2O under the developed Ir(I)-catalysed conditions (Scheme **45a**). High deuterium incorporation was observed at the *ortho*-position (0.93 D, *93% deuteration*) and at the methylene group (0.30 D, *15% deuteration*) of *deuterio*-**98**. This result suggests that the lack of rotation of the directing group does not inhibit oxidative addition of the Ir(I)-catalyst into the *ortho* C–H bond. When the reaction was carried out with styrene **91a'**, under otherwise identical Ir(I)-catalysed conditions, desired hydroarylation product **99a'** was generated in modest yield (11%) and with complete branch selectivity (Scheme **45b**). The low yield indicates that there is a greater barrier to C–C reductive elimination with the rigid directing group of **98**, compared to the more freely rotating benzamide unit of **90c** (93% yield, Scheme **44a**). Therefore, it is postulated that for successful reductive elimination to occur, the directing group must be able to dissociate and twist out of the plane of the arene, as demonstrated in Scheme 45c.



Scheme 45: *Evaluation of cyclic benzamide **98** in the Ir(I)-catalysed hydroarylation of styrene.*

Subsequent studies focused on exploring the electronic constraints of the directing group for successful Ir(I)-catalysed styrene hydroarylation. Arenes, bearing a range of directing groups were exposed to the Ir(I)-catalysed conditions developed for benzamide derivatives (*see* Scheme **44a**), in the presence of D_2O instead of an alkene coupling partner. Notably, only small amounts of deuterium incorporation were observed in pyridine *N*-oxide *deuterio*-**100**, ester *deuterio*-**101** and sulfonamide derivative *deuterio*-**102** and none of the desired hydroarylation products were formed in the presence of styrene (Table **1**). Presumably, the *N*-oxide of **100** competes for coordination to the Ir(I)-catalyst. Previously, alkyl esters underwent hydroarylation of styrene under $[Ir(cod)_2]BARF/d^Fppb$ conditions, albeit in poor yield (18%).[116] Nevertheless, phenyl ester **101** failed to undergo oxidative addition, most likely due to cross conjugation of the O-atom with the phenyl group. Likewise, sulfonamide **102** was unsuccessful at directing the Ir(I)-catalyst into the ortho C–H bond; however, sulfonamides have previously been utilised as efficient directing groups for *ortho* C–H activation with Rh, Pd and Co catalysts.[119-121] Additionally, 2-pyridyl units have been employed as directing groups for Co(I)-catalysed hydroarylation of styrenes[84] and Ir(I)-catalysed hydroarylation of vinyl ethers (*see* Section **1.3.2**).[99] High deuterium incorporation was observed in both *ortho*-positions when strongly coordinating pyridyl arene **103** was exposed to D_2O under Ir(I)-catalysis (0.95 D, *95% deuteration*). However, when **103** was exposed to styrene under Ir(I)-catalysed conditions, no conversion to the expected hydroarylation product was observed. Presumably, the nitrogen of pyridyl arene **103**, stabilises the Ir(III)-chelate, preventing the directing group from dissociating to facilitate C–C reductive

elimination. These results validate that amide and anilide-based directing groups are the most efficient for promoting branch-selective alkene hydroarylation, so these were selected for the development of an enantioselective alkene hydroarylation.

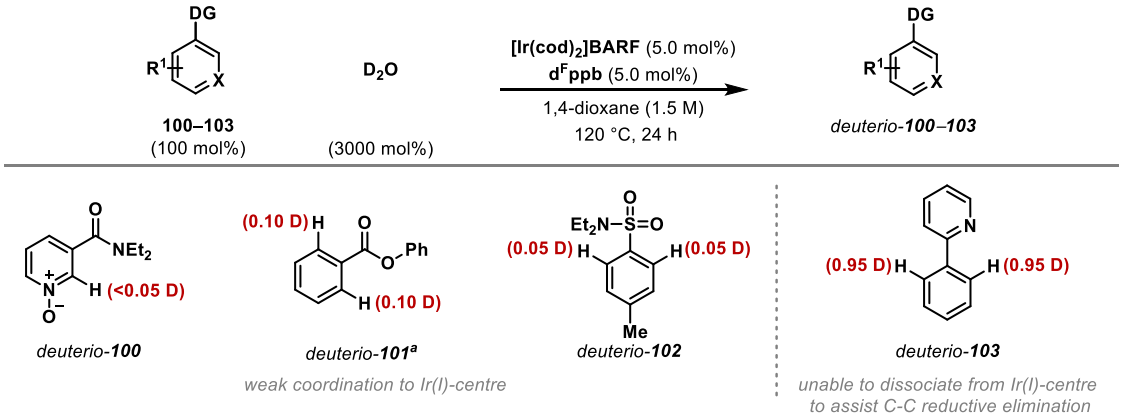


Table 1: *Deuterium exchange reactions with arenes **100–103** bearing alternative directing groups.* [a] *The reaction was conducted at 150 °C.*

2.2 – Studies Towards a Branch- and Enantioselective Alkene Hydroarylation Reaction

2.2.1 – Investigating Commercially Available Chiral Ligands

Branch-selective hydroarylation protocols are an atom economical and efficient method to generate benzylic stereocentres enantioselectively (*see* Section **1.3.2**). Towards this ideal, Dr. Crisenza examined several commercially available chiral ligands for enantioselective Ir(I)-catalysed hydroarylation of styrene **91a'** with benzamide **90d**. These initial studies revealed that a broad range of wide bite angle bisphosphine ligands afforded desired product **93da'** with high branch selectivity. Notably, a member of the Walphos-ligand family gave hydroarylation product **93da'** in 30% yield, with excellent branch selectivity (>25:1) and promising levels of enantiopurity (71:29 *e.r.*). Following these preliminary results, further ligands from the Walphos and Josiphos families were investigated and the key results are reported in Table 2. However, none of those examined provided an improvement in enantioselectivity for styrene **91a'** hydroarylation with benzamide **90d**.

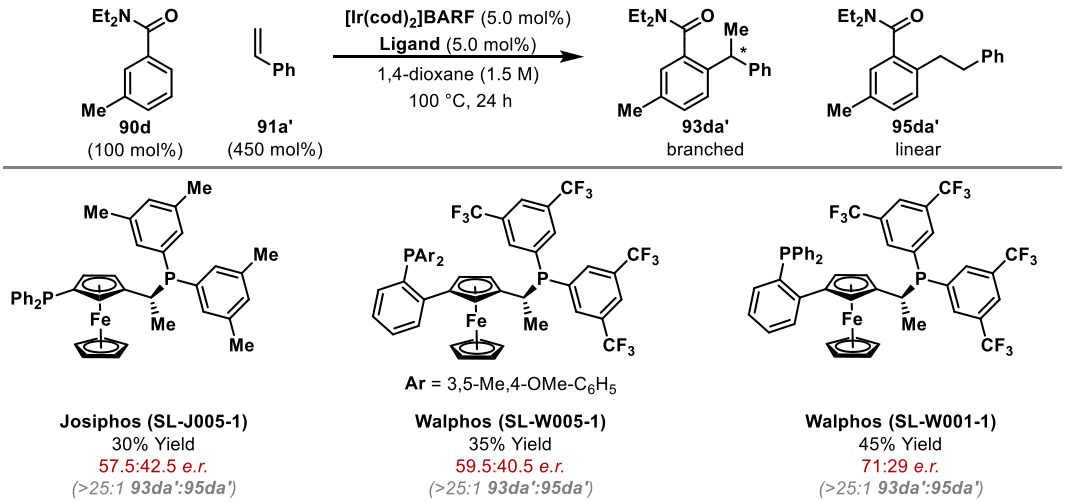


Table 2: *Key results for the screening of commercially available chiral ligands for enantioselective styrene hydroarylation with benzamide* ***90d****.*

Alongside enantioselective styrene hydroarylation with benzamide **90d**, acetanilides **60a** and **60c** were also investigated. Over 50 bidentate chiral phosphine ligands were evaluated under Ir(I)-catalysis and the selected key results are reported in Table 3. The screening showed that ligands with wide bite angles and bulky aryl substituents on phosphorus generated the desired branched hydroarylation product (**96aa'** or **96ca'**). However, in contrast to the reaction with benzamide **90d**, none of the ligands tested demonstrated the efficiency and branch selectivity previously achieved with d^Fppb (Scheme **44b**). In some cases, alkene side-product **104** was also observed. For example, when (*S*,*S*)-f-binaphane was used as the ligand, none of branched product **96aa'** was isolated and instead alkenylated product **104aa'** was observed in 51% yield, alongside linear regioisomer **97aa'** in 39% yield. It is postulated that alkenylation product **104aa'** forms *via* an alternative β-hydride elimination pathway, which will be discussed further in Chapter 5. Ligands including MeOBIPHEP, SEGPHOS, Josiphos and Kelliphite all gave **96aa'**/**96ca'** with promising levels of enantiopurity (67:33–76.5:23.5 *e.r.*), albeit in low yields (14–44%). Notably, Kelliphite was the only ligand that provided desired hydroarylation product **96ca'** with complete branch selectivity (>25:1). Despite failing to identify an efficient commercially available ligand that gave hydroarylation products **93da'** and, **96aa'** and **96ca'**, in high yield and selectivity (enantio- and regio-), these studies confirmed that the enantioselective hydroarylation of styrenes is a feasible approach for the generation of benzylic stereocentres.

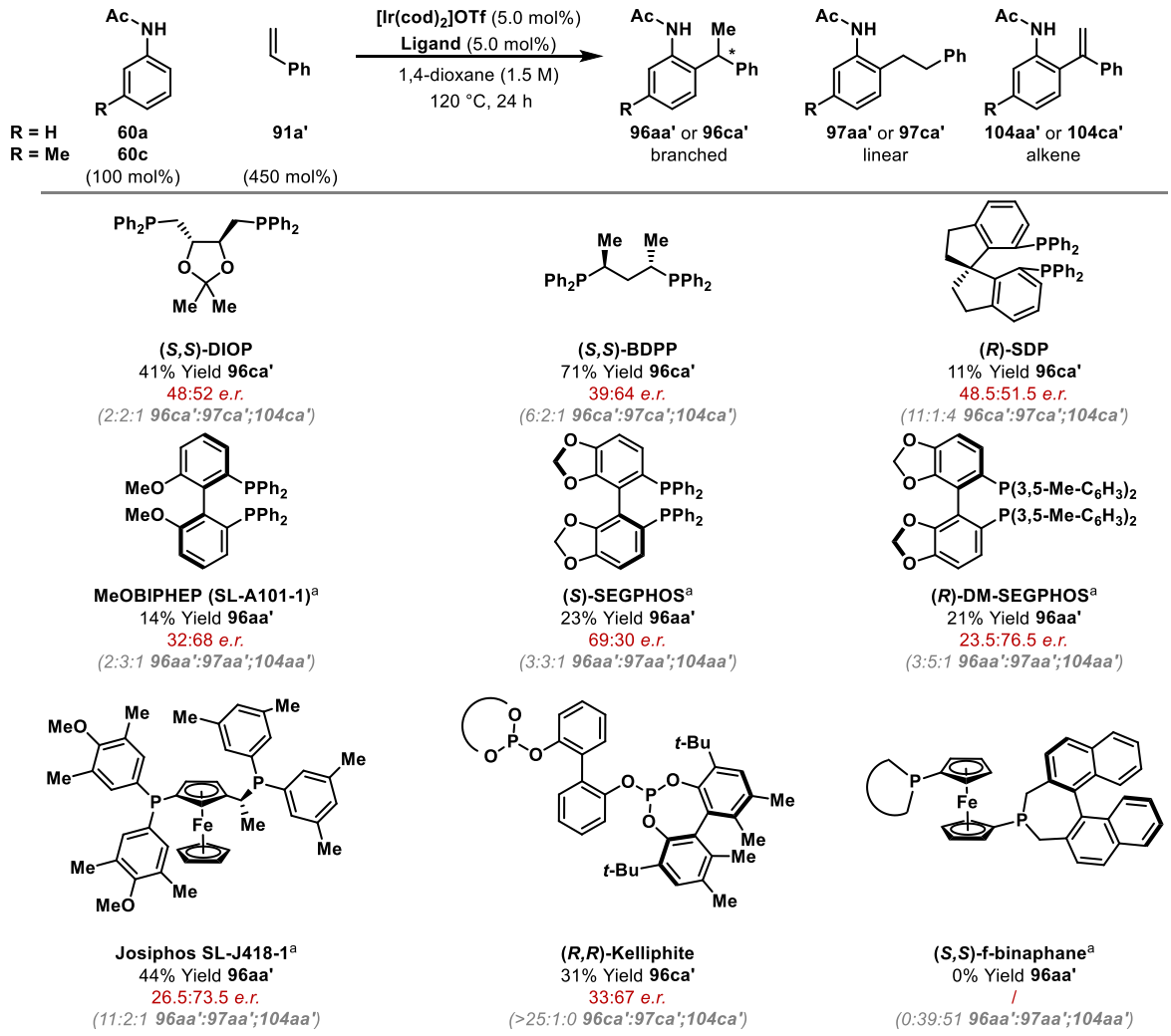
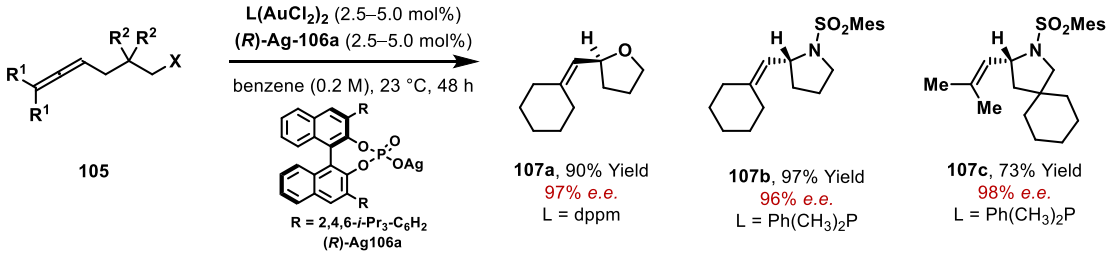


Table 3: *Key results for the screening of commercially available chiral ligands for the enantioselective styrene hydroarylation with acetanilides* ***60a*** *and* ***60c****.* [a]*The reaction was performed at 130 °C.*

2.2.3 – Investigating Chiral Anions

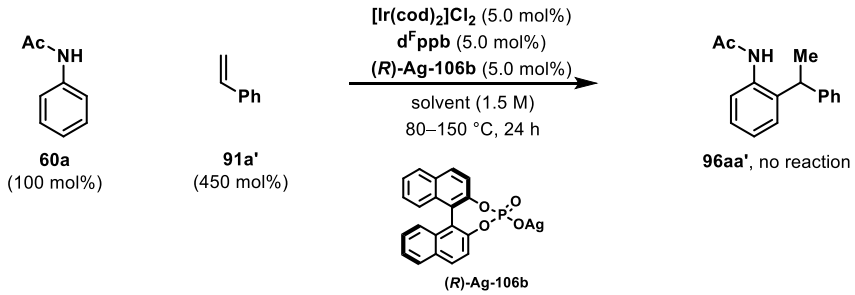
In addition to the screening of commercially available chiral ligands (Scheme **Table 2** and **3**), chiral anions were considered as an alternative strategy to render the branch-selective hydroarylation of styrenes asymmetric. The employment of chiral anions in asymmetric catalysis is a well-established method.[122-124] Rather than coordinating tightly to the metal centre like ligands, chiral anions interact with the metal through electrostatic interactions; however, whether a chiral moiety is acting as a ligand or an anion can often not be unequivocally distinguished. In 2007, Toste and co-workers reported significant examples of the use of chiral counterions in an asymmetric metal-catalysed reaction (Scheme **46**).[125] They employed achiral binuclear gold catalyst $L(AuCl_2)_2$ (*where* L = dppm or $Ph(CH_3)_2P$), alongside chiral silver binaphthol-derived phosphate (*R*)-Ag-**106a**, to promote the cyclisation of allenol and allenamine substrates **105**, giving the hydroalkoxylation products in excellent yields (e.g. **107a–c**, 73–97%) and enantiopurity (96–98% *e.e.*). The enantioselectivity of this transformation improved in non-polar solvents, such as benzene, indicating that a strong interaction between the counterion and

cationic centre is necessary. Additionally, the enantioselectivity of the asymmetric hydroalkoxylation of unactivated allenes could be improved (80% to 92% *e.e.*) by combining a chiral ligand and chiral anion to afford a 'matched pair' effect.



Scheme 46: *Toste and co-workers pioneering chiral anion strategy for asymmetric metal catalysis.*

In order to investigate the use of chiral anions in the hydroarylation of styrene with acetanilide **60a**, binaphthol silver salt (*R*)-Ag-**106b** was synthesised. Acetanilide **60a** and styrene **91a'** were subjected to Ir(cod)Cl_2, d^Fppb and silver cation (*R*)-Ag-**106b** in 1,4-dioxane at 80–150 °C (Scheme **47**); however, branched hydroarylation product **96aa'** was not observed. Additionally, **60a** did not afford target **96aa'** when the reaction was conducted in THF, 1,2-DCB or DMSO, at 120–150 °C. It was postulated that [Ir(cod)$_2$]Cl_2 and (*R*)-Ag-**106b** might not be forming the desired Ir(I)-precatalyst efficiently *in situ*. Consequently, [Ir(cod)]Cl_2 and (*R*)-Ag-**106b** were stirred at ambient temperature in CH_2Cl_2/acetone to prepare the precatalyst prior to reaction; however, conversion to desired product **96aa'** was not observed.



Scheme 47: *Ir(I)-catalysed styrene hydroarylation with acetanilide **60a** in the presence of silver phosphoric acid salt (R)-Ag-**106b**.*

For the branch-selective hydroarylation of styrene to proceed, a cationic Ir(I)-species is required (*see* Section **1.4**, Scheme **41**). It was hypothesised that the phosphate anion of (*R*)-Ag-**106b** could be binding to the cationic Ir(I)-centre relatively strongly. Consequently, dissociation of (*R*)-**106b** from the Ir(I)-centre would be unfavourable and oxidative addition of the active Ir(I)-catalyst into the *ortho* C–H bond of acetanilide **60a** might be inhibited (*see* Section **1.4**, Scheme **41**). Therefore, alternative chiral anions with more stable conjugate bases were investigated for asymmetric hydroarylation of styrene with acetanilide **60a** (Table **4**). In 2009, both List and co-workers,[126] and Giernoth and co-workers[127] independently designed and synthesised variations of chiral disulfonimide **108b** for use in asymmetric

catalysis. Disulfonimide anion Ag-**108b** is reported to be more acidic and therefore, has a lower pK_{aH} value than phosphoric acid salt (*R*)-Ag-**106b** (pK_{aH} value of 1.8 *vs* 3.4 in DMSO).[128] Styrene hydroarylation with acetanilide **60a** was initially carried out in the presence of achiral silver anion **108a** (pK_{aH} value of 2.4 in DMSO) (Table **4a**).[129] Under the reaction conditions with $[Ir(cod)Cl]_2$, d^{F}ppb and sulfonamide Ag-**108a**, hydroarylation product **96aa'** was generated in excellent yield (88%). Following this positive result, (*R*)-Ag-**108b** was synthesised and utilised in the hydroarylation reaction, but no conversion to desired product **96aa'** was observed. This result suggests that either (*R*)-**108b** is too acidic, and hence the interactions with the metal centre are too weak, or the electron-withdrawing groups ($-CF_3$) on **108a** are required. Consequently, chiral anions with similar pK_{aH} values to **108a** were identified; **106c** and **109** both have pK_{aH} values of 2.4 in DMSO (Table **4b**).[128] Additionally, **108c** and **108d** with electron-deficient R-groups on the binaphthyl backbone of the disulfonimide were considered; however, this area of research was not pursued further.

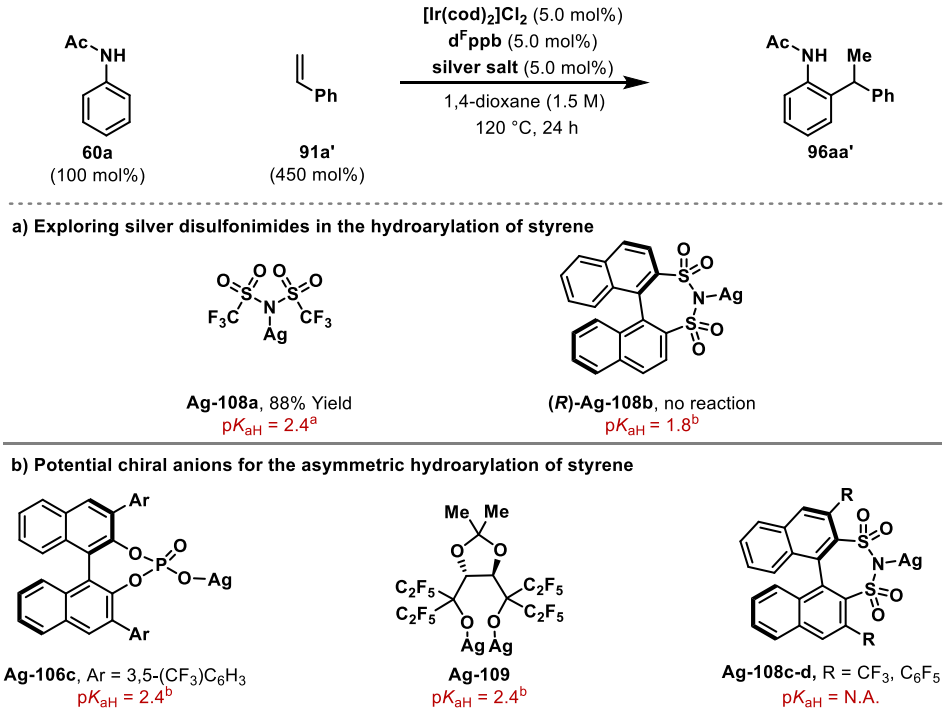


Table 4: *Ir(I)-catalysed styrene hydroarylation with acetanilide **60a** in the presence of disulfonamide anions. [a]See reference 128; [b]See reference 128.*

2.2.2 – Design and Synthesis of Chiral BINOL-Based Bisphosphite and Bisphosphonite Ligands

With chiral anions unsuitable for enantioselective hydroarylation, attention moved back to the use of chiral ligands. During the screening of commercially available chiral ligands for asymmetric hydroarylation of styrene **91a'** with acetanilide **60a**, some key structural requirements for high conversion, high branch regioselectivity and enantioselectivity were identified (Table **3**). Notably, only Kelliphite was able to offer the same level of branch selectivity (>25:1) achieved with d^{F}ppb for

acetanilide **60a**. Based on these observations, it was envisaged that modular modification of the backbone and end units of d^{F}ppb and/or Kelliphite would provide a ligand that could give the high levels of enantioselectivity desired, whilst maintaining excellent branch selectivity (Figure **1**). To this end, wide bite angle chiral ligands with similar structural features to both d^{F}ppb and Kelliphite were designed.

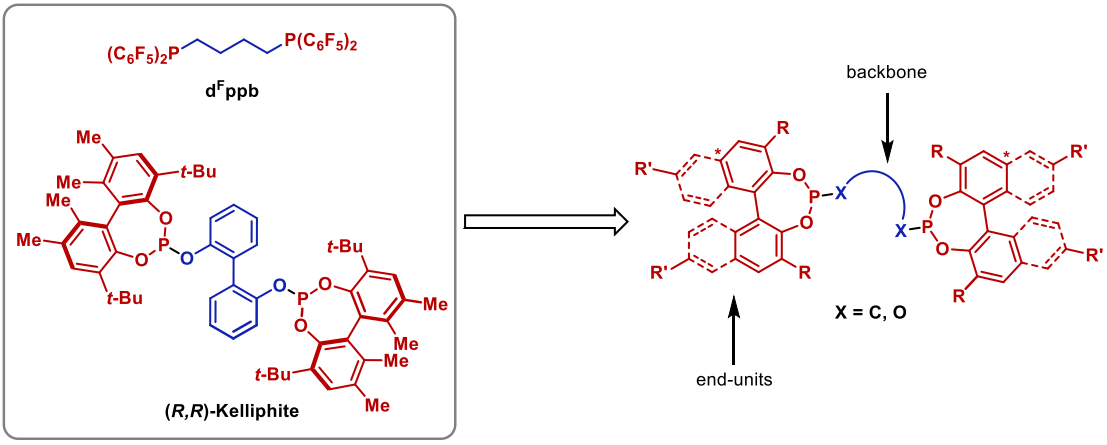
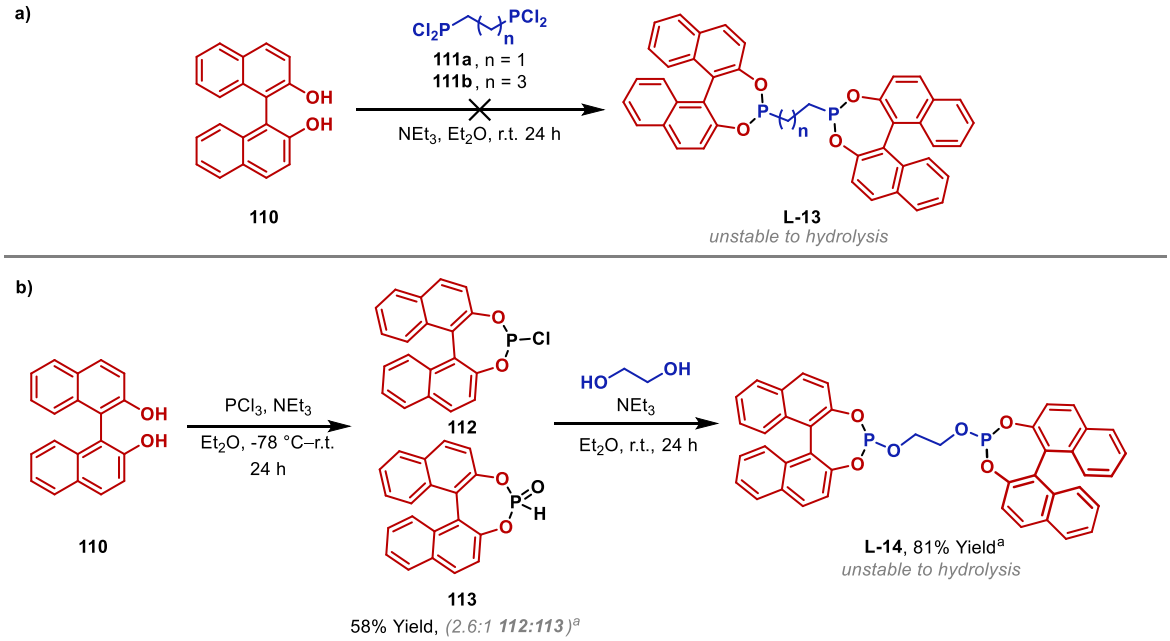


Figure 1: *Modular chiral ligand design for an enantioselective Ir(I)-catalysed alkene hydroarylation.*

Ideally, a modular chiral ligand synthesis would allow rapid evaluation of each of the structural components of the ligand, enabling an optimal system to be designed for a general and enantioselective alkene hydroarylation. This approach would allow chirality to be introduced into either the backbone or the end units of the ligand. Initially, BINOL-based bisphosphite ligand **L-13** was targeted owing to the ease of synthesis and ready availability of substituted BINOL moieties (Scheme **48a**). The butane backbone was chosen to replicate the wide bite angle of d^{F}ppb; however, other backbone lengths were considered to ensure that the correct bite angle was identified. Initially, for proof-of-concept, commercially available 1,2-bis(dichlorophosphino)ethane **111a** and *rac*-BINOL **110** were subjected to triethylamine under a rigorously inert and anhydrous atmosphere (Scheme **48a**). However, a complex mixture was formed and ligand **L-13** was found to be highly susceptible to hydrolysis, inhibiting its isolation.[130] P–O bonds have greater bond energies than P–C bonds (84 *vs* 62 kcal/mol) and so should be more stable.[131] Based on this, phosphonite ligand **L-14** was investigated due to its similar design features (Scheme **48b**). The synthesis began by exposing *rac*-BINOL **110** to phosphorus trichloride, in the presence of triethylamine under inert and anhydrous conditions. Desired chlorophosphite intermediate **112** was generated in 58% yield in a 2.6:1 mixture with hydrolysed side-product **113**. The mixture was then reacted with ethylene glycol and triethylamine to give desired ligand **L-14** in 81% yield, alongside 19% of unknown impurities as measured by ^{31}P NMR analysis. After extensive purification under an inert atmosphere it was found that bisphosphonite ligand **L-14** was also highly susceptible to hydrolysis, preventing its isolation. Ligands based on the structure of Kelliphite have successfully been complexed with Rh(acac)(cod),[132] and hence the complexation of ligand **L-14** to the Ir(I)-precatalyst prior to the reaction was investigated. However, this approach was unsuccessful. Due,

to other successful research avenues, which are presented in Chapter 5, this area was not explored further until Dr. Simon Grélaud began work on this topic (*see* Section **2.3**).



Scheme 48: *Design of bisphosphite and bisphosphonite ligands **L-13** and **L-14**. [a]Yield measured by ^{31}P NMR analysis against oxidised side-products (19%).*

2.3 – Asymmetric Hydroarylation of Alkenes with Acetanilides

2.3.1 – Optimisation and Scope

Following the commercially available chiral ligand studies (Table **2** and **3**), Dr. Simon Grélaud successfully designed and synthesised a family of chiral bisphosphite ligands based on the structure of Kelliphite (Figure **2**). The ligands consist of a highly substituted biphenyl backbone (end units in Kelliphite, which are shown in red), with biphenol units bearing various R-substituents at the C4-position. Unlike ligands **L-13** and **L-14** (Scheme **48**), which bear an ethyl linker, bisphosphite ligands **L-15** are relatively stable to air and moisture. This is presumably due to steric hindrance from the *t*-butyl groups and stabilisation from the aromatic groups, which make the P–O bonds more resistant to hydrolysis.

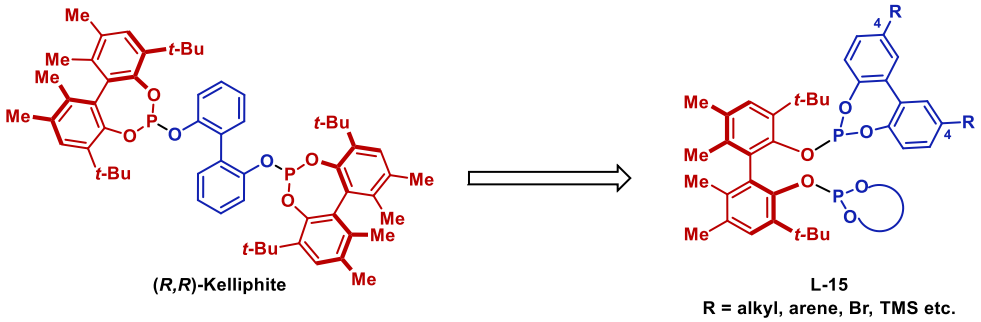


Figure 2: *Bisphosphite ligands **L-15** designed and synthesised by Dr. Simon Grélaud.*

Under optimised conditions ($Ir(cod)_2BF_4$/**(*S*)-L-15a** (R = *t*-Bu)) (Table **5**), hydroarylation of styrene **91a'** with acetanilide **60c** proceeded to generate desired product **96ca'** in excellent yield (93%) and enantiopurity (95:5 *e.r.*) and with complete branch selectivity (Table **5**). The methodology tolerates a wide range of acetanilides; a summary is outlined in Table 5a. Substitution was tolerated in each position around the arene of the acetanilide (e.g. **96ca'**, **96ea'** and **96ga'**). The absolute stereochemistry of **96ea'** was determined by X-ray analysis of its (+)-CSA salt, allowing tentative stereochemical assignment of the other hydroarylation products. For acetanilides with two available *ortho*-positions, e.g. **60g**, complete selectivity for mono-*ortho*-alkylation was achieved. Furthermore, C−C bond formation was highly selective for the less hindered *ortho* position of *meta*-substituted substrates (**60c** and **60i**), which presumably reflects the steric demands of the ligand. Acetanilides bearing potentially sensitive groups, including bromine-substituted system **60i**, which gave desired product **96ia'** in good yield (69%) and enantiopurity (94:6 *e.r.*), were tolerated and the reaction conditions also accommodated protic functionality e.g. **96ha'** (82% yield). Additionally, the protocol offers good scope with respect to the styrene component (Table **5b**). *Ortho*- and *para*-substituted systems (**91f'** and **91g'**) participated efficiently to give the desired products **96jf'** and **96jg'**, where no decrease in enantiopurity was observed (97.5:2.5 and 96:4 *e.r.*). Significantly, the process extended to aliphatic alkenes, as demonstrated by hydroarylation of hex-1-ene, which generated **96jb'** in 96% yield and 94:6 *e.r.* Sterically demanding alkene **91i'** and ester substituted alkene **91j'**, generated desired products **96ji'** and **96jj'** in excellent yields (81% and 83%) and enantiopurity (95:5 and 91.5:8.5 *e.r.*).

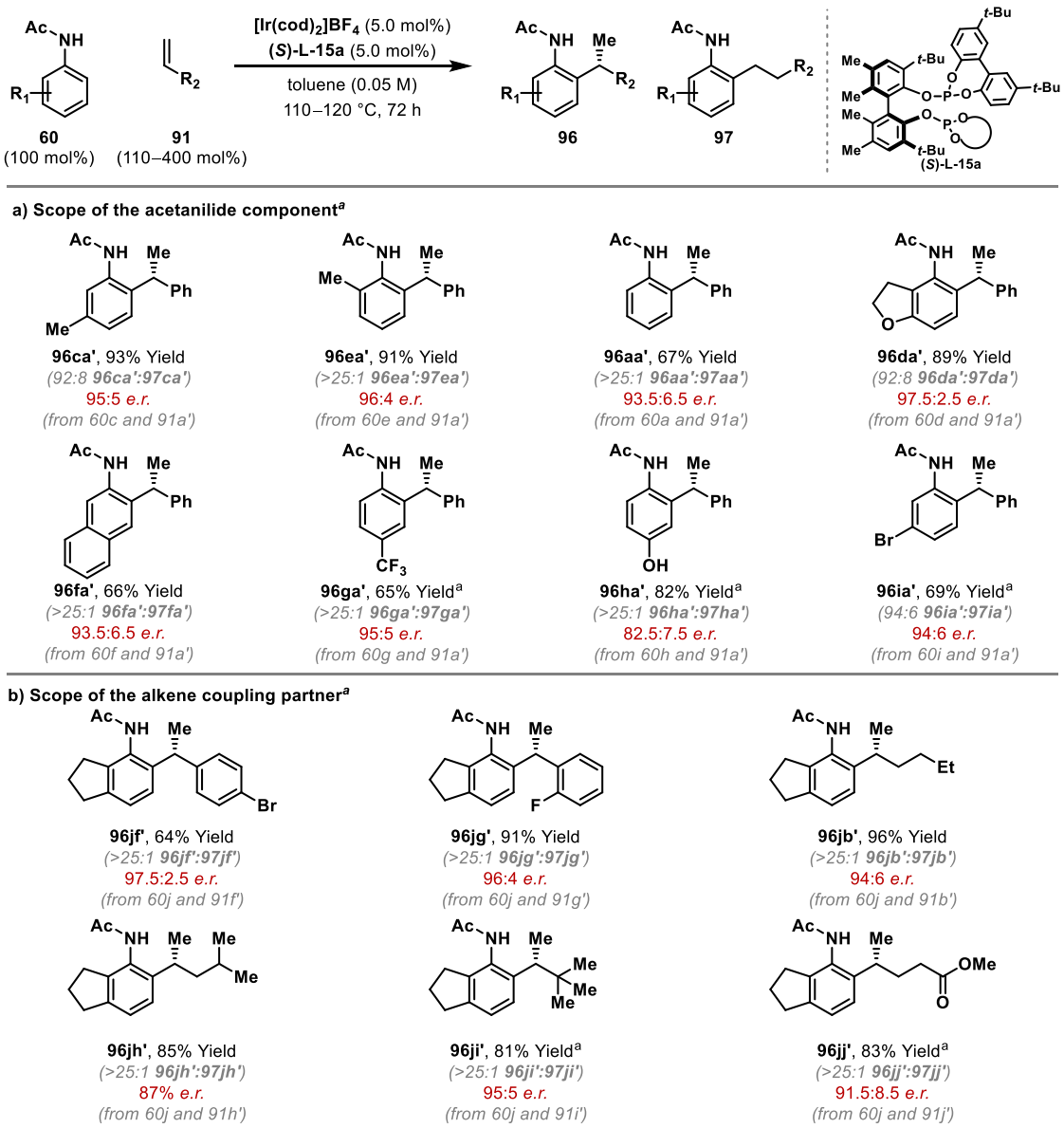
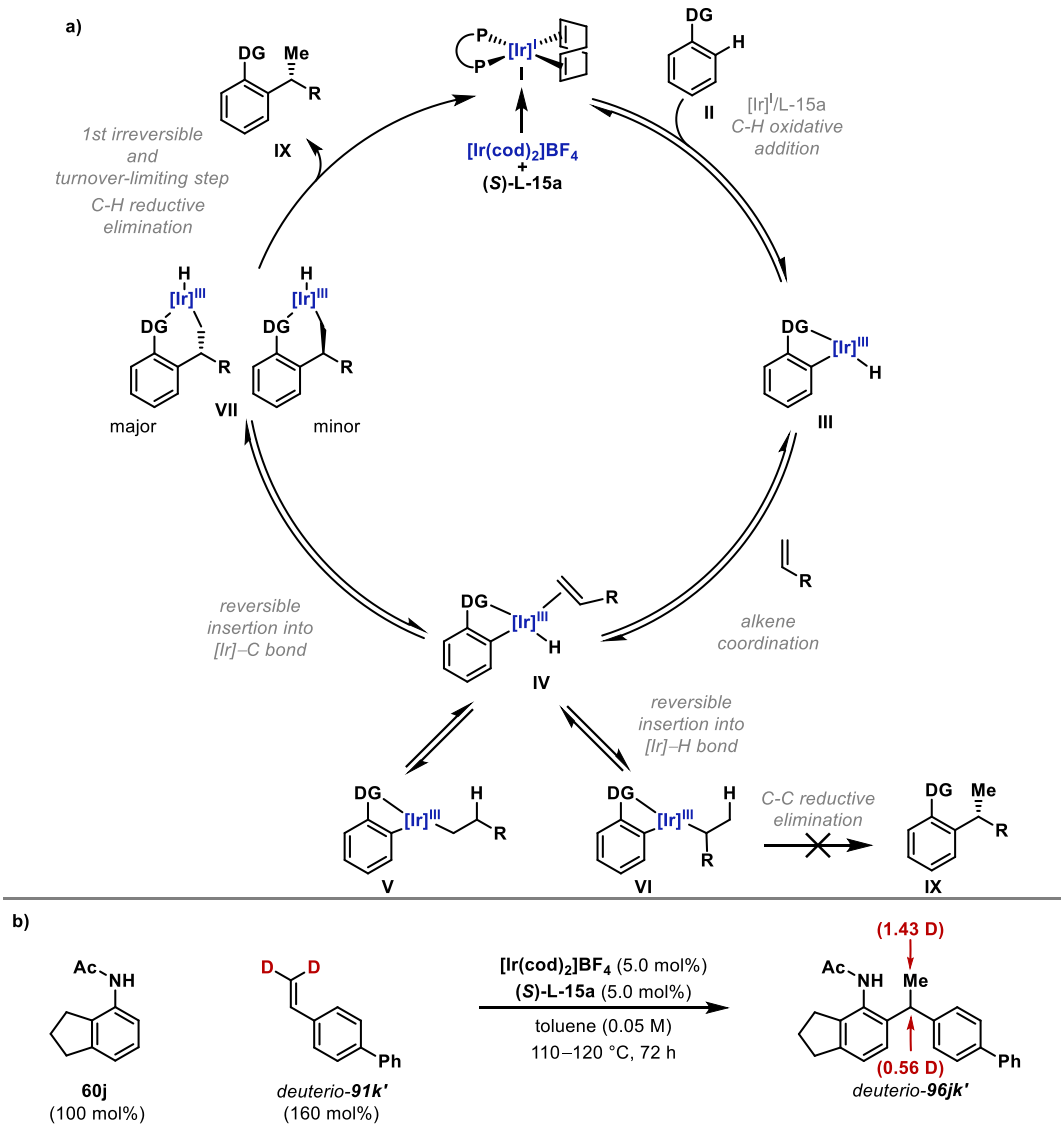


Table 5: *Scope of the enantioselective alkene hydroarylation with acetanilide derivatives.* [a]*The reaction was run at 0.025 M.*

2.3.2 – Mechanistic Studies

Following the successful development of an enantioselective alkene hydroarylation reaction (Table **5**), Dr. Simon Grélaud probed the mechanism by carrying out a series of deuterium labelling and natural abundance ^{13}C KIE experiments (*see* Section **4.4**). This led to the mechanistic pathway proposed in Scheme 49a. It is suggested that the process commences with reversible carbonyl-directed oxidative addition of the active Ir(I)-catalyst into the *ortho* C–H bond to form **III**, followed by reversible alkene hydrometallation to form **V** and **VI** respectively. A deuterium exchange experiment was conducted with acetanilide **60j** and *deuterio*-**91k'** to afford *deuterio*-**96jk'** (Scheme **49b**). Deuterium incorporation was observed at both the benzylic position (0.56 D, *56% deuteration*) and the methyl group (1.43 D, *48% deuteration*). Deuterium incorporation at the benzylic position shows that the deuterium labels are

scrambled during the reaction, which supports reversible C–H oxidative addition and reversible alkene hydrometallation. In contrast to the non-enantioselective protocol with d^Fppb, ^{13}C KIE experiments (*see* Section **4.4**) revealed C–C bond formation occurs *via* carbometallation from **IV**, as opposed to C–C reductive elimination from **VI**. Interestingly, these experiments concluded that carbometallation was in fact occurring reversibly and C–H reductive elimination was the first irreversible and therefore rate determining step. This will be discussed further in Section 4.4. The observation that the stereocentre generating step is reversible is unusual. This could mean that the facial selectivity for alkene carbometallation is low, so that both enantiomers of **VII** exist in equal amounts. Subsequent C–H reductive elimination to the major enantiomer may then be faster than to the minor enantiomer, obtaining the high levels of enantioselectivity observed. Alternatively, carbometallation facial selectivity may be high and subsequent C−H reductive elimination may be less discriminating for both enantiomers.



Scheme 49: *Proposed catalytic cycle for the Ir(I)-catalysed enantioselective hydroarylation of monosubstituted alkenes with acetanilides.*

2.3.3 – Application to Thiophene Derivatives

To expand the scope of the enantioselective, branch-selective alkene hydroarylation, thiophene substrates were synthesised in collaboration with Dr. S Grélaud. Thiophene **114a** performed poorly under the optimised Ir(I)-catalysed conditions with bisphosphite ligand **(*S*)-L-15a** (44% yield, 26:74 *e.r.*), and so redesign of the chiral ligand was necessary (Table **6**). It was envisaged that a ferrocene-based bisphosphine backbone (*see* Section **5.3.1**) would have a wide bite angle like that of ligand **(*S*)-L-15a**. Additionally, SPINOL moieties were investigated as the chiral unit, due to them bearing readily modifiable substituents. Chiral SPINOL-based ligands have previously been utilised at Bristol for enantioselective Narasaka–Heck cyclisations.[133] Ligand **(*R*)-L-16a** was found to be effective, providing hydroarylation product **115aa'** in 77% yield and 97.5:2.5 *e.r.* with complete branch selectivity. The

absolute stereochemistry of **115aa'** was determined by X-ray diffraction. The synthesis of ligand **(*R*)-L-16a** will be discussed in Section 4.3.3.1 (*also see* experimental)

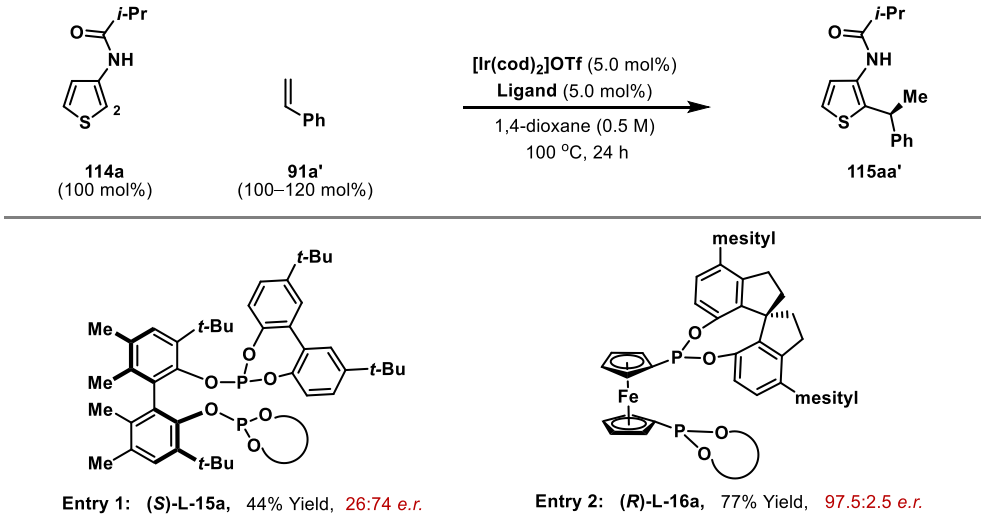


Table 6: *Ir(I)-catalysed enantioselective alkene hydroarylation protocol with thiophene **114a** with bisphosphite and bisphosphonate ligands.*

With optimised conditions in hand (Table **6**, entry 2), alongside Dr Simon Grélaud, the scope of the reaction was explored with respect to the alkene coupling partner and the thiophene substrate (Table **7**). The reaction tolerates aliphatic alkene coupling partners, with *n*-butyl derivative **115ac'** generated in excellent yield and enantiopurity (98:2 *e.r.*). Furthermore, hydroheteroarylation of hex-1-ene **91c'** with C4 and C5-substituted thiophene derivatives **114b** and **114c** gave desired products **115bc'** and **115cc'** in good yields (79% and 71%) and enantiopurity (92:8 and 96.5:3.5 *e.r.*). The hydroheteroarylation of aliphatic alkenes bearing heteroatoms **91i'** and **91j'** generated desired products **115al'** and **115aj'** in excellent enantiopurity (92:8 and 96:4 *e.r.*), however, ester derivative **115aj'** was generated in moderate yield (30%). Additionally, complex steroid alkene **91m'** was tolerated, which gave product **115am'** in excellent yield and diastereoselectivity (>19:1 *d.r.*).

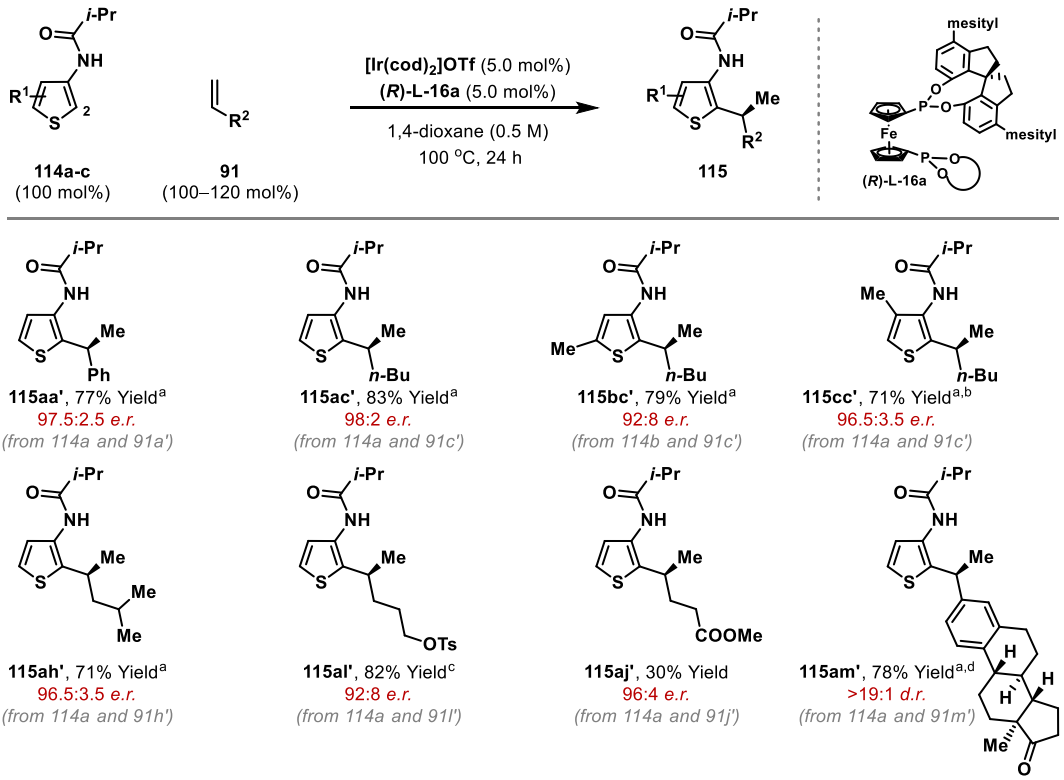
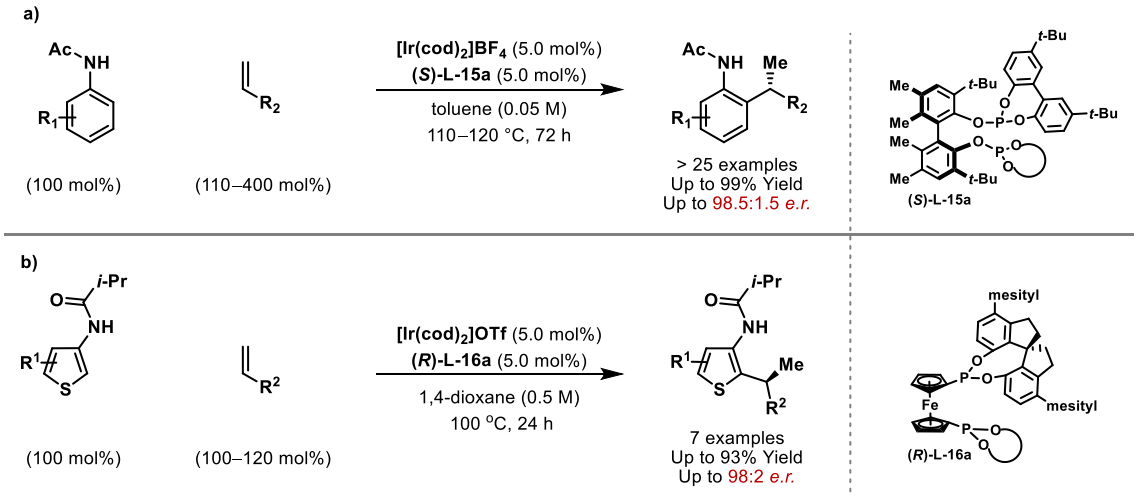


Table 7: *Scope of enantioselective alkene hydroarylation with thiophene derivatives. [a]The reaction was carried out by S. Grélaud; [b]150 mol% of alkene was used; [c] The reaction was performed at 90 °C; [d]100 mol% of alkene was used.*

2.4 – Summary and Conclusions

Insight into the requirements of a directing group for successful oxidative addition and subsequent alkene hydroarylation has been gained through deuterium exchange experiments. These experiments highlighted the superior directing ability of amide and anilide units, which were selected for the development of an enantioselective alkene hydroarylation. An extensive screen of commercially available chiral ligands highlighted some key structural features required for high yield, high branch regioselectivity and high enantioselectivity. Based on these observations, Dr. Simon Grélaud designed and synthesised a family of bisphosphite ligands, including ligand **(*S*)-L-15a**, which promote the highly enantio- and branch-selective hydroarylation of alkenes with acetanilides (Scheme **50a**). Development of ferrocene-based bisphosphonite ligand **(*R*)-L-16a** expanded the scope of the hydroarylation reaction to include thiophene substrates (Scheme **50b**). This work represents the first example of a general, enantioselective and branch-selective protocol for the hydroarylation of unactivated aliphatic alkenes, addressing the first aims in Section 1.5. This approach offers an alternative strategy to metal-catalysed cross-coupling reactions, providing access to valuable benzylic stereocentres from feedstock materials in an atom- and step-economical approach.



Scheme 50: *Enantioselective Ir(I)-catalysed alkene hydroarylation with acetanilides and thiophenes.*

Chapter 3 – Branch- and Enantioselective Iridium Catalysed Alkene Hydroheteroarylation (5-Membered Chelates)

3.1 – Exploring 5,6-Fused *N*-Heteroaromatics for the Branch-Selective Hydroheteroarylation of Styrene

Having successfully expanded the enantioselective alkene hydroarylation methodology to thiophenes, alternative heteroaromatics were explored in earlier studies. Branch-selective alkene hydroheteroarylation with 5,6-fused heteroaromatics remains challenging and few enantioselective protocols exist (*see* Section **1.3.2**). Those that have been reported are limited in scope to styrenes, with aliphatic alkenes resulting in poor enantioselectivity.[89, 94-95] However, there is a demand for such methods, as they form benzylic stereocentres which are privileged structures in the pharmaceutical industry. For example, tadalafil consists of an indole framework possessing a defined benzylic stereocentre and is used to treat erectile dysfunction (Figure **3**).[134] Additionally, liphagal comprises of a benzofuran and inhibits cell growth enzymes.[135] Therefore, a general method for the asymmetric hydroheteroarylation of alkenes with 5,6-fused heteroaromatics would be of great significance.

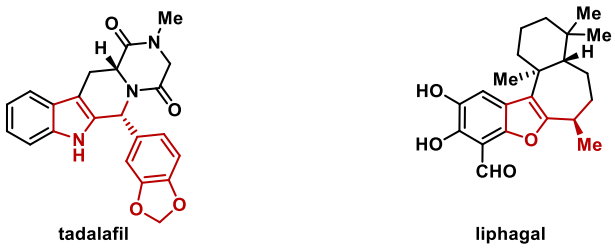
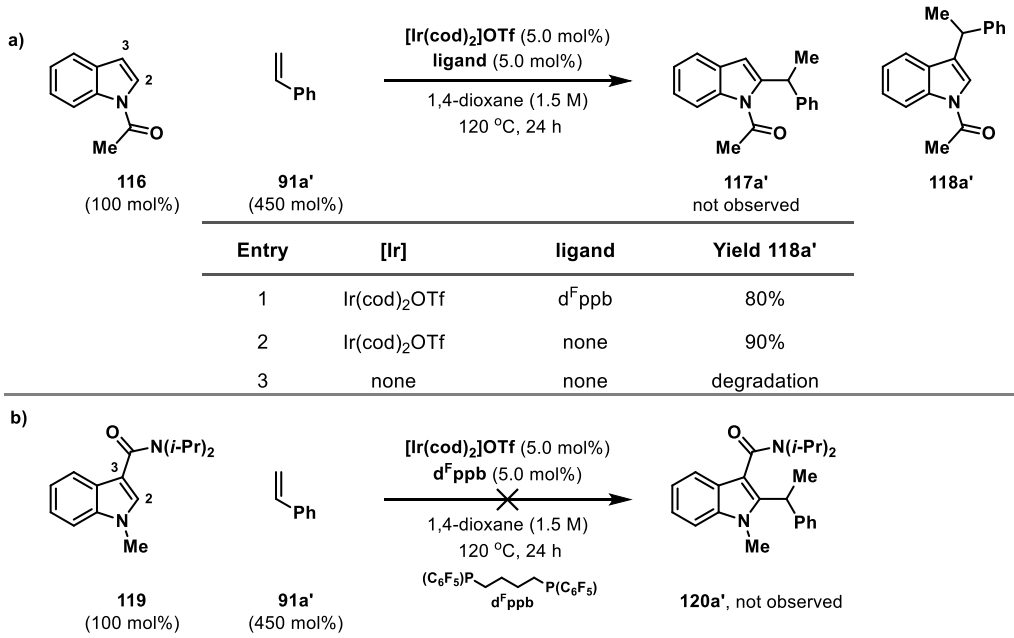


Figure 3: *Natural products and drug molecules featuring 5,6-fused heteroaromatics, which bear tertiary benzylic stereocentres.*

Having successfully expanded the scope of the enantioselective Ir(I)-catalysed alkene hydroarylation methodology to thiophene derivatives (*see* Section **2.3.2**), alternative heteroaromatics were investigated. These studies began with indole **116**, which is equipped with an *N*-acetyl directing group. Previously Shibata showed that indoles of this type are suitable substrates for Ir(I)-catalysed directed hydroarylation of alkenes ($Ir(cod)_2BARF$/*(R)*-SDP, Scheme **28**, Section **1.3.2**).[92] A non-enantioselective protocol was initially pursued for proof-of-concept, whereby indole **116** was exposed to the previously developed $Ir(cod)_2OTf/d^Fppb$ system (*see* Section **1.4**) (Table **8a**).[117] Under these conditions alkylation occurred exclusively at the C3-position, generating alkyl indole **118a'** (80% yield, entry 1), which is in contrast to Shibata's methodology.[92] To override the inherent reactivity of indole and generate C2-alkylated indole **117a'** alternative commercially available bisphosphine ligands were explored; however, only alkylation at C3 was observed. Additionally, when the reaction was repeated in the absence of a phosphorus ligand, C3-alkylated product **118a'** was generated in 90% yield (entry 2), whereas no reaction occurred in the absence of an Ir(I)-source (entry 3). These results suggest that

rather than oxidatively inserting into the indole C–H bond as desired, the Ir(I)-precatalyst is acting as a π-Lewis acid to promote a Friedel-Crafts type alkylation.[136] Indole **119**, with an alternative diisopropyl-amide directing group installed at the C3-position, was investigated to develop a protocol in which alkylation occurs selectively at C2 (Table **8b**). However, under otherwise identical Ir(I)-catalysed conditions, C2-alkylated product **120a'** was not observed.



Entry	[Ir]	ligand	Yield 118a'
1	$Ir(cod)_2OTf$	d^Fppb	80%
2	$Ir(cod)_2OTf$	none	90%
3	none	none	degradation

Table 8: *Studies towards Ir(I)-catalysed alkene hydroarylation with indole derivatives.*

3.2 – Studies Towards a Branch- and Enantio-selective Hydro-heteroarylation of Styrene with Pyrroles

At this stage, indole derivatives were unsuitable for hydroheteroarylation of styrenes under Ir(I)-catalysed conditions; consequently, alternative heteroaromatics were examined. 5-Membered heteroaromatics bearing benzylic stereocentres are also common structural features in many natural products and drug molecules (Figure **4**). Significant examples include, duloxetine[137], an antidepressant, and pallescensin B[138], which is isolated from a marine sponge.

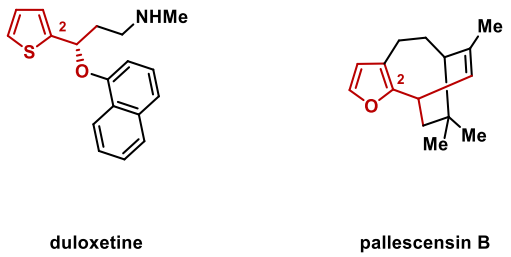


Figure 4: *Natural products and drug molecules featuring 5-membered heteroaromatics, which bear tertiary benzylic stereocentres.*

Enantio- and branch-selective hydroarylation of alkenes with 5-membered heteroaromatics is currently limited to electronically predisposed alkenes (e.g. norbornene, enol ethers, 1,3-dienes) (*see*

Section **1.2.3**). [96, 106, 139] A general protocol for the hydroarylation of styrenes and α-olefins is yet to be reported. Initially, pyrrole **121a**, which bears a benzoyl directing group, was subjected to the previously developed Ir(I)-catalysed conditions (Table **9a**).[92] However, alkylation occurred on both the pyrrole and the phenyl of the directing group. To avoid alkylating the phenyl unit, a methyl-substituent was added to the *ortho*-position of the benzoyl directing group, as in pyrrole **121b** (*see* Scheme **39**, Section **1.4**). This time, under the hydroarylation conditions, alkylated pyrrole **122ba'** was generated selectively, albeit in moderate yield (26% yield). Next, pyrrole **121c**, which bears a dimethylated directing group, was employed; however, no alkylation was observed, which further highlights the narrow constraints of the directing group. The additional methyl group likely forces the benzoyl directing group to twist out-of-plane of the pyrrole moiety (**I** to **II**), thereby preventing the directed oxidative addition step (Table **9b**).

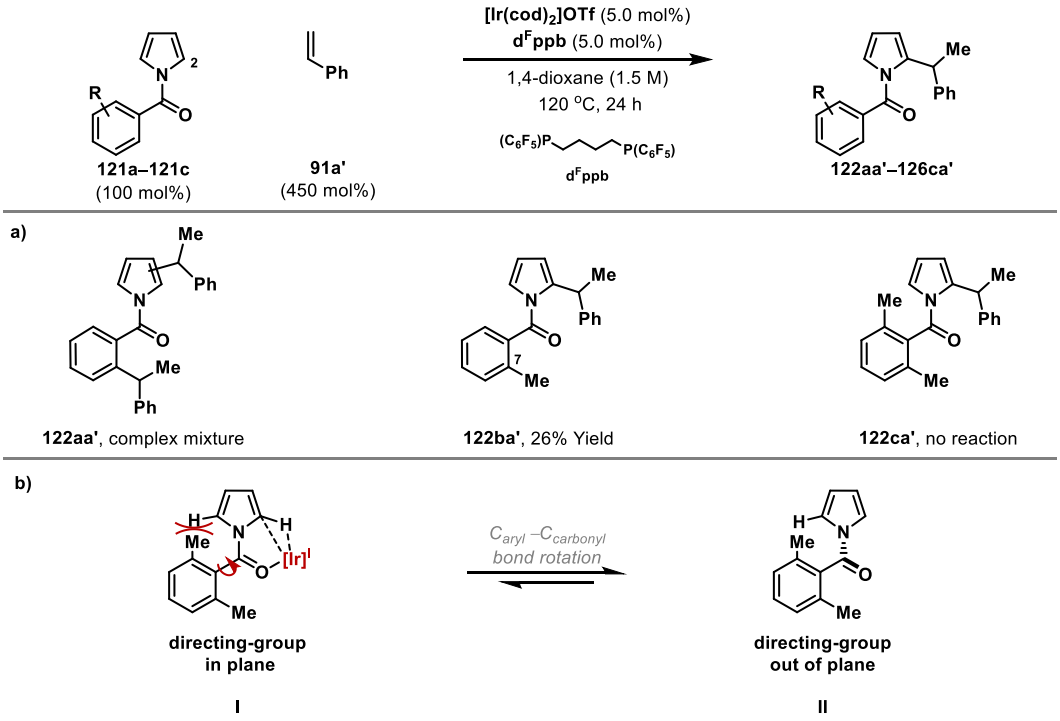
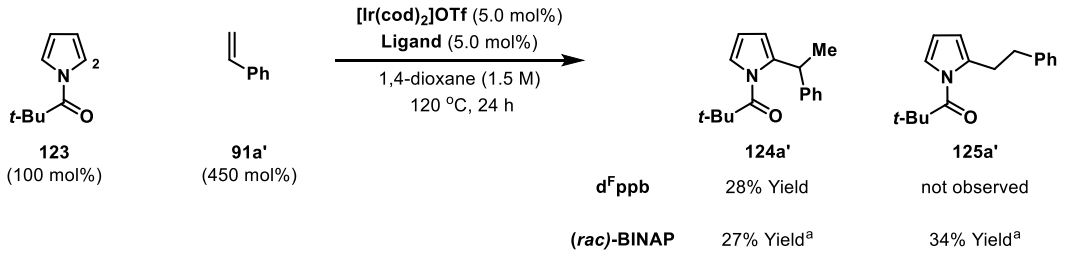


Table 9: *Ir(I)-catalysed styrene hydroarylation with benzoyl protected pyrroles.*

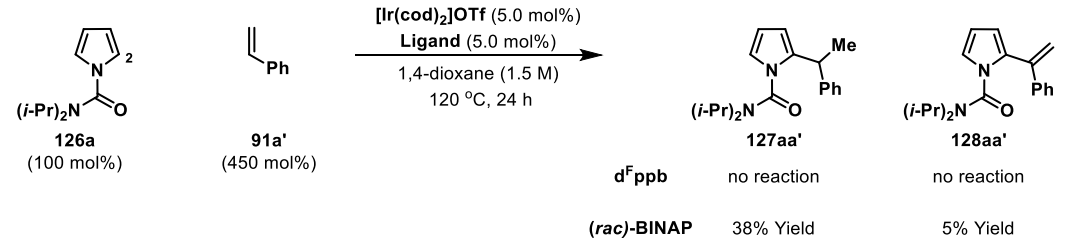
Considering the limitations of *N*-benzoyl pyrroles, investigations turned to pivaloyl protected pyrrole **123** (Scheme **51**). Pivaloyl directing groups have previously been utilised in Rh(I)-catalysed linear selective alkenylations of indolines.[140] When *N*-pivaloyl pyrrole **123** and styrene **91a'** were exposed to the Ir(I)-catalysed conditions used above, branched alkyl pyrrole **124a'** was generated, although in poor yield (28%, Scheme **51**). Optimisation of this transformation began by investigating over 60 commercially available mono- and bidentate phosphine ligands; however, none of these resulted in an improved yield of **124a'**. Notably, when (*rac*)-BINAP was used, linear regioisomer **125a'** was observed in 34% yield, alongside branched product **124a'** (27% yield), which indicates that migratory insertion of the alkene is not regioselective in this case (*see* Section **1.4**, Scheme **41**). Alternative Ir(I)-precatalysts

and solvents resulted in decreased or no conversion. Additionally, no improvements were achieved by altering the reaction temperature, time, concentration or precatalyst and ligand loadings.



Scheme 51: *Styrene hydroarylation with N-pivaloyl pyrrole **123**. [a] Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

Optimisation of the hydroarylation of styrene **91a'** with pivaloyl pyrrole **123** was unsuccessful, therefore more electron-rich *N*-carbamoyl directing groups were investigated. Carbamoyl directing groups have successfully been utilised for the Ir(I)-catalysed hydroarylation of alkenes with arenes, whereby a five-membered Ir(III)-chelate is produced (*see* Section **1.4**).[116] Pyrrole **126a** was reacted with styrene **91a'** under the standard hydroarylation conditions (Ir(I)/d^{F}ppb), but no reaction was observed (Scheme **52**). However, when using (*rac*)-BINAP as the ligand, branched-product **127aa'** was generated in modest yield (38%), alongside alkene side-product **128aa'** (5%). It is postulated that alkenylation product **128aa'** forms *via* an alternative β-hydride elimination pathway, which will be discussed further in Chapter 5. Following this promising result, pyrrole **126a** was selected for optimisation studies.



Scheme 52: *Ir(I)-catalysed styrene hydroarylation with pyrrole **126a**.*

Optimisation began by investigating the R-substituent on the directing group. Under Ir(I)-catalysed conditions (Ir(cod)$_2$OTf/(*rac*)-BINAP) *N*-diethylcarbamoyl pyrrole **126b** did not afford target **127ba'** (Table **10a**). However, *N*-dicyclohexylcarbamoyl pyrrole **126c** gave alkyl pyrrole **127ca'** in excellent yield (78% yield) and with good selectivity over alkenylation side-product **1128ca'**. The reaction is suggested to proceed with oxidative addition of the Ir(I)-catalyst into the C2 C–H bond (to **I**), followed by alkene coordination and migratory insertion into either the Ir(III)–H bond (to generate **II**) or into the Ir(III)–C bond (giving **III**) (Table **10b**). The increase in yield observed when changing the size of the R-substituent from ethyl to cyclohexyl, may be explained by a steric interaction between the *ortho* C–H bond of the pyrrole and the R-substituent on the directing group in rigid 5-membered-

iridacycle **II**. These steric interactions could potentially be relieved through carbometallation to form more flexible 7-membered iridacycle **III** or by C–C reductive elimination from **II** to generate **IV**. Consequently, the rate of carbometallation/C–C reductive elimination is enhanced for derivatives with larger R groups, such as in *N*-dicyclohexyl system **126c**.

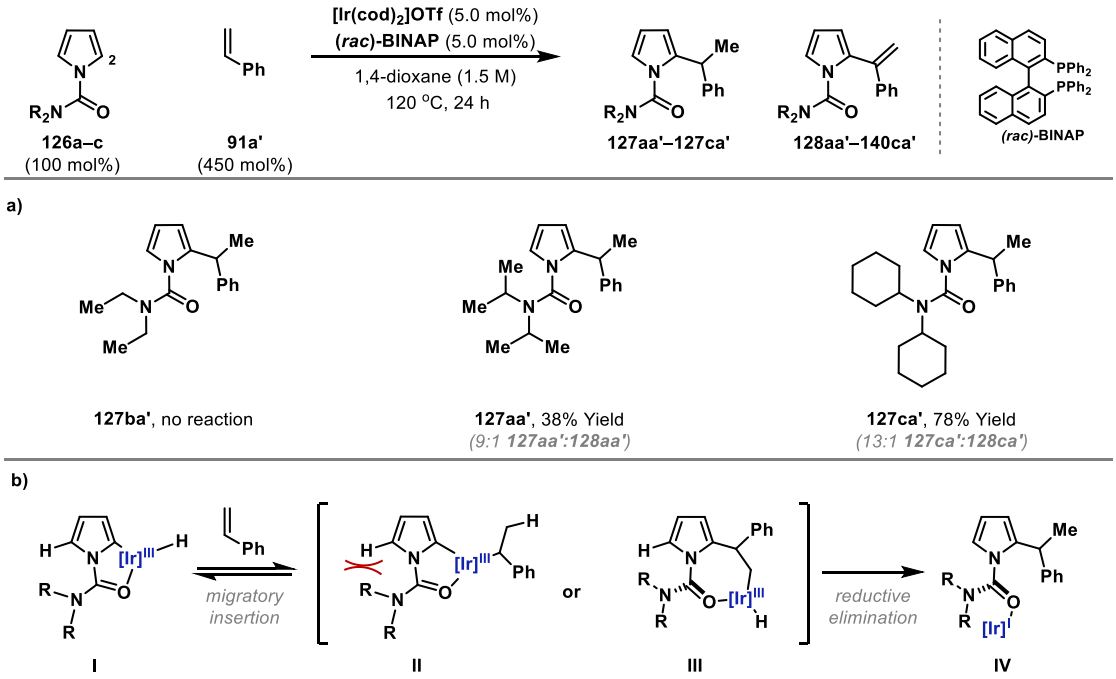
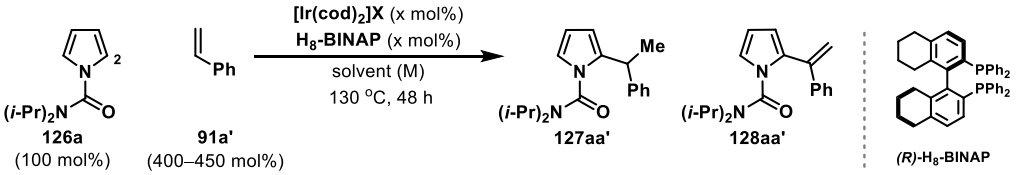


Table 10: *Ir(I)-catalysed styrene hydroarylation with pyrroles **126a–126c**.*

Despite styrene undergoing a high yielding hydroarylation with pyrrole **126c**, the requirement of a large directing group was undesirable (Table **10**). Therefore, investigations were directed towards developing improved conditions that would allow more varied directing groups to be employed. *N*-Diisopropylcarbamoyl pyrrole **126a** was selected for further optimisation studies and the key results are presented in Table 11. Initially, different commercially available bisphosphine ligands were investigated. When the reaction was run with (*R*)-H_8-BINAP for 48 hours at 130 °C, alkyl pyrrole **127aa'** was generated branch-selectively in 57% yield (entry 1). Changing the concentration had minor effect (entry 2–3), whilst higher precatalyst and ligand loadings were beneficial to the yield (entry 4). Optimal conditions were achieved when acetonitrile was employed as the solvent, which afforded **127aa'** in 74% yield, although with little enantioselectivity (51:49 *e.r.*) (entry 7). Alternate Ir(I)-sources, including $[Ir(cod)_2]BF_4$, $[Ir(cod)_2]OMe$ and $[Ir(cod)_2]BARF$, all resulted in reduced conversion to **127aa'** (entry 8–10).



Entry	X (mol%)	solvent (M)	Yield[a] 127aa'	Yield[a] 128aa'	*e.r.*
1	OTf (5.0)	1,4-dioxane (1.5)	57%[b]	0%	/
2	OTf (5.0)	1,4-dioxane (1.0)	56%	3%	/
3	OTf (5.0)	1,4-dioxane (2.0)	59%	2%	/
4	OTf (7.5)	1,4-dioxane (1.5)	68%	2%	/
5	OTf (7.5)	EtOAc (1.5)	23%	0%	/
6	OTf (7.5)	toluene (1.5)	38%	0%	/
7	**OTf (7.5)**	**MeCN (1.5)**	**74%[b]**	**2%**	**51:49**
8	BF_4 (7.5)	MeCN (1.5)	61%	6%	/
9	OMe (7.5)	MeCN (1.5)	no reaction	no reaction	/
10	BARF (7.5)	MeCN (1.5)	69%	5%	/

Table 11: *Key optimisation results for hydroheteroarylation of styrene **91a'** with pyrrole **126a** using H_8-BINAP as the ligand. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard; [b]Isolated yield.*

3.2.1 – Development of an Enantioselective Protocol

The branch-selective styrene hydroarylation methodology developed above gives branched alkyl pyrrole **127aa'** in good yield (74%), albeit in poor enantiopurity (51:49 *e.r.*) (Table **11**, entry 7). Under these optimised conditions, pyrroles **126b** and **126c** with sterically varied directing groups (Et and Cy) generated target products **127ba'** and **127ca'** in good to excellent yields (72% and 83%), with minimal enantioselectivity (up to 58:42 *e.r.*) (Table **12**). Despite the low levels of enantioselectivity achieved, these results suggest that the enantioselective hydroarylation of styrenes with pyrroles is a viable route to generate benzylic stereocentres. Additionally, these Ir(I)-catalysed conditions allow the high yielding formation of alkyl pyrroles **127ba'** and **127aa'**, which bear smaller R substituents. Expanding the scope to different heteroaromatics, including azoles **129** and **130**, thiophene **131** and indole **132**, was unsuccessful at this stage (Table **12**).

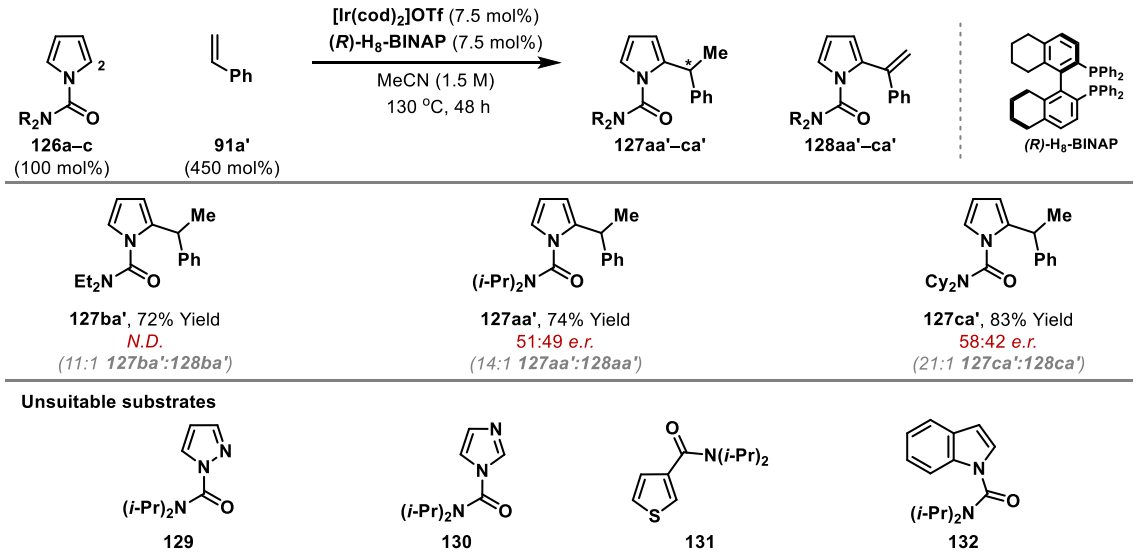


Table 12: *Scope of Ir(I)-catalysed hydroheteroarylation of styrene with pyrroles using (R)-H$_8$-BINAP as the ligand.*

After obtaining preliminary enantioselectivity results with (*R*)-H$_8$-BINAP (Table **12**), over 20 commercially available chiral ligands were screened for Ir(I)-catalysed styrene hydroarylation with *N*-diisopropylcarbamoyl pyrrole **126a**. In all cases the reaction suffered from poor conversion and selectivity. Next, chiral ligands previously developed by Dr. Simon Grèlaud (*see* Section **2.3**) were explored and the key results are presented in Table 13. Bisphosphite ligand **(*S*)-L-15b** gave alkyl pyrrole **127aa'** in good yield (60%) and high branch selectivity, but with poor enantiopurity (60:40 *e.r.*) (entry 1). Utilising ferrocene-based bisphosphonite ligand **(*S*)-L-16b** bearing H$_8$-BINOL moieties (entry 2), resulted in an improvement in both yield (78%) and enantioselectivity (77:23 *e.r.*); however, minor conversion to alkene side-product **128aa'** was also observed (*see* Chapter **5**). Changing the H$_8$-BINOL moieties to SPINOL units (entry 3, **(*S*)-L-16a**) gave hydroarylation product **127aa'** in excellent yield (95%), albeit in poor enantiopurity (62:38 *e.r.*). However, improved enantioselectivity (80.5:19.5 *e.r.*) was achieved by changing the R-groups at C4 on the SPINOL units to phenyl groups (entry 4, **(*S*)-L-16c**). No increase in yield or enantioselectivity was obtained through further modification of the R-groups (entry 5 and 6, **(*S*)-L-16d** and **(*S*)-L-16e**).

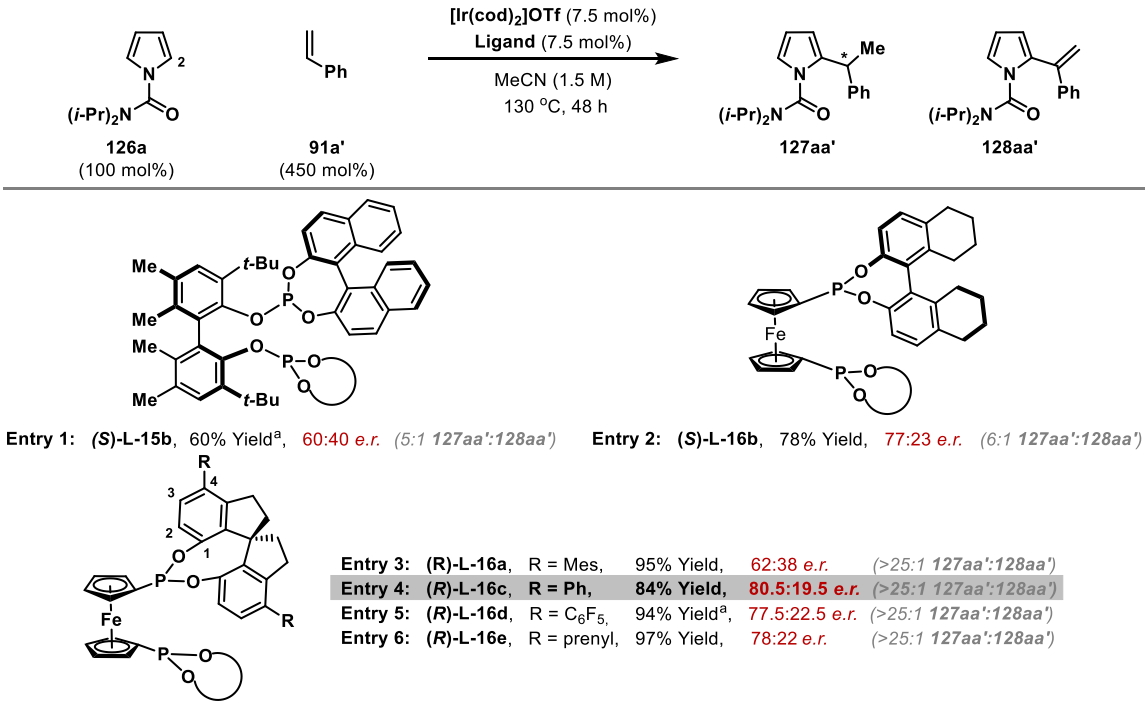


Table 13: *Enantioselective Ir(I)-catalysed styrene hydroarylation with pyrrole* ***126a****.* [a]*Yields were determined by* ^{1}*H NMR analysis of crude material against an internal standard*

Pyrroles **126a**–**d** with sterically varied directing groups (R = Me *vs* Cy), were subjected to the optimised conditions using bisphosphonite ligand **(*R*)-L-16c** (Table **13**, entry 4). In all cases hydroarylation products **127aa'**–**127da'** were generated in good to excellent yields (65–88%) and with complete selectivity over the alkenylated side-products (Table **14**). *N*-Dimethylcarbamoyl pyrrole derivative **126d** generated product **127da'** in moderate enantiopurity (74:26 *e.r.*), whereas diethyl- and *N*-diisopropylcarbamoyl pyrrole moieties **127ba'** and **127aa'** were both generated in 80.5:19.5 *e.r.* Additionally, a decrease in enantioselectivity was observed for the hydroarylation of styrene **91a'** with pyrrole **126c**, which bears large cyclohexyl groups (75:25 *e.r.*). This variation in enantioselectivity suggests that the R-substituents on the directing group can influence the facial selectivity of alkene migratory insertion, therefore effecting the enantiopurity of the hydroarylation product. Further fine-tuning of the ligand (**(*R*)-L-16f**, R = H), resulted in an increase in enantiopurity (86.5:13.5 and 88:12 *e.r.*), whilst maintaining good yields for *N*-diethyl- and diisopropylcarbamoyl hydroarylation products **127ba'** and **127aa'** (90% and 75% yield). Alternative carbonyl-based directing groups (**121a**, **121b**, **133**, **123**) were unsuitable under these Ir(I)-catalysed conditions (**(*R*)-L-16c**, R = Ph) (Table **14**).

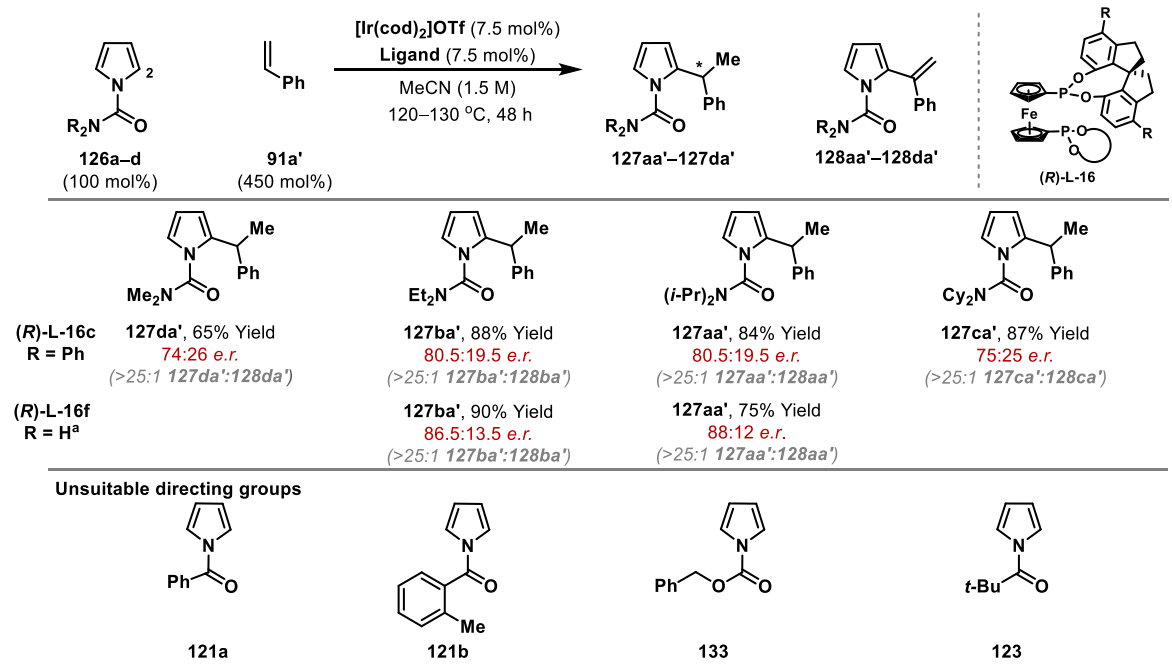
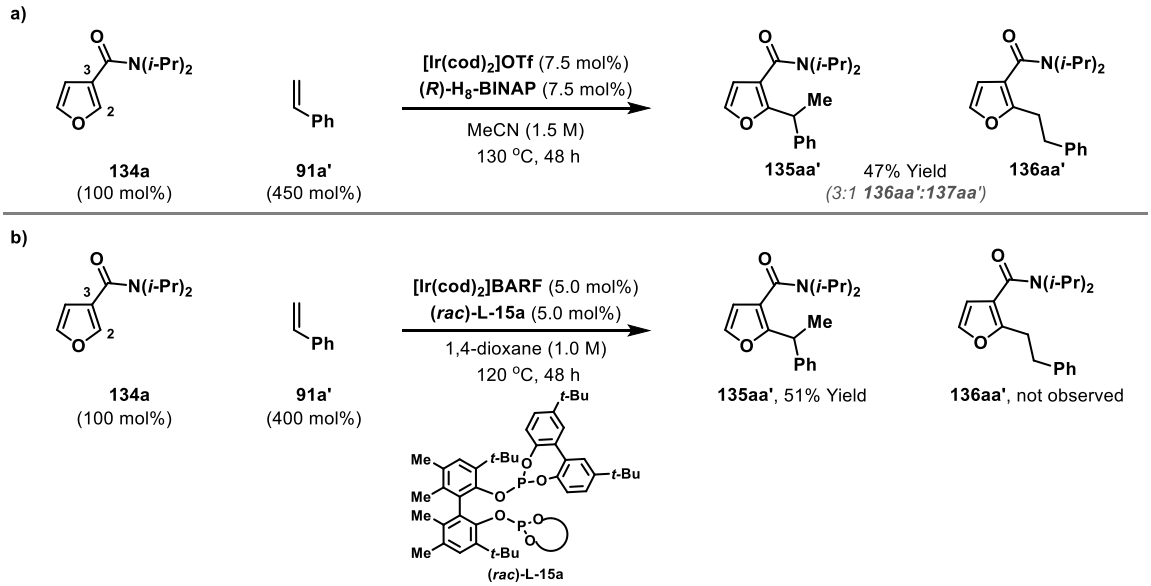


Table 14: *Scope of Ir(I)-catalysed enantioselective styrene hydroarylation with pyrroles **126a–d**.*

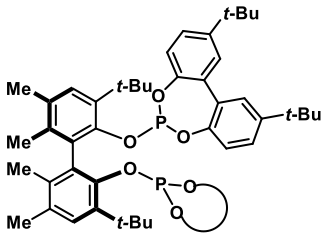
3.3 – Exploring Furans for the Branch- and Enantioselective Hydroheteroarylation of Styrene

Having developed conditions for the hydroarylation of styrene **91a'** with pyrrole derivatives **126a**–**d** (Table **14**), other 5-membered heteroaromatics were explored. Furan **134a**, equipped with a diisopropylamide directing group at the C3-position, and styrene **91a'** were exposed to Ir(I)-catalysis, using H_8-BINAP as the ligand (Table **11**, entry 7) (Scheme **53a**). Alkyl furan **135aa'** was formed, albeit in poor selectivity over linear regioisomer **136aa'** (3:1) (Scheme **53a**). It was postulated that furan **134a** would behave similarly to benzamide **90c** (*see* Section **4.2.2**) as alkene hydroarylation with both substrates proceeds *via* a 5-membered iridacycle. Accordingly, conditions developed for alkene hydroarylation with benzamide **90c** were employed ($Ir(cod)_2BARF$, **(*rac*)-L-15a**, 1,4-dioxane, *see* Section **4.2.2**), which provided hydroarylation product **135aa'** in 51% yield, and with complete branched selectivity (Scheme **53b**).

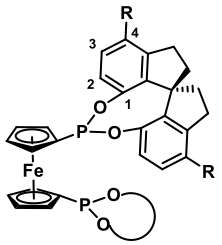


Scheme 53: *Ir(I)-catalysed styrene hydroheteroarylation with furan **135a**.*

With regioselective conditions for styrene hydroarylation with furan **134a** in hand, studies towards an enantioselective alkene hydroarylation protocol began. Utilising enantiopure ligand **(*S*)-L-15a**, under otherwise identical conditions to those above (Scheme **53b**), hydroarylation product **135aa'** was generated with moderate enantiopurity (43.5:56.5 *e.r.*) (Table **15**, entry 1). Ferrocene-based bisphosphonite ligand **(*R*)-L-16f**, with SPINOL moieties, resulted in a dramatic increase in the enantiopurity of **135aa'** to 84.5:15.5 *e.r.*, whilst maintaining an acceptable yield (59%) (entry 2). Improvements to the yield and enantioselectivity were achieved by modifying the R-substituents at C4 of the SPINOL units of the ligand; **(*R*)-L-16c**, where R = Ph gave **135aa'** in 59% yield and with 87:13 *e.r.* (entry 3), whereas **(*R*)-L-16a**, where R = mesityl generated **135aa'** in 72% yield and 90:10 *e.r.* (entry 4). Ligands **(*R*)-L-16g** and **(*R*)-L-16h**, where R = naphthyl and bromine respectively, did not provide any improvement to the enantioselectivity (89.5:10.5 and 86:14 *e.r.*) (entry 5 and 6).



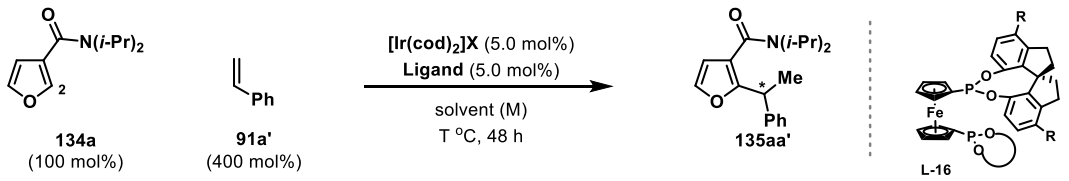
Entry 1: (*S*)-L-15a, 52% Yield, 43.5:56.5 *e.r.*



Entry 2: (*R*)-L-16f, R = H,	59% Yield[a],	84.5:15.5 *e.r.*[a]
Entry 3: (*R*)-L-16c, R = Ph,	59% Yield[a],	87:13 *e.r.*
Entry 4: (*R*)-L-16a, R = Mesityl,	**72% Yield,**	**90:10 *e.r.***
Entry 5: (*R*)-L-16g, R = 1-naphthyl,	71% Yield,	89.5:10.5 *e.r.*
Entry 6: (*R*)-L-16h, R = Br,	56% Yield[a],	86:14 *e.r.*

Table 15: *Enantioselective Ir(I)-catalysed hydroarylation of styrene **91a'** with furan **134a**. [a]Yields were determined by ^{1}H NMR analysis of crude material against an internal standard.*

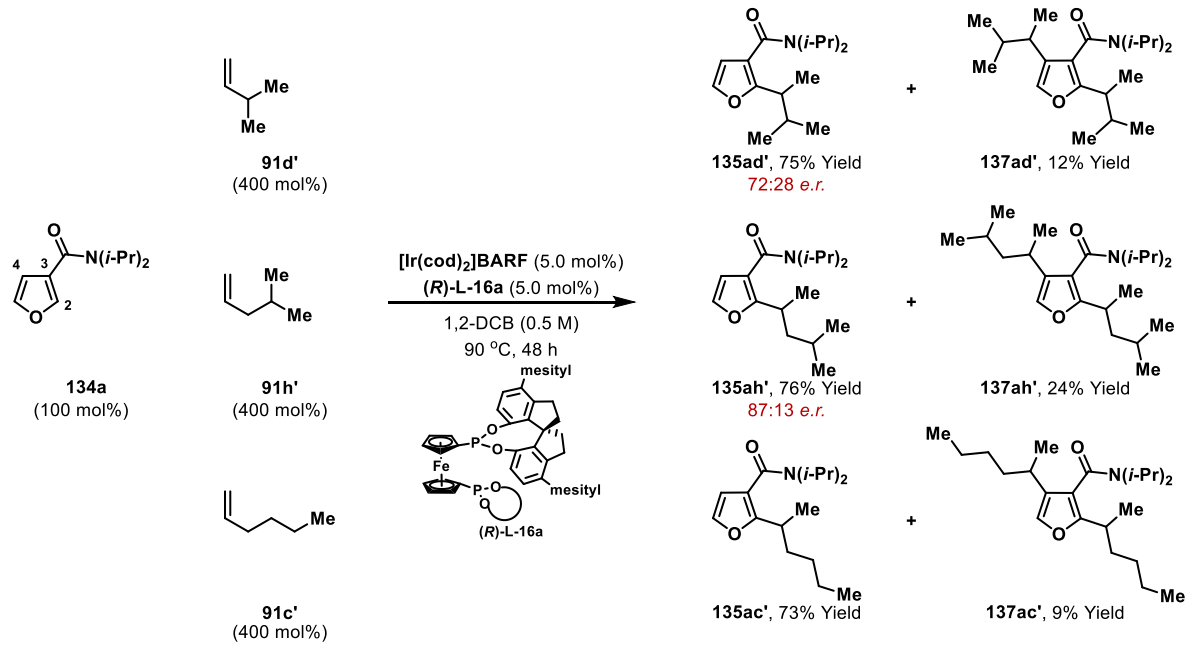
Further optimisation of the enantioselective styrene hydroheteroarylation with furan **134a** commenced with ferrocene-based bisphosphonite ligand **(*R*)-L-16a** and the key results are presented in Table 16. Alternative Ir(I)-sources, including $Ir(cod)_2BF_4$ and $Ir(cod)_2PF_6$ gave alkyl furan **135aa'** in good yields (80% and 68%) but diminished enantiopurity (86:14 and 85:15 *e.r.*) (entry 2–3). A decrease in concentration was beneficial (entry 4) and lower temperature provided an increase to both the yield and enantiopurity (entry 6–8, 92:8 to 93:7 *e.r.*). Changing the solvent to either toluene or 1,2-DCB gave a minor improvement (entry 10–12, 94:6 *vs* 93.5:6.5 *e.r.*), whilst fine tuning of the ligand (ligand **(*R*)-L-16j**, where R = C_6F_5) provided alkyl furan **135aa'** in excellent yield and an *e.r.* of 95:5 (entry 16).



Entry	Ligand	X	Conc.	T	solvent	Yield[a] 135aa'	*e.r.*
1	(*R*)-**L-16a**, R = mesityl	BARF	1.0 M	120 °C	1,4-dioxane	72%	90:10
2	(*R*)-**L-16a**, R = mesityl	BF_4	1.0 M	120 °C	1,4-dioxane	80%[b]	86:14
3	(*R*)-**L-16a**, R = mesityl	PF_6	1.0 M	120 °C	1,4-dioxane	68%[b]	85:15
4	(*R*)-**L-16a**, R = mesityl	BARF	0.5 M	120 °C	1,4-dioxane	87%[b]	91:9
5	(*R*)-**L-16a**, R = mesityl	BARF	1.5 M	120 °C	1,4-dioxane	72%[b]	90:10
6	(*R*)-**L-16a**, R = mesityl	BARF	1.0 M	110 °C	1,4-dioxane	81%[b]	92:8
7	(*R*)-**L-16a**, R = mesityl	BARF	1.0 M	100 °C	1,4-dioxane	76%	93:7
8	(*R*)-**L-16a**, R = mesityl	BARF	1.0 M	90 °C	1,4-dioxane	82%	93:7
9	(*R*)-**L-16a**, R = mesityl	BARF	1.0 M	80 °C	1,4-dioxane	33%	93:7
10	(*R*)-**L-16a**, R = mesityl	BARF	0.5 M	90 °C	1,4-dioxane	80%	93.5:6.5
11	(*R*)-**L-16a**, R = mesityl	BARF	0.5 M	90 °C	toluene	62%	94:6
12	**(*R*)-L-16a, R = mesityl**	**BARF**	**0.5 M**	**90 °C**	**1,2-DCB**	**83%**	**94:6**
13	(*R*)-**L-16a**, R = mesityl	BARF	0.5 M	80 °C	toluene	28%	94:6
14	(*R*)-**L-16i**, R = TMS	BARF	0.5 M	90 °C	1,2-DCB	63%	91:9
15	(*R*)-**L-16j**, R = 3,5-Me-C_6H_3	BARF	0.5 M	90 °C	1,2-DCB	70%	94:6
16	**(*R*)-L-16d, R = C_6F_5**	**BARF**	**0.5 M**	**90 °C**	**1,2-DCB**	**82%**	**95:5**

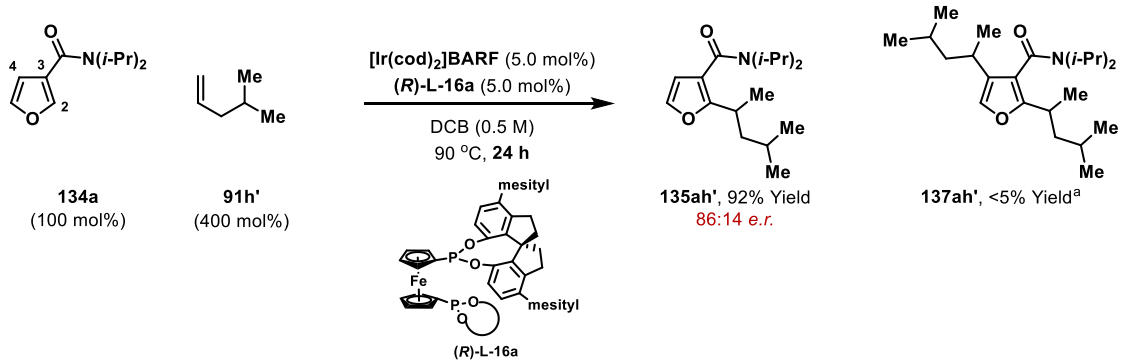
Table 16: *Selected optimisation results for the asymmetric hydroarylation of styrene **91a'** with furan **134a**. [a]Isolated yield; [b]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

Having developed optimised conditions for styrene hydroheteroarylation with furan **134a** (Table **16**) the scope of the reaction was explored by investigating aliphatic alkenes (Scheme **54**). Mesityl-substituted ligand **(*R*)-L-16a** was chosen for initial studies owing to its ease of synthesis. Under Ir(I)-catalysed conditions (Table **16**, entry 12), hydroarylation of 3-methyl-but-1-ene **91d'** with furan **134a** generated alkylated product **135ad'** in good yield (75%), but with poor enantiopurity (72:28 *e.r.*) (Scheme **54**). Additionally, dialkylated side-product **137ad'** was isolated in 12% yield, with alkylation occurring at both the C2- and C4-positions of the furan moiety. Alkylation at the C4-position does not occur when styrene **91a'** is utilised as the alkene coupling partner, likely due to its more sterically demanding phenyl group preventing a second alkylation event. Furan **134a** underwent alkylation with 4-methylpent-1-ene **91h'** to give monoalkylated product **135ah'** with a significant increase in enantiopurity (87:13 *e.r.*), alongside dialkylated product **137ah'** (3:1 selectivity). It is proposed that the enantiopurity of **135** is subject to the steric demands of both the alkene coupling partner and directing group effecting the facial selectivity (*see* Section **2.3.2**). Studies are currently ongoing in this area, with investigations into optimising the enantioselectivity for furan **135ac'** underway.



Scheme 54: *Hydroheteroarylation of aliphatic alkenes with furan **134a**.*

It is possible that the second alkylation event observed on furan **134a** (Scheme **54**) has inherent diastereoselectivity, and therefore could occur selectively on one enantiomer of mono-alkylated product. Subsequently, this could enrich/erode the enantiopurity of remaining mono-alkylated product. To explore this, dialkylation was suppressed by reducing the reaction time to 24 hours (Scheme **55**). For the hydroarylation of 4-methylpent-1-ene **91h'** with furan **134a**, alkyl furan **135ah'** was formed in excellent yield (92%), with less than 5% of dialkylated product **137ah'** observed. The enantiopurity of **135ah'** remained similar (86:14 *vs* 87:13 *e.r.*), which suggests that there is minimal preference between the enantiomers of **135ah'** for the second alkylation event.

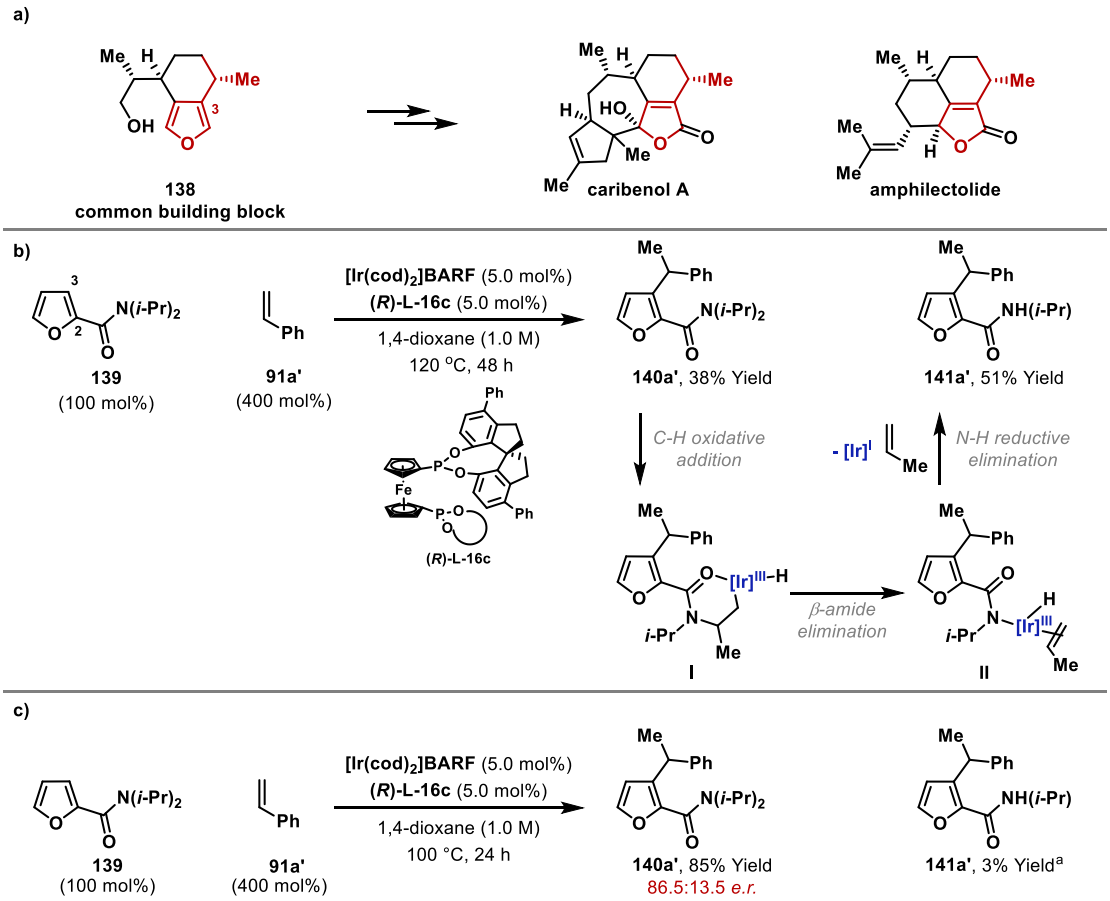


Scheme 55: *Hydroheteroarylation of 3-methyl-but-1-ene **91h'** with furan **134a**. [a] Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

3.3.2 – Expansion of the protocol to Alternative Furan Derivatives

With Ir(I)-catalysed conditions in hand for alkylation of furan **134a** at the C2 position, studies to expand the protocol to alkylate furans at the C3 position began. Furans with benzylic stereocentres

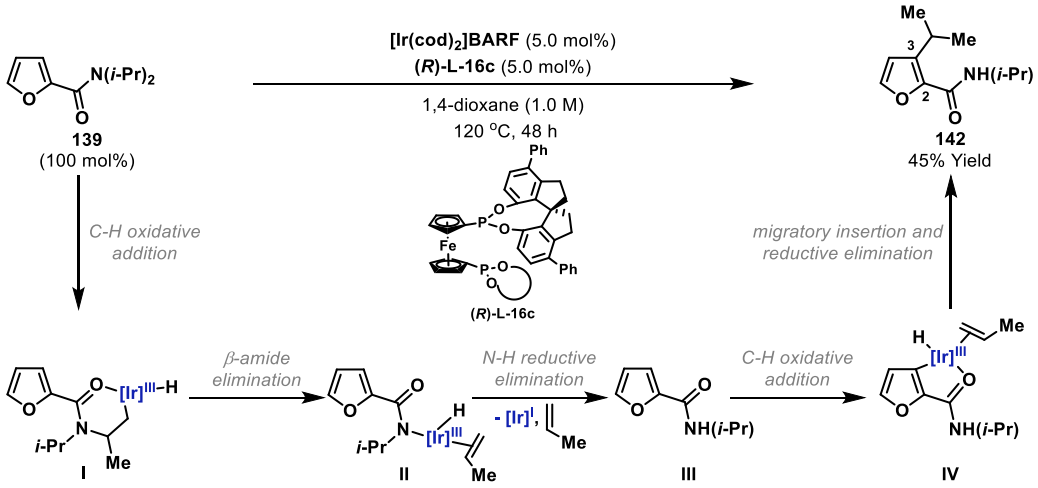
at the C3-position are valuable building blocks in the total synthesis of natural products (Scheme **56a**). For example, in 2017 Trauner and Hao utilised **138** as an intermediate for synthesising members of the norditerpenoids family; caribenol A and amphilectolide.[141] Initial studies began by exposing furan **139**, with an amide directing group at the C2-position, to Ir(cod)$_2$BARF/**(*R*)-L-16c** (Table **15**, entry 3) in the presence of styrene **91a**'. Alkyl furan **140a'** was produced in moderate yield (38%), alongside mono-dealkylated product **141a'** in 51% yield (Scheme **56b**). It was postulated that mono-dealkylated product **141a'** was forming *via* dealkylation of the directing group of hydroarylation product **140a'**. Specifically, following oxidative addition of the Ir(I)-catalyst into the terminal C–H bond of the isopropyl group of **140a'**, β-amide elimination then occurs from **I** to give Ir(III)-intermediate **II**.[142] N–H reductive elimination from **II** then affords mono-dealkylated furan **141a'** and prop-1-ene. Lower reaction temperatures and shorter reaction times were trialled to suppress dealkylation of the directing group (Scheme **56c**). For example, running the reaction at 100 °C for 24 hours generated **140a'** in excellent yield (85%) and good enantiopurity (86.5:13.5 *e.r.*), and with high selectivity over dealkylated side-product **141a'** (>25:1).



Scheme 56: *Ir(I)-catalysed hydroarylation of styrene **91a'** with furan **139**. [a] Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

To probe the mechanism for the dealkylation of the diisopropyl directing group, furan **139** was subjected to Ir(cod)$_2$BARF/**(*R*)-L-16c** in the absence of an alkene coupling partner (Scheme **57**).

Surprisingly, **142** was isolated in 45% yield, where the isopropyl group had migrated from the nitrogen of the directing group to the C3-position of the furan. It is postulated that in the absence of an alkene coupling partner, directed C–H oxidative addition of an Ir(I)-species is followed by β-amide elimination to generate **II**.[142] Subsequent N-H reductive elimination gives **III** and prop-1-ene. Oxidative addition of the Ir(I)-catalyst into the C3-position of dealkylated furan **III**, followed by coordination of prop-1-ene gives **IV**. Finally, migratory insertion of prop-1-ene and reductive elimination affords rearranged product **142**. This is not observed in the presence of styrene, most likely due to styrene undergoing more favourable coordination and migratory insertion over prop-1-ene.

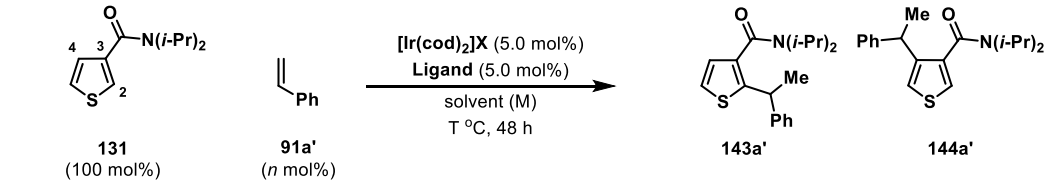


Scheme 57: *Subjection of furan **139** to Ir(I)-catalysed conditions in the absence of styrene.*

3.4 – Exploring Thiophenes for the Branch- and Enantioselective Hydroheteroarylation of Styrene

In efforts towards a general alkene hydroarylation protocol, thiophene derivatives were also investigated. Under the first-generation conditions for the alkylation of pyrrole **126a** (Table **11**, entry 7), thiophene **131** did not give target **143a'** (Table **17a**, entry 1). Nevertheless, **143a'** was generated in good yield (51%), albeit in poor selectivity under Ir(I)-catalysed conditions developed for furan **134a** (Scheme **53b**) (Table **17a**, entry 2). Alkylation occurred at the C2- and C4-position of the thiophene, in a 1.6:1 ratio (**143a'**:**144a'**). Decreasing the number of equivalents of styrene had a beneficial effect (entry 3). Additionally, alternative ferrocene-based bisphosphonite ligand **(*R*)-L-16c** generated hydroarylation product **143a'** in increased yield (79%), although in poor selectivity over C4 alkylated product **144a'** (entry 4). Consequently, benzothiophene **145** in which the C4-position is blocked by an arene, was synthesised and exposed to hydroarylation conditions (Table **17b**). Alkylated product **146a'** was produced with complete branch-selectivity, but in modest yield (45%).

a)



Entry	T	Ligand (mol%)	solvent	X (mol%)	*n* (mol%)	Yield 143a'[a]	Yield 144a'
1	130 °C	(*R*)-H_8-BINAP (7.5)	MeCN (1.5 M)	OTf (7.5)	400	0	0
2	120 °C	(*rac*)-L-15a (5.0)	1,4-dioxane (1.0 M)	BARF (5.0 mol%)	400	51%	31%
3	120 °C	(*rac*)-L-15a (5.0)	1,4-dioxane (1.0 M)	BARF (5.0 mol%)	150	59%	35%
4	120 °C	(*R*)-L-16c (5.0)	1,4-dioxane (1.0 M)	BARF (5.0 mol%)	400	79%	20%

b)

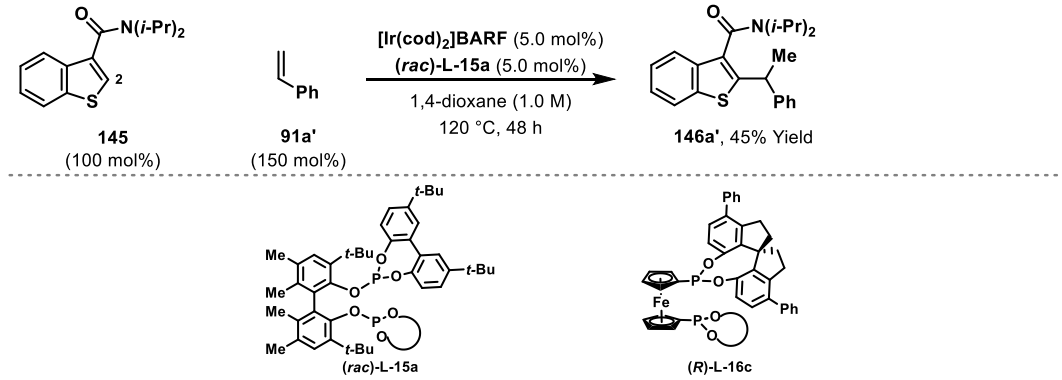
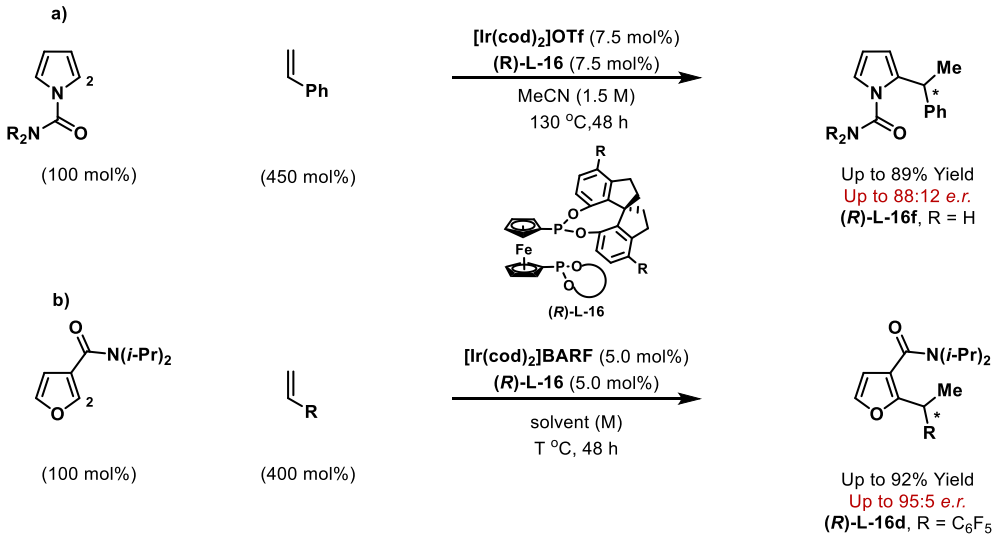


Table 17: *Styrene hydroheteroarylation with thiophene derivatives **131** and **145**. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard; [b]Isolated yield.*

3.5 – Summary and Conclusions

Significant developments towards a general and simple method for the Ir(I)-catalysed hydroheteroarylation of styrenes have been made. The methodology has been expanded to include pyrroles, furans and benzothiophenes. Using ferrocene-based bisphosphonite ligands **(*R*)-L-16**, enantioenriched products bearing benzylic stereocentres were afforded in good to excellent yields, with promising levels of enantioselectivity (Scheme **58**). The methodology has been expanded to the hydroarylation of aliphatic alkenes with furan derivatives, to give the desired products in good yields, although with limited enantiopurity. Further fine-tuning of the ligand and mechanistic studies might allow efficient asymmetric hydroheteroarylation of a broad range of alkenes.



Scheme 58: *Enantioselective styrene hydroheteroarylation with pyrroles and furans.*

Chapter 4 – Iridium-Catalysed Hydroarylation of 1,1-Disubstituted Alkenes

4.1 – The Importance of All-Carbon Quaternary Centres

The development of methods that readily generate quaternary centres is of great importance to modern synthetic chemistry. However, these highly substituted moieties are often difficult to synthesise, owing to steric repulsion between the carbon substituents during bond formation. There has been a plethora of research into the formation of cyclic systems bearing quaternary centres, employing well-established reactions, including the Diels-Alder reaction, Pd-catalysed alkylations and intramolecular Heck reactions.[143-149] Conversely, acyclic systems which have quaternary centres, including benzylic quaternary stereocentres, are much harder to access, owing to the difficulty in controlling the greater degrees of freedom during bond formation.[148] However, synthetic methods for the generation of quaternary stereocentres are highly desirable because these motifs are present in biologically active natural products.[150] A few noteworthy examples include morphine,[151] a common analgesic, elacomine,[152] which shows antimicrobial activity, verapamil,[153] used to treat high blood pressure and cuparene,[154] derivatives of which show antifungal properties (Figure **5**).[155]

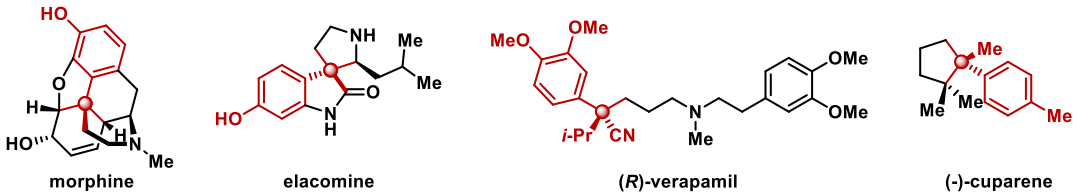
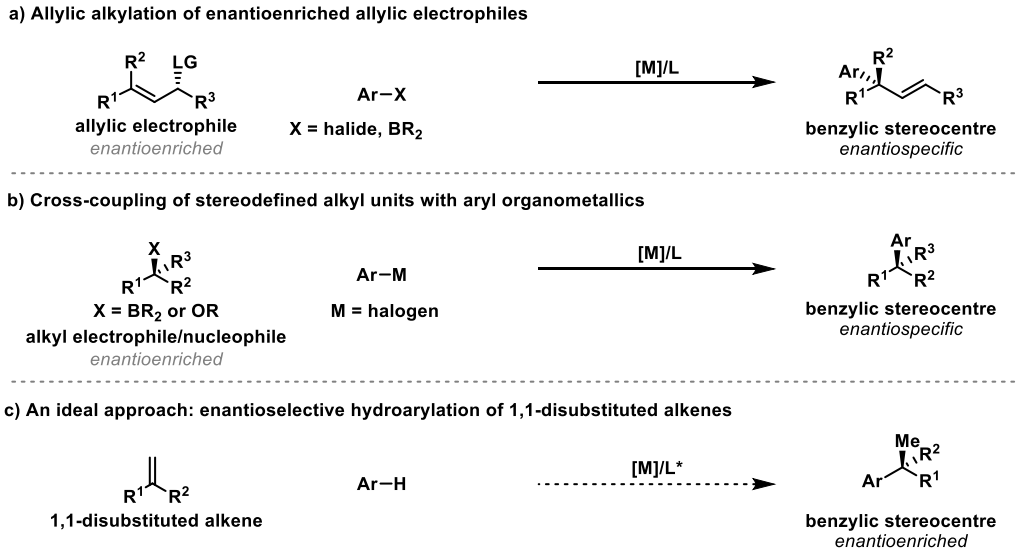


Figure 5: *Natural products and drug molecules bearing quaternary benzylic stereocentres.*

Methods that generate arenes bearing all-carbon quaternary centres, particularly where a benzylic C–C bond is created in the stereocentre determining step, remains a challenge, with few examples reported.[156] One approach is alkylation of enantioenriched substituted allylic electrophiles or racemic substrates under chiral catalysis, which forms the benzylic quaternary centres adjacent to an alkene (Scheme **59a**).[157-160] Additionally, a few cross-coupling reactions that allow the formation of benzylic quaternary centres remote from specific functionality (e.g. alkenes) have been reported, as demonstrated in Section 1.2 (Scheme **59b**).[46, 161] However, both of these approaches involve multiple steps to synthesise functionalised starting materials, resulting in significant waste. Enantioselective hydroarylation of simple alkenes *via* C–H activation of an arene would provide an environmentally green and step-economical route to these privileged motifs. Currently, only a few non-enantioselective methodologies exist to establish quaternary centres *via* alkene hydroarylation (*see* Section **1.3.2**).[113-114] However, these are limited to hydroarylations of electronically favourable alkenes (acrylates and acrylamides) with highly specific *N*-containing heteroaromatics. A facile alkene hydroarylation method

that affords challenging quaternary centres enantioselectively and in high atom economy is likely to have widespread application (Scheme **59c**).



Scheme 59: *The current state of the art methods, including an ideal route, to synthesise quaternary benzylic stereocentres.*

4.2 – Generation of All-Carbon Quaternary Centres on Benzamide Substrates

4.2.1 – Reaction Discovery and Optimisation

To expand the scope of the Ir(I)-catalysed hydroarylation methodologies developed at Bristol to generate benzylic quaternary centres, the hydroarylation of 1,1-disubstituted alkenes was investigated. Previously Dr. Crisenza explored the hydroarylation of α-methylstyrene **147a'** with benzamide **90c** under various Ir(I)-catalysed conditions with d^Fppb as the ligand (Table **18**). However, **148ca'**, bearing a desired quaternary centre was not observed. After the development of more efficient bisphosphite ligands for asymmetric hydroarylations of monosubstituted alkenes, Dr. Simon Grèlaud found that when *N,N*-diethylbenzamide **90c** and α-methylstyrene **147a'** were exposed to $[Ir(cod)_2]$BARF in the presence of bisphosphite binaphthyl ligand **(*rac*)-L-15b**, desired product **148ca'** was produced in moderate yield (51%) (Table **18**). This promising initial result forms the basis for the studies outlined in this chapter.

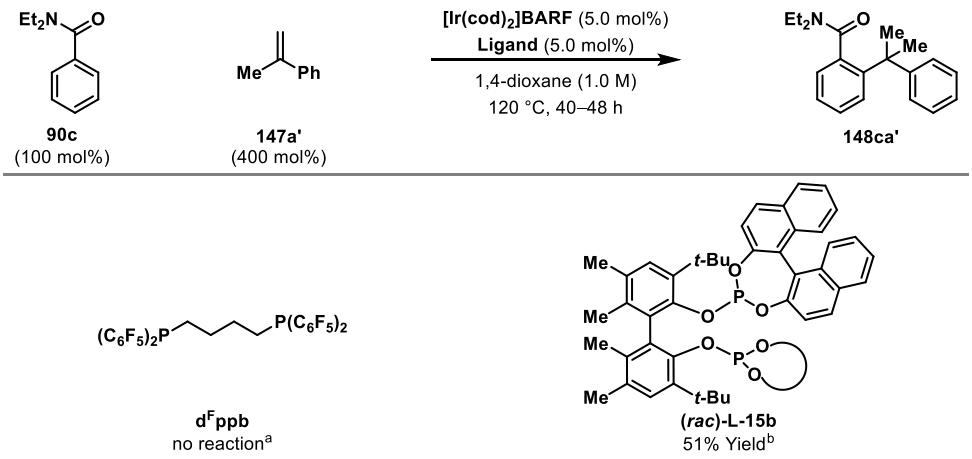
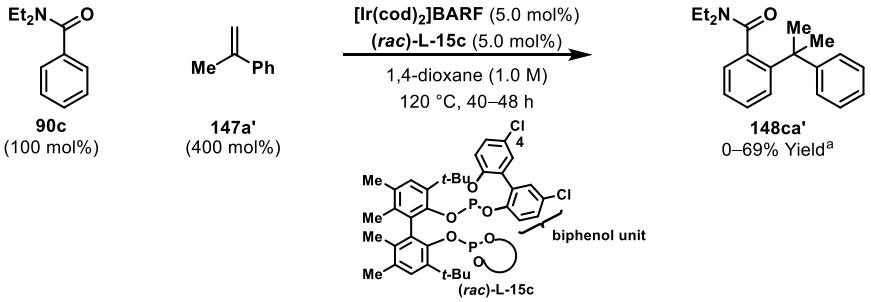


Table 18: *Ir(I)-catalysed hydroarylation of α-methylstyrene **147a'** with N,N-diethylbenzamide **90c**. [a]Reaction conducted by Dr. Giacomo Crisenza; [b]Reaction conducted by Dr. Simon Grélaud.*

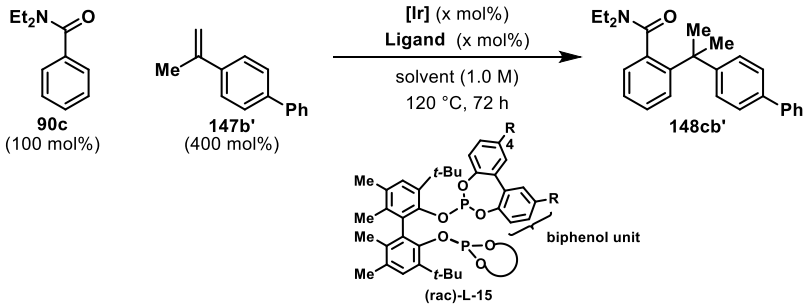
Following the preliminary results described above (Table **18**), an extensive screen of bisphosphite ligands previously developed at Bristol (*see* Section **2.3**) was carried out for the hydroarylation of 1,1-disubstituted alkene **147a'** with benzamide **90c**. Initially, ligands bearing biphenol units with various R-substituents at the C4-position were investigated. Chloro-substituted ligand **(*rac*)-L-15c** resulted in an increase in yield to 69% (Scheme **60**). However, under these Ir(I)-catalysed conditions the reaction was poorly reproducible, with yields ranging from 0–69%, which led to extensive re-evaluation of the reaction conditions. It was postulated that this demanding reaction might be sensitive to water/oxygen. To test this, the hydroarylation protocol was carried out in the presence of air and water, both of which resulted in inhibited conversion of **90c**. Therefore, to eliminate water and oxygen from the reaction mixture, several modifications were trialled, including the addition of

Na_2SO_4 or molecular sieves to the reaction tube, flame-drying the reaction tubes prior to use (instead of oven drying) and freeze-pump-thawing the solvent. Eventually, reproducibility was achieved by distilling the 1,4-dioxane solvent from Na/benzophenone and setting up the reaction in a glove box. The hydroarylation of monosubstituted alkenes previously developed at Bristol exhibited good reproducibility under less stringent conditions and the issue seems to be specific to benzamide substrates. One possibility for the need for more rigorous conditions for the hydroarylation of 1,1-disubstituted alkenes, is that the reaction may occur less readily owing to the steric constraints of the disubstituted alkene. Consequently, small amounts of water/oxygen in the reaction tube could deactivate the Ir(I)-catalyst before hydroarylation of the alkene can occur.



Scheme 60: *Ir(I)-catalysed hydroarylation of α-methylstyrene with N,N-diethylbenzamide* ***90c****. [a] Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

With reproducible conditions developed, further optimisation studies began with *para*-phenyl alkene **147b'**, as it is an easily handled solid (for ease of use in glovebox) and a selection of the key results is given in Table 19. Under these more stringent conditions, the hydroarylation of *para*-phenyl styrene derivative **147b'** with benzamide **90c**, utilising chloro-substituted ligand **(*rac*)-L-15c** (R = Cl at C4), proceeded to generate product **148cb'** in 55% yield after 48 hours at 120 °C (Table **19**, entry 1). Changing the R substituent of the bisphosphite ligand to an electron-donating group (i.e. R = OMe, **(*rac*)-L-15d** or *t*-Bu, **(*rac*)-L-15a**) and increasing the reaction time to 72 hours, gave an increase in yield of **148cb'** from 55% to 64% and 68%, respectively (entry 1 *vs* 2 and 3). Conversely, the addition of an electron-withdrawing trifluoromethyl group at the C4-position of the ligand had a detrimental effect on conversion of **90c** to **148cb'** (entry 4, **(*rac*)-L-15e**). When utilising ligand **(*rac*)-L-15f** (*see* experimental for synthesis), where R = H, an optimal yield of 75% was achieved (entry 5). Next, alternative solvents were screened (e.g. toluene, 1,2-DCB, entry 6 and 7), but none of these resulted in improved yield. Different Ir(I)-sources, including $[Ir(cod)_2]OTf$ and $[Ir(cod)_2]BF_4$ (entry 8 and 9), higher precatalyst and ligand loadings (entry 10) and higher temperatures (entry 11) all failed to increase the yield.



Entry	[Ir]	X/mol%	Ligand	solvent	Yield[a] 148cb'
1	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15c**, R = Cl	1,4-dioxane	55%[d]
2	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15d**, R = OMe	1,4-dioxane	64%
3	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15a**, R = *t*-Bu	1,4-dioxane	68%
4	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15e**, R = CF_3	1,4-dioxane	37%
5	$[Ir(cod)_2]BARF$	**5.0**	**(*rac*)-L-15f, R = H**	1,4-dioxane	**75%[b]**
6	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15f**, R = H	1,2-DCB	52%
7	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15f**, R = H	toluene	63%
8	$[Ir(cod)_2]OTf$	5.0	(***rac*)-L-15f**, R = H	1,4-dioxane	44%
9	$[Ir(cod)_2]BF_4$	5.0	(***rac*)-L-15f**, R = H	1,4-dioxane	34%
10	$[Ir(cod)_2]BARF$	7.5	(***rac*)-L-15f**, R = H	1,4-dioxane	45%
11	$[Ir(cod)_2]BARF$	5.0	(***rac*)-L-15f**, R = H	1,4-dioxane	52%[c]

Table 19: *Selected optimisation results for the hydroarylation reaction of alkene **147b'** with N,N-diethylbenzamide **90c**. [a]Yield determined by ^1H NMR analysis of crude material against an internal standard; [b]Isolated yield; [c]The reaction was performed at 130 °C; [d]The reaction was run for 48 h.*

4.2.2 – Scope with Respect to the Benzamide Substrates

With optimised conditions in hand (Table **19**, entry 5), the scope with respect to *N*,*N*-diethylbenzamide derivatives was explored (Table **20**). Initially, various directing groups were investigated. Methyl derivative **90e**, and cyclic amides **90f** and **90g** underwent alkylation with alkene **147b'** under the Ir(I)-catalysed conditions to deliver quaternary products **148eb'–148gb'**, albeit in moderate yields (31–51%). However, alternative directing groups, including more sterically demanding **90h** and ketone derivative **89b** were unsuccessful (Table **20**). Following these initial studies, arene **90c**, which bears an *N*,*N*-diethylamide unit, was selected to further explore the scope of this transformation.

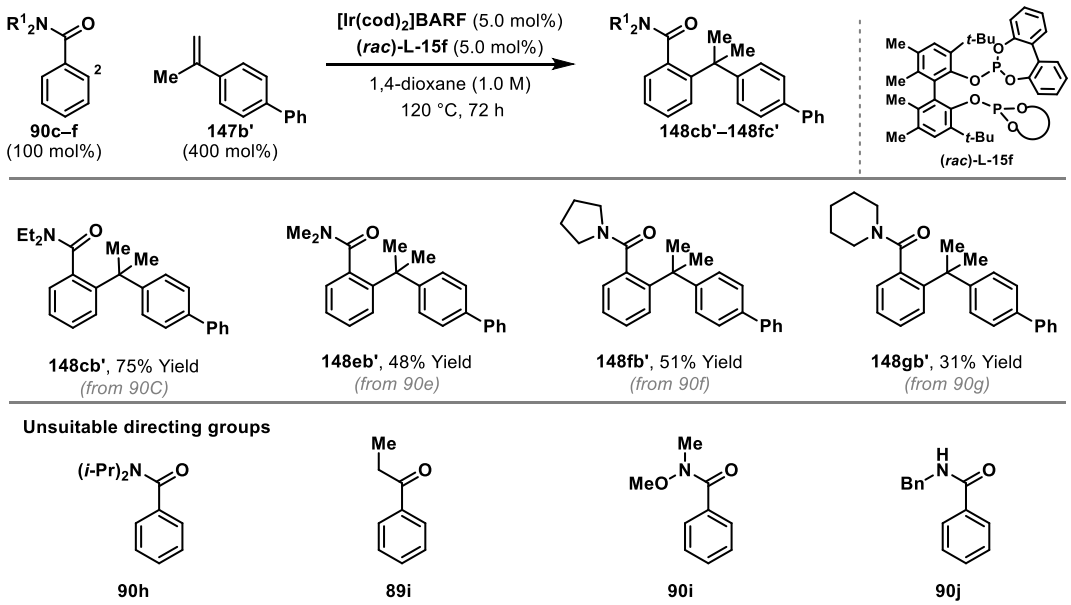


Table 20: *Scope of the hydroarylation reaction of 1,1-disubstituted alkene **147b'** with benzamide substrates with respect to the directing group.*

Having identified *N,N*-diethylamide as the optimal directing group, the alkene hydroarylation reaction was conducted with benzamides bearing both electron-rich and -poor substituents (Table **21**). Notably, in cases where two *ortho*-positions are differentiated (e.g. **90d**, **90k** and **90l**), complete selectivity for the less hindered *ortho*-position (C6 *vs* C2) was observed. This is in contrast to the selectivity observed in the hydroarylation of mono-substituted alkenes with *meta*-substituted substrate **93aa'** (*see* Section **1.4**, Scheme **39**), which is most likely attributed to the steric-constraints of the newly formed quaternary centre.[116] Methyl-substituents and electron-donating methoxy groups were well tolerated in both the *meta*- and *para*-positions of the benzamide unit as shown in the high yielding formation of **148db'**, **148kb'**, **148mb'**, **148nb'** (52–73% yield). Hydroarylation product **148lb'**, bearing a sensitive B(pin) group was generated in a 18% yield, demonstrating the mild nature of the reaction conditions. However, electron poor substituents, such as in **90p** and **90q** were not tolerated, along with *para*-nitro derivative **90r**. Additionally, pyridine derivative **90t** was unsuitable, which is presumably due to the basic nitrogen atom coordinating to the Ir(I)-species and preventing insertion into the desired *ortho* C–H bond. Benzamides bearing *ortho*-substituents, such as in of **90u**–**90w**, and benzamide **98**, with a cyclic directing group, both failed to undergo hydroarylation. This illustrates that the directing group must be able to freely rotate for hydroarylation to occur. It is likely that the *ortho*-substituents force the directing group to twist out of the plane of the arene, and therefore it is ineffective at directing the Ir(I)-catalyst into the *ortho* C–H bond of **90u**–**90w** (Scheme **61**). For this reason, bis-*ortho*-functionalisation is not observed. In the case of cyclic benzamide **98**, the lack of rotation may inhibit alkene migratory insertion/reductive elimination (*see* Section **2.1**).

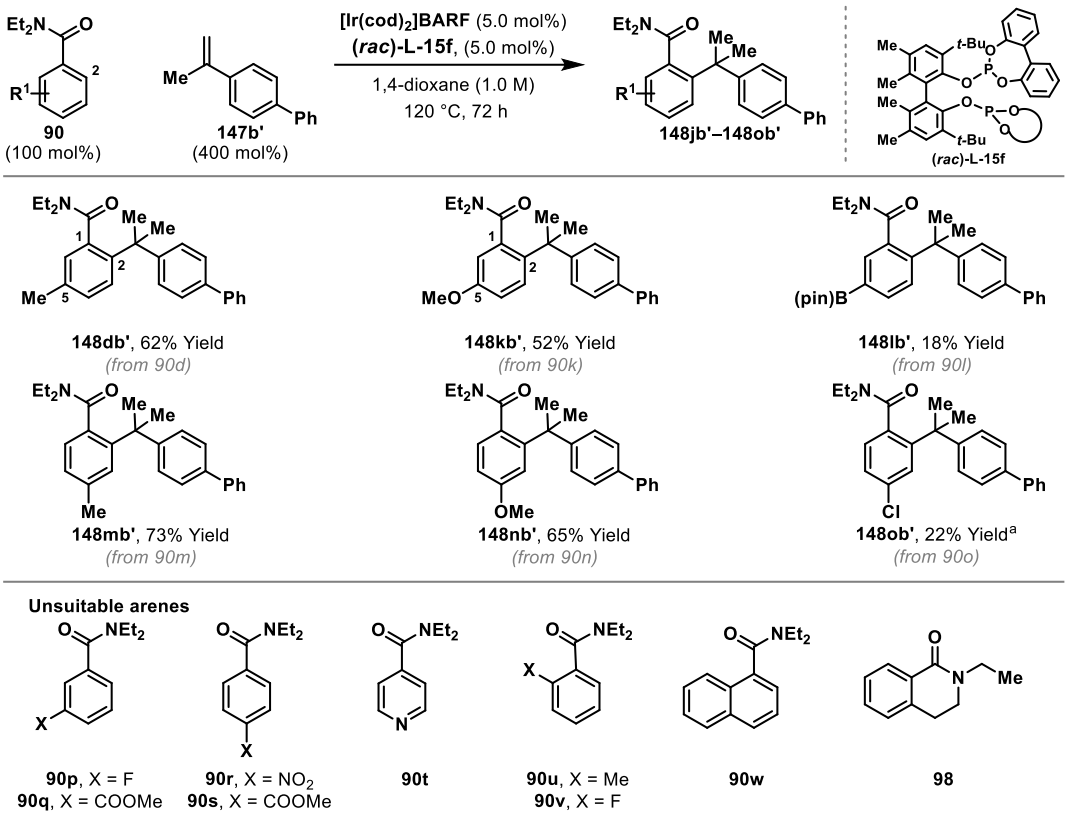
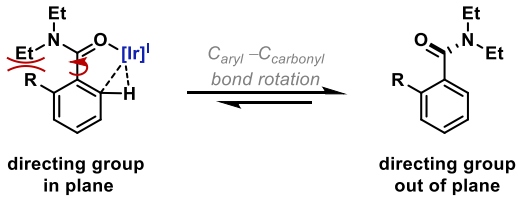


Table 21: *Scope of the hydroarylation reaction of 1,1-disubstituted alkene **147b'** with benzamide substrates with respect to substitution of the benzamide. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*



Scheme 61: *The effect of ortho-substituents on Ir(I) oxidative addition.*

4.2.3 – Scope with Respect to the Alkene Coupling Partner

Next, electronically diverse styrenes with substituents in the *meta*- and *para*-position (**147c'–147g'**) were evaluated (Table **22**). *Para*-fluoro styrene derivative **147c'** reacted with benzamide **90c** efficiently to afford fluorinated product **148cc'** in good yield (74%), but *para*-bromo-derivative **147d'** gave desired product **148cd'** with lower efficiency (24% yield). Electron-donating *para*-methoxy-derivative **147e'** also behaved poorly, generating desired product **148ce'** in 25% yield. However, *meta*-chloro and *meta*-methoxy styrenes **147f'** and **147g'** were tolerated, producing hydroarylation products **148cf'** and **148cg**' in 65% and 70% yield respectively. Interestingly, hydroarylation of aliphatic alkene **147h'** with benzamide **90c** generated **148ch'** in 22 % yield, alongside structural isomer **148ch''** (37% yield).

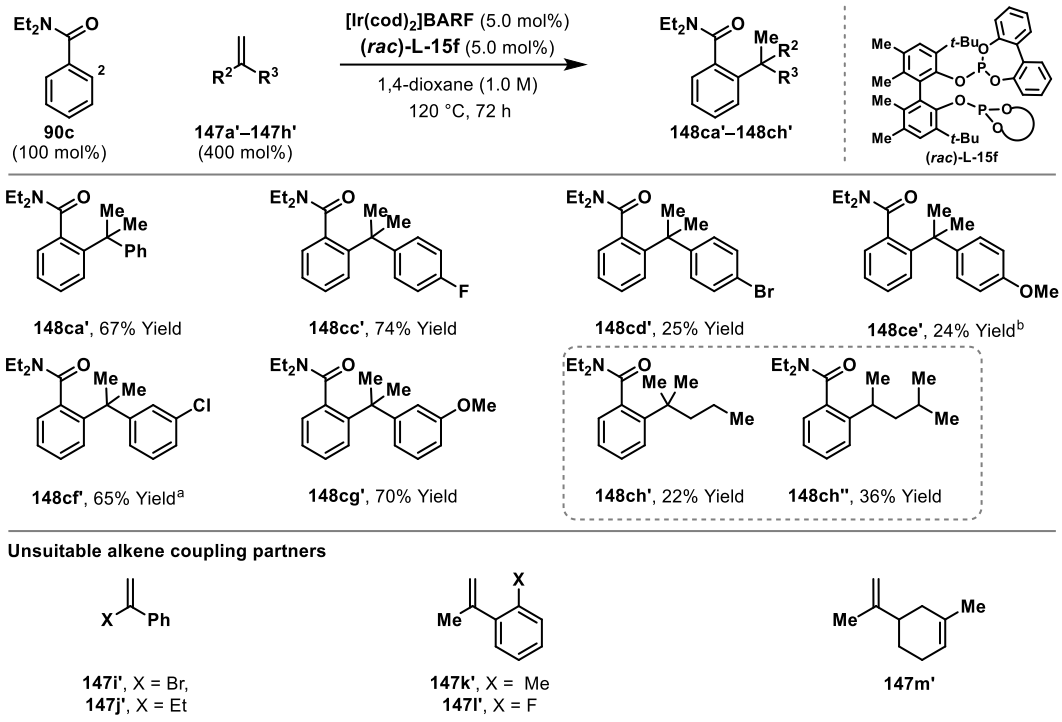
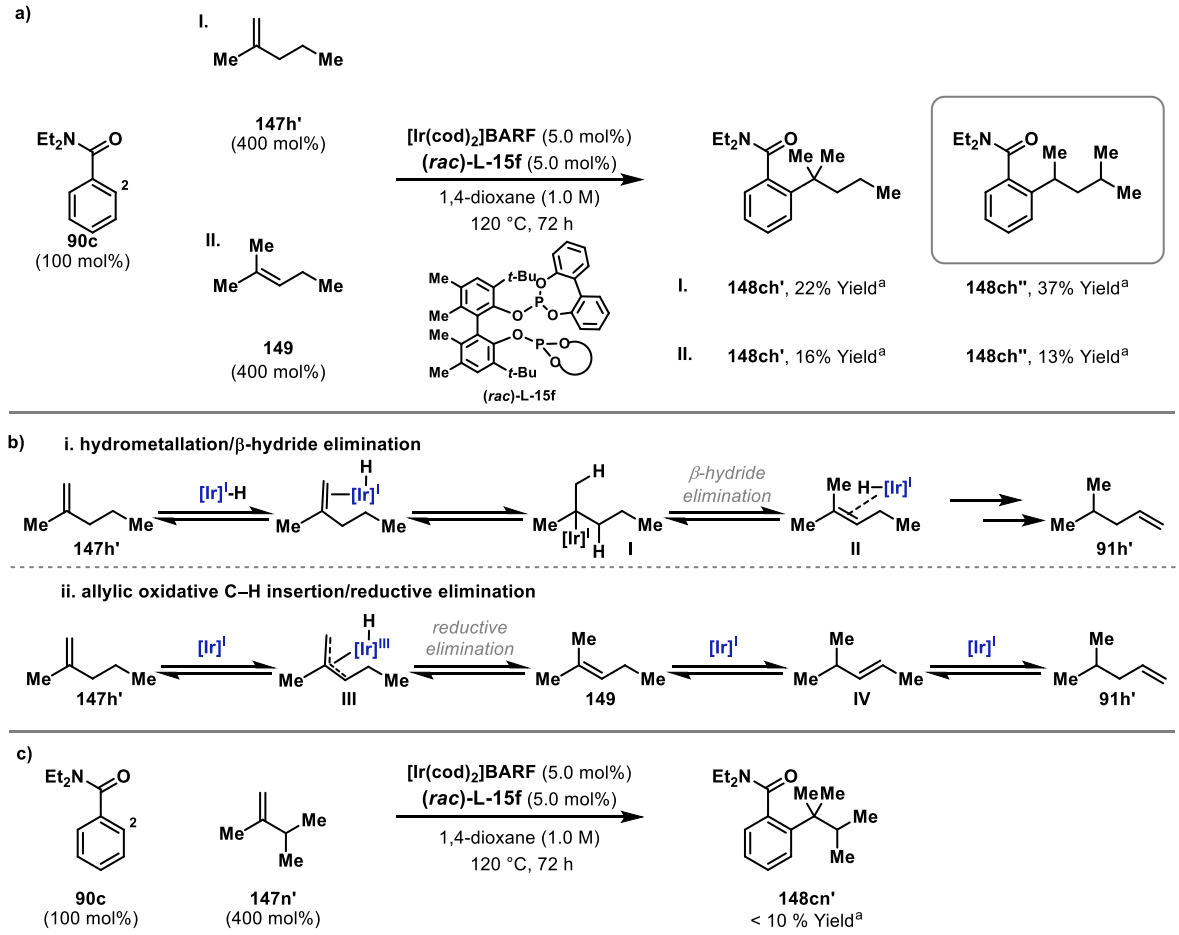


Table 22: *Scope of the hydroarylation reaction of 1,1-disubstituted alkenes with benzamide **90c**. [a]7.5 mol% of Ir(cod)$_2$BARF and ligand was used; [b]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

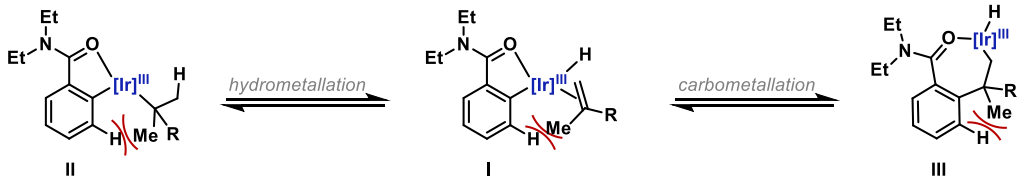
The unexpected formation of isomer **148ch''** is presumed to result from hydroarylation of alkene **91h'**, which is likely formed by alkene isomerisation of starting alkene **147h'** under the Ir(I)-catalysed conditions (Scheme **62b**). To investigate this, regioisomeric alkene **149** was subjected to Ir(I)-catalysis, which generated **148ch'** in 16% yield, alongside structural isomer **149ch''** in 13% yield (Scheme **62a**). The fact that both product isomers **148ch'** and **148ch''** are formed from alkene **147h'** and **149** suggests that they are isomerising under the reaction conditions. This could occur by two processes; an Ir–H mediated hydrometallation/β-hydride elimination mechanism, or *via* allylic oxidative C–H insertion/reductive elimination.[162] For example, addition of an Ir(I)–H species across the alkene to give **I**, followed by β-hydride elimination to give **II**, would isomerise the alkene as shown in Scheme 62bi. Alternatively, the alkene may migrate *via* oxidation of the allylic C–H bond to form η^3-allyl complex **III**, followed by reductive elimination to give isomerised alkene **149** (Scheme **62bii**).[163] Under this process, the point of unsaturation moves along the chain until **91h'** forms and undergoes hydroarylation with benzamide **90c**. Related processes involving alkene migration *via* Ir(I)-catalysed allylic C–H insertion have been reported.[162] More highly substituted alkenes are often more thermodynamically stable,[164] therefore **91h'** is likely the more kinetically stable isomer. Ir(I)-catalysed alkene isomerisation occurs in competition with alkene hydroarylation, hence isomers **148ch'** and **148ch''** are observed. The hydroarylation of sterically demanding alkene **147n'** was trialled to avoid isomerisation of the alkene (Scheme **62c**). However, less than 10% conversion to alkyl quaternary

product **148cn'** was observed. The low reactivity is most likely due to less favourable coordination of bulkier alkene **147n'** to the Ir(III)-intermediate and a greater energy barrier to insertion of the alkene into the Ir(III)–H/Ir(III)–C bond.



Scheme 62: *Hydroarylation of aliphatic alkenes with N,N-diethylbenzamide **90c**. [a] Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

To summarise, the development of ligand **(*rac*)-L-15f** has allowed the formation of challenging all-carbon quaternary centres on benzamides. The protocol tolerates substitution in the *meta*- and *para*-position of the benzamide unit and the styrene coupling partner (e.g. OMe, halogens). Current limitations include substitution in the *ortho*-position of both coupling partners and alternative substituents to methyl at R^2 of the styrene. These results are significant considering the challenges associated with hydroarylation of sterically congested 1,1-disubstituted alkenes. A bulkier alkene would undergo less favourable coordination to Ir(III)-intermediate **I** formed after oxidative addition and a greater energy barrier for the hydrometallation (**I** to **II**) or carbometallation step (**I** to **III**) would lead to a low catalyst turnover (Scheme **63**).



Scheme 63: *Steric constraints in the hydroarylation of 1,1-disubstituted alkenes.*

4.3 – Expansion of the Hydroarylation of 1,1-Disubstituted Alkenes to Five-Membered Heteroaromatics

4.3.1 – Hydroarylation of 1,1-Disubstituted Alkenes with Pyrrole Substrates

Having successfully developed methodology for 1,1-disubstituted alkene hydroarylation with benzamide derivatives, evaluation of five-membered heteroaromatics began. In initial studies, *N*-methyl-pyrrole **150a**, equipped with a diisopropyl directing group at the C3-position, was exposed to the optimised Ir(I)-catalysed conditions. Desired alkylated product **151aa'** was generated in excellent yield after just 24 hours (87% yield, Table **23**). The scope of the reaction was explored with respect to the alkene coupling partner, whereby electron-deficient fluorinated styrene **147c'** gave **151ac'** in 77% yield. The α-methyl substituted styrenes used so far have generated achiral molecules, so α-ethylstyrene **147j'** was investigated. When pyrrole **150a** was exposed to α-ethylstyrene **147j'**, chiral hydroarylation product **151aj'** was produced in 73% yield after 16 hours. Interestingly, when exposed to 2-methyl-1-pentene **147h'**, pyrrole **150a** underwent facile conversion to desired product **151ah'** (83% yield). This is in contrast to hydroarylation of **147a'** with *N*,*N*-diethyl benzamide **90c**, which formed a mixture of two regioisomers (Scheme **62**). The fact that none of the tertiary regioisomer is formed in this case, suggests that the formation of alkene regioisomer **91h'** is dependent upon the substrate (Scheme **62**). This might suggest that the alkene isomerisation is facilitated by an Ir(III)-H species, which is formed *via* oxidative addition of the Ir(I)-catalyst into the starting material (Scheme **62**). The protocol was also extended to more elaborate systems such as steroid-derived alkene **147o'** and ferrocene-based alkene **147p'**; however, regio-selectivity for **151ap'** is poor, with a 1.3:1 ratio between alkylation at C2 and C4. Next alternative substituents on the pyrrole *N*-atom were investigated. For example, TIPS protected pyrrole **151b** was unsuccessful, presumably due to the larger protecting group hindering alkene coordination. Additionally, N–H pyrrole **151c** did not provide the target product, most likely due to metallation of the free N–H bond.

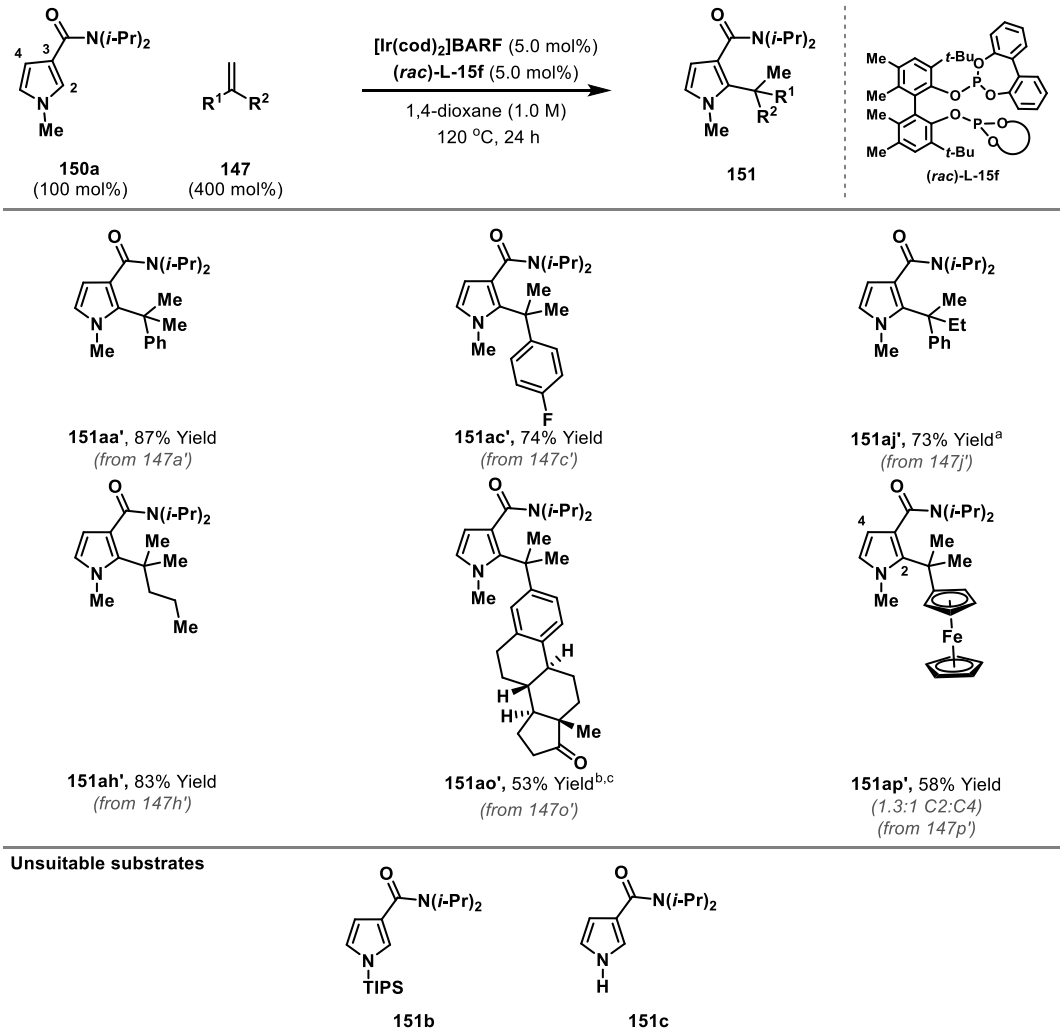
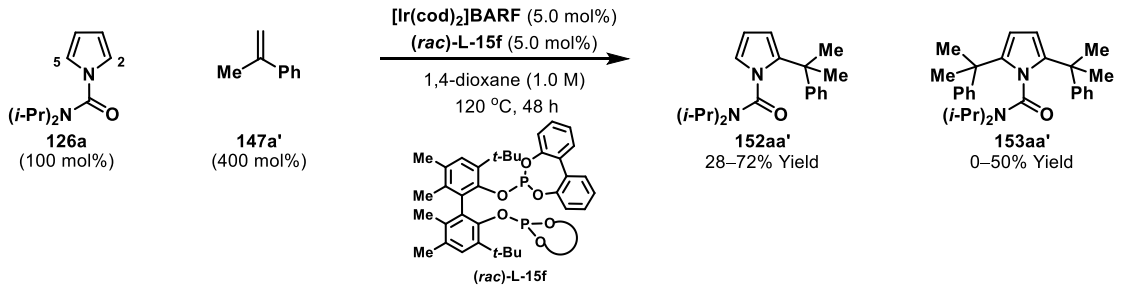


Table 23: *Scope of the hydroarylation reaction of 1,1-disubstituted alkenes with N-methyl-pyrrole* ***150a****.* [a]*The reaction was run for 16 h;* [b]*150 mol% of alkene was used;* [c]*The reaction was run for 72 h.*

The broad applicability of the Ir(I)-catalyst system was further demonstrated by expanding the scope to pyrrole derivate **126a**, which bears an *N*-carbamoyl directing group (Scheme **64**). When pyrrole **126a** was exposed to α-methylstyrene **147a'**, desired product **152aa'** was produced in a 72% yield. Unfortunately, the reaction exhibited poor reproducibility, with yields ranging from 28–72%. In some cases, up to 50% of di-alkylated product **153aa'** was also observed. However, distillation of the 1,4-dioxane solvent over Na/benzophenone and distillation of α-methyl styrene before use, resulted in reproducible results, affording product **152aa'** in good yield and selectivity over di-alkylated species **153aa'** (72% yield, Table **24**).



Scheme 64: *Ir(I)-catalysed hydroarylation of α-methylstyrene with pyrrole **126a**. [a] Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

Having developed reproducible conditions, alternative alkene coupling partners (e.g. **147f'**, **147c'** and **147b'**) with electronically diverse groups in the *meta* and *para*-positions were explored in the Ir(I)-catalysed hydroarylation with pyrrole **126a**. A significant drop in yield was observed for hydroarylation of halogenated and biphenyl alkenes **147f'**, **147c'** and **147b'** (31–53% yield), albeit with complete selectivity for monoalkylated product **152** in each case. When pyrrole **126a** was subjected to 2-methyl-1-pentene **147h'** under Ir(I)-catalysed conditions alkene isomerisation occurred resulting in structural isomers **152ah'** and **152ah''** (2.5:1) (Table **24**). This mirrors the hydroarylation of 2-methyl-1-pentene **147h'** with benzamide **90c** (Scheme **62**). Next, substitution around the pyrrole was explored; however, phenyl-substituted pyrrole **126e** was unreactive under standard catalytic conditions. Additionally, azoles **129** and **130** remained unfunctionalised, suggesting that the nitrogen atoms were potentially coordinating to the Ir(I)-catalyst and deactivating it. Pyrrole **126a** was also unreactive towards more complex alkenes, such as ferrocene-based **147p'** and steroid **147o'**.

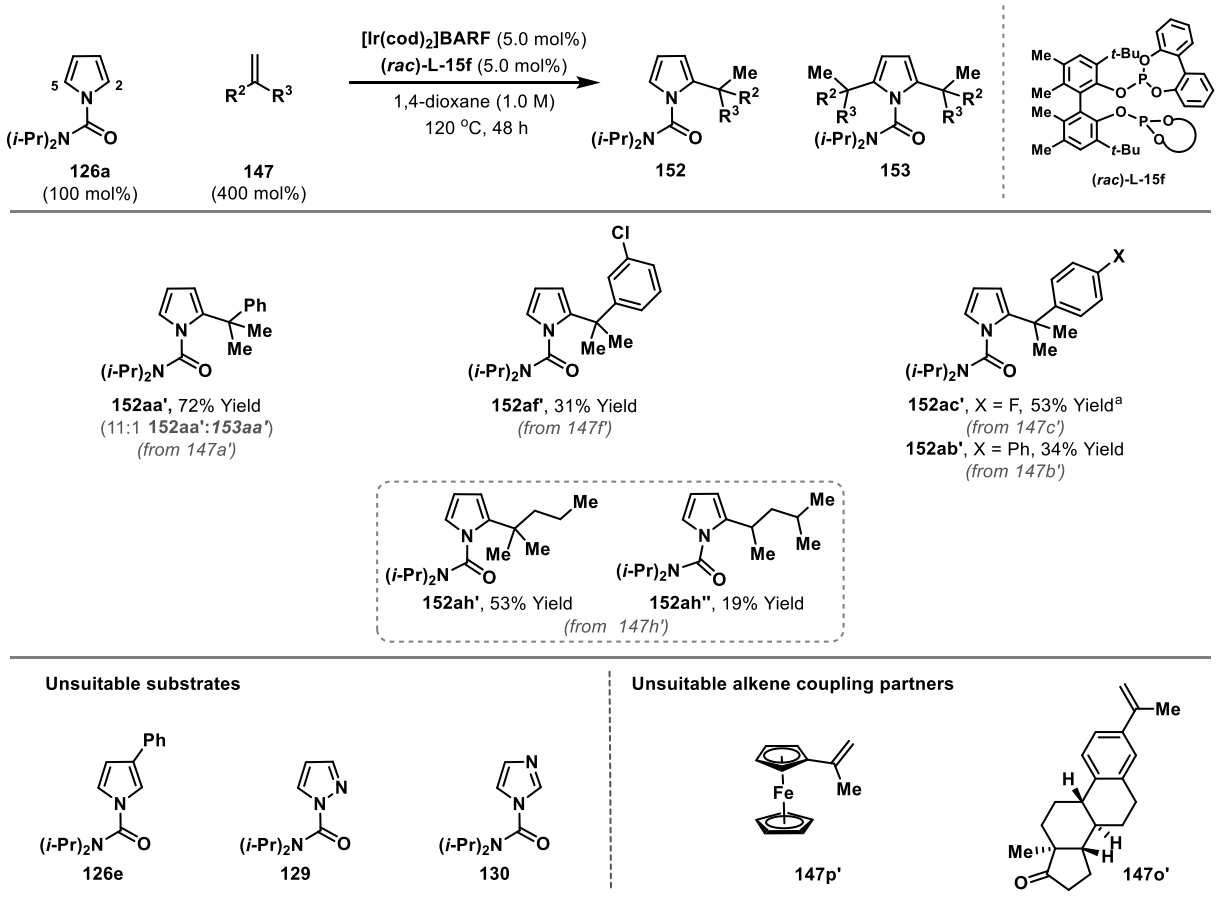
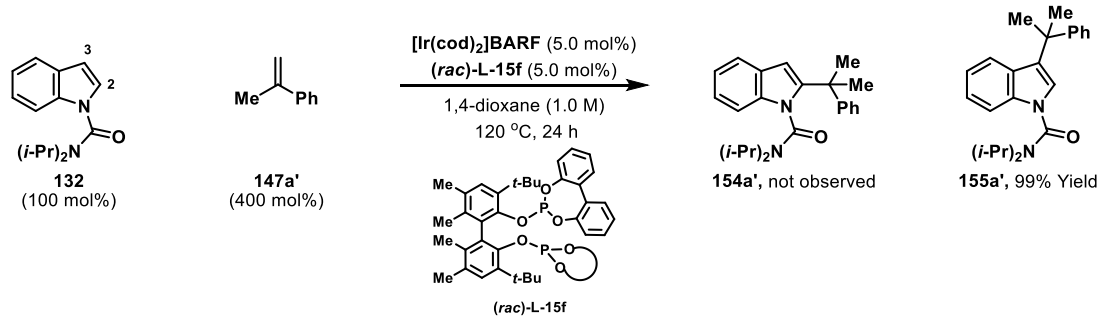


Table 24: *Scope of the hydroarylation reaction of 1,1-disubstituted alkenes with pyrroles **126a**. [a]The reaction was run for 72 h.*

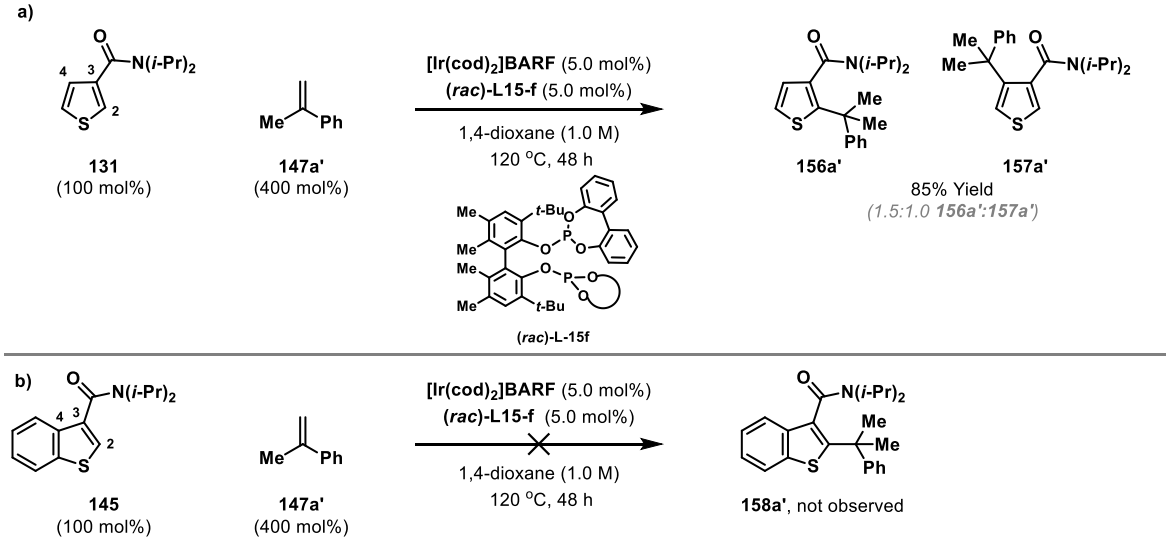
To expand the scope further, indole **132** was investigated. When exposed to α-methylstyrene **147a'** under standard hydroarylation conditions, the reaction proceeded with full conversion to give C3-alkylated indole **154a'**, with no directed alkylation at C2 observed (**155a'**) (Scheme **65b**). This indicates that a Friedel-Crafts-type reaction is occurring, whereby the Ir(I)-catalyst is acting as a π-Lewis acid. This type of reaction was previously observed for the reaction of styrene **91a'** with *N*-acetyl indole **116** (Section **3.3.1**, Table **8**).



Scheme 65: *Alkylation of indole **154** via a Friedel-Crafts type mechanism. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

4.3.2 – Hydroarylation of 1,1-Disubstituted Alkenes with Thiophene Substrates

Having successfully expanded the hydroarylation of 1,1-disubstituted alkenes to include pyrrole derivatives, other five-membered heteroaromatics, including thiophene derivative **131**, were investigated. Under standard catalytic conditions hydroarylation of α-methylstyrene **147a'** with thiophene **131** proceeded in excellent yield (85%), albeit in poor selectivity, with alkylation occurring at C2 and C4 of the thiophene, in a 1.5:1 **156a'**:**157a'** ratio respectively (Scheme **66a**). At present it is not understood why this selectivity issue is not observed for furan **134** and only for ferrocene-based alkene **147p'** with pyrrole **126a**. Towards a regioselective protocol, benzothiophene **145**, in which C4 is blocked by an arene, was exposed to the Ir(I)-catalysed conditions (Scheme **66b**). However, no conversion to **158a'** was observed. Previously the hydroarylation of styrene **91a'** with benzothiophene **145** was successful (Section **3.4**, Table **17**), which further highlights the greater barrier to alkene migratory insertion/reductive elimination with more sterically demanding 1,1-disubstituted alkenes.

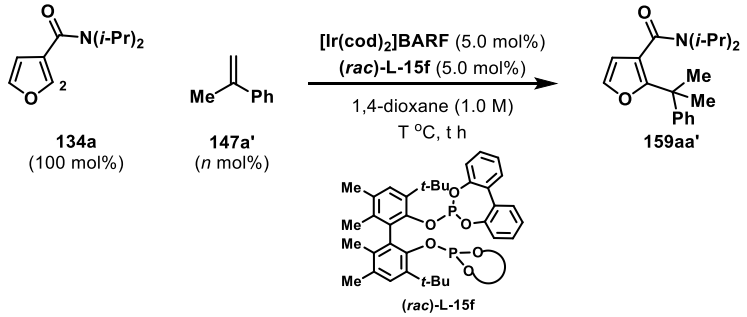


Scheme 66: *Hydroarylation of α-methylstyrene **147a'** with thiophene derivatives **131** and **145**.*

4.3.3 – Hydroarylation of 1,1-Disubstituted Alkenes with Furan Substrates

Thiophene substrates were unselective in the hydroarylation protocol and therefore alternative 5-membered heteroaromatics were investigated. Alongside Miss Ellie Lester, the Ir(I)-catalysed conditions were adapted to allow the successful alkylation of furan derivative **134a** with 1,1-disubstituted alkenes. Under the standard reaction conditions, desired product **159aa'** was produced in excellent yield, with no starting material remaining (90% yield, Table **25**, entry 1). However, it was found that decreasing the number of equivalents of α-methylstyrene gave comparable yields (entry 2–3), with 1.5 equivalents of **147a'** giving **159aa'** in 90% yield (entry 4). Lowering the temperature to 110 °C gave decreased conversion (entry 5) and at 100 °C the reaction did not proceed (entry 6). Combining the lower equivalents of alkene with a shorter reaction time of 24 hours generated desired product **159aa'**

in a yield of 94% (entry 7). The structure of **159aa'** was confirmed by single-crystal X-ray diffraction of crystals grown from a concentrated $CHCl_3$ solution.



Entry	*n*/mol%	T	t	Yield 159aa'
1	4	120 °C	48 h	90%
2	3	120 °C	48 h	95%[a]
3	2	120 °C	48 h	91%a
4	1.5	120 °C	48 h	90%[a]
5	1.5	110 °C	48 h	88%[a]
6	1.5	100 °C	48 h	no reaction
7	**1.5**	**120 °C**	**24 h**	**94%[a]**

Table 25: *Selected optimisation results for the hydroarylation reaction of α-methylstyrene **147a'** with furan **134a**.* *[a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

Having optimised the hydroarylation of α-methylstyrene **147a'** with furan **134a**, the scope of the reaction, with regards to the alkene coupling partner and directing group, was explored (Table **26**). Styrene derivatives bearing electron-donating (OMe) and electron-withdrawing (CF_3) substituents in the *meta* and *para*-positions proceeded efficiently, giving alkylated products **159ag'**, **159aq'**, **159ab'** and **159ae'** in excellent yields (81–94% yield). The methodology tolerates alkenes **147j'** and **147r'** with other carbon-based substituents (e.g. ethyl and *n*-propyl) in the α-position, which generated chiral quaternary stereocentres **159aj'** and **159ar'** (75% and 77% yield). Aliphatic alkenes were also successfully employed, with propyl derivative **147h'** and (*S*)-limonene **147s'** both affording desired products **149ah'** (77% yield) and **149as'** (64% yield) in good yields. Variation of the directing group found that diethyl furan derivative **134b** gave desired alkylated product **159ba'** in a 63% yield. The protocol also demonstrated limitations, with heteroatoms in the α-position of the alkene not tolerated, as exemplified by bromo derivative **147i'** and silane derivative **147t'**. Alkenes bearing larger groups in the α-position, including isopropyl (**147u'**), presumably proved too sterically demanding for efficient alkene coordination and resulted in no conversion to the desired quaternary product.

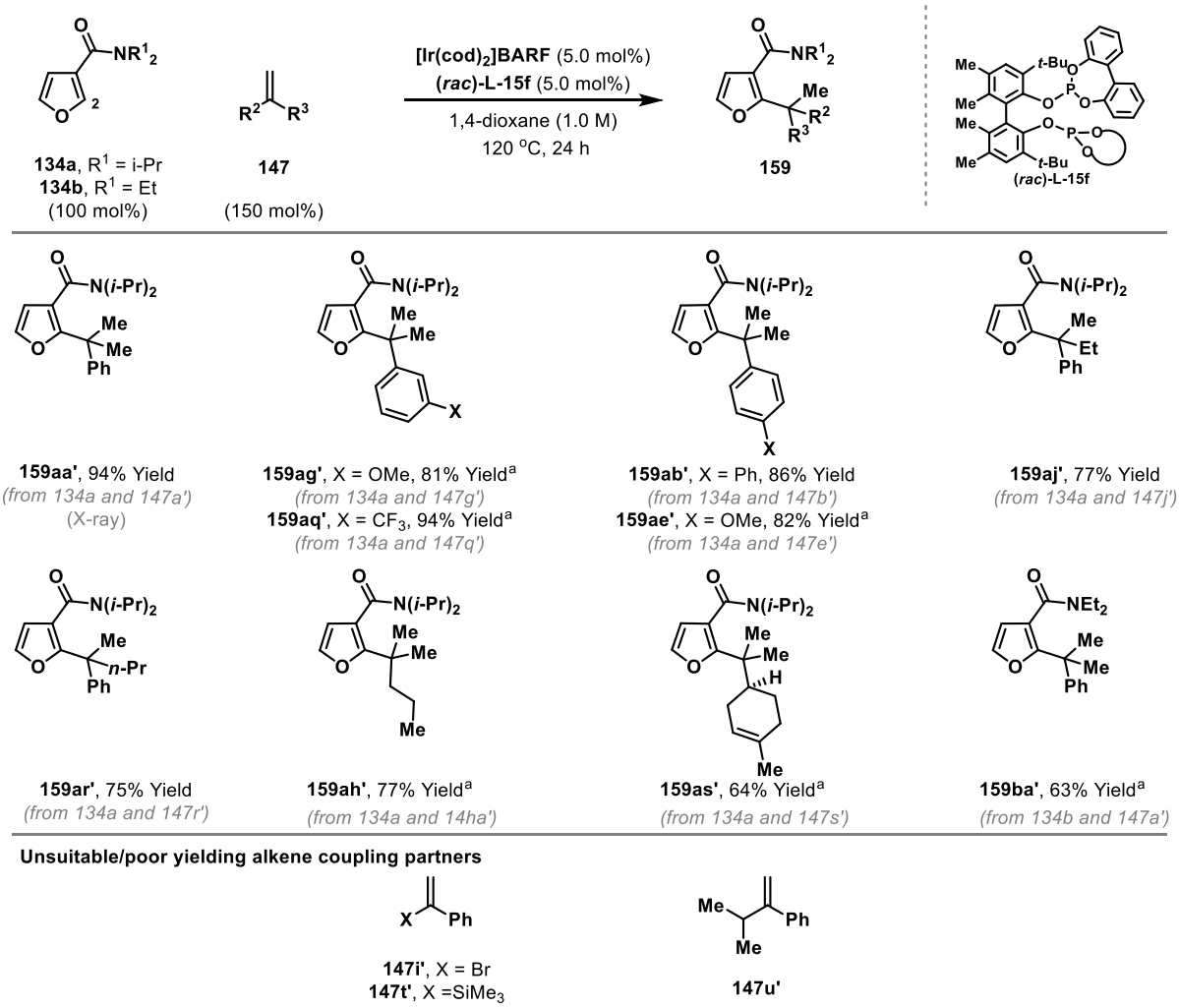
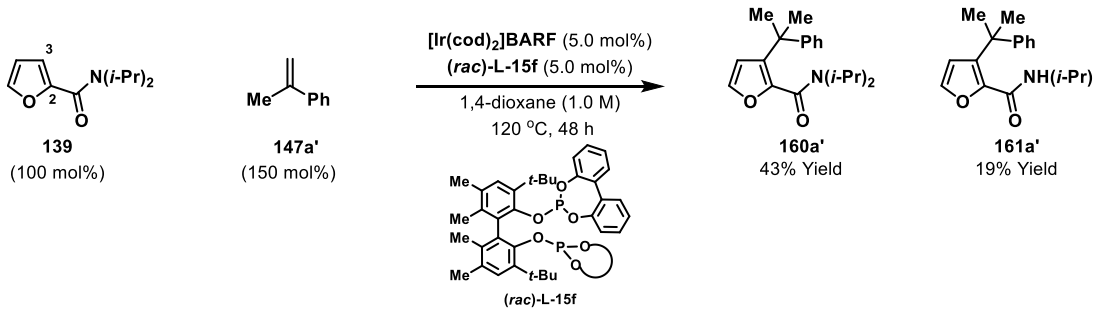


Table 26: *Scope of the hydroarylation reaction of 1,1-disubstituted alkenes with furans **134a** and **134b**.* [a] *Reaction was conducted by Miss Ellie Lester;* [b] *Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

The hydroarylation of α-methylstyrene **147a'** with furan **139**, which bears an amide directing group at the C2-position, gave desired product **160a'** in 43% yield, alongside dealkylated product **161a'** in 19% yield (Scheme **67**). This dealkylation event was previously observed for the Ir(I)-catalysed hydroarylation of styrene **91a'** with furan **139** (*see* Section **3.3.2**, Scheme **56b**). To suppress dealkylation of the directing group from occurring lower reaction temperatures and shorter reaction times were trialled. However, all of the changes made, resulted in no conversion to **160a'**.



Scheme 67: *Ir(I)-catalysed hydroarylation of α-methylstyrene **147a'** with furan **139**.*

4.3.3.1 – Development of an Enantioselective Protocol

All-carbon quaternary stereocentres are present in many biologically active compounds (Figure **5**) and hence, the development of a step-efficient and atom economical protocol for the enantioselective construction of these stereocentres would be of great importance to modern chemists. Towards an enantioselective protocol, enantiopure bisphosphite ligand **L-15f** was trialled under the optimised conditions and gave desired hydroarylation product **159aj'** with 60:40 *e.r.* (Table **27**, entry 1). Addition of a *t*-butyl substituent to the biphenyl moiety of the ligand at the C4-position resulted in decreased enantioselectivity (54.5:45.5 *e.r.*, entry 2, **(*S*)-L-15a**), whereas switching to ferrocene-based bisphosphonite ligand **(*R*)-L-16f** resulted in a dramatic increase in enantioselectivity to 90:10 *e.r.* (entry 3), whilst maintaining a good yield (73%). No improvements were achieved when changing the substituents at C4 on the SPINOL moiety of the ligand (entry 4–7).

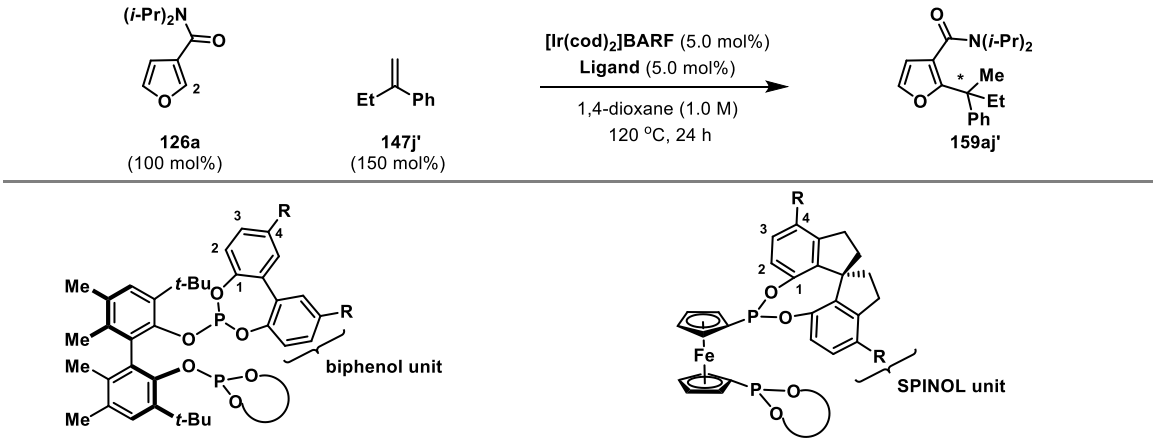
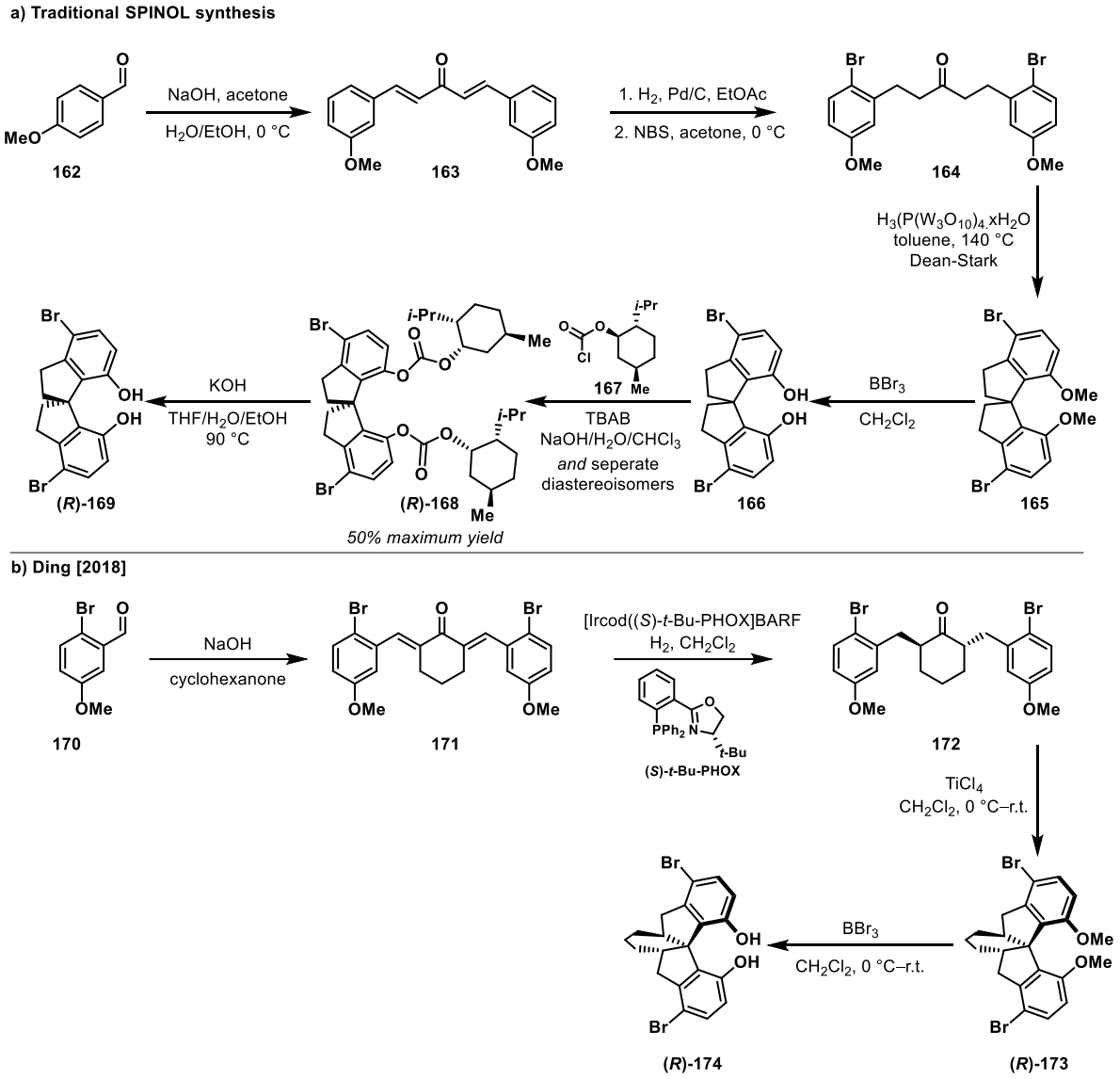


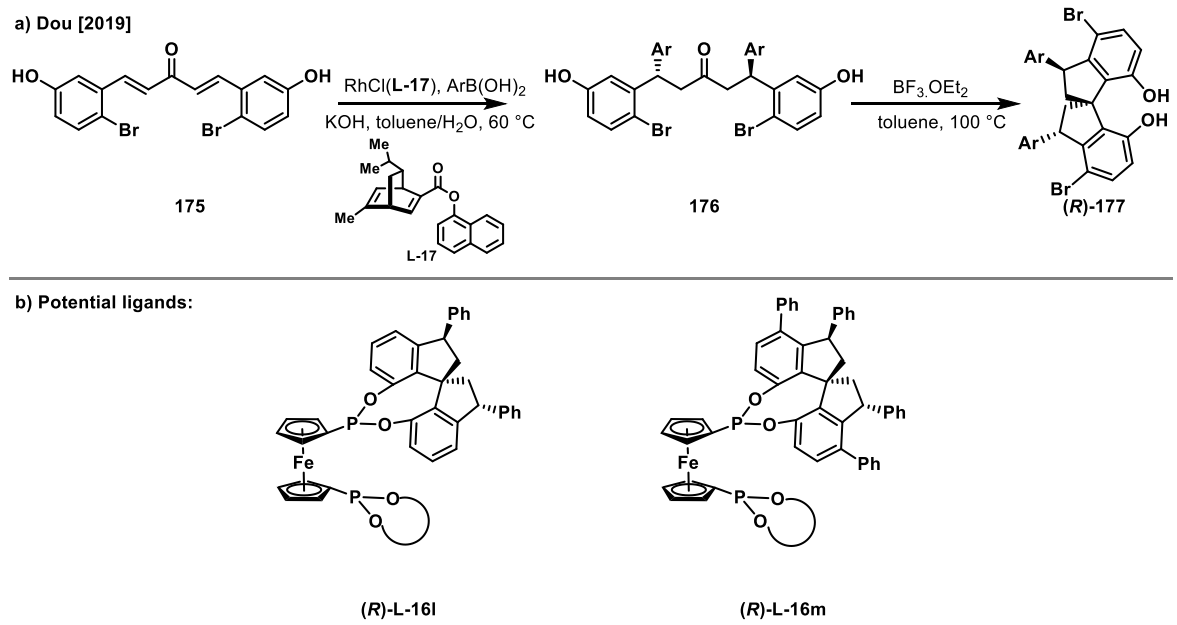
Table 27: *Development of an asymmetric protocol for the hydroarylation reaction of α-ethylstyrene **147j'** with furan **126a**. [a] Reaction was conducted by Miss Ellie Lester; Yields were determined by ^{1}H NMR analysis of crude material against an internal standard.*

SPINOL derived bisphosphonite ligands **L-16** are efficient for the asymmetric hydroheteroarylation of 1,1-disubstituted alkenes (Table **27**) and monosubstituted alkenes (*see* Chapter 3), but further improvements in enantioselectivity (87:13–95:5 *e.r.*) are desirable. Therefore, optimisation of the SPINOL unit of the ligand began, with a particular focus on the addition of substituents onto the cyclopentyl units. Despite being privileged frameworks for the synthesis of chiral ligands, the current approach used to synthesise SPINOL moieties consists of 7 steps, beginning with the condensation of **162** with acetone to generate aldol product **163**. Following hydrogenation, selective bromination generates **164**, which cyclises upon exposure to phosphotungstic acid to form SPINOL **165**. After removal of the methoxy units, optical resolution of racemic SPINOL **166** with (*R*)-menthyl chloroformate **167**, generates enantiopure menthyl SPINOL derivative **168**. Finally, removal of the menthyl units generates bromo-SPINOL **169**, which can undergo Suzuki cross-coupling reactions with boronic acids to form various SPINOL derivatives. This method uses stochiometric quantities of a resolving agent, which makes the synthesis of libraries expensive and time-consuming (Scheme **68a**).[133] Recently, interest has been placed on streamlining the synthesis of SPINOL moieties, resulting in fewer steps and a greater variation in the points of modification.[165-168] In 2018, Ding and co-workers reported an alternative approach to synthesising cyclohexyl-fused SPINOL moieties in 4 steps, which demonstrated similar levels of reactivity and enantioselectivity to well-established SPINOL-based chiral ligands (Scheme **68b**).[167] To achieve this they developed an iridium catalysed asymmetric hydrogenation of α,α′-bis(arylidene)-cyclohexanone **171**, followed by $TiCl_4$ catalysed spiroannulation of chiral ketone **172**. This method can therefore be viewed as a more rapid synthetic approach to SPINOL units. Efforts to replicate Ding and co-workers synthesis of cyclohexyl-SPINOL variant **174**, commenced with condensation of **170** with cyclohexanone. **171** was then subjected to the reported hydrogenation conditions (H_2 (50 atm), [Ir] (5 mol%)); however, no conversion to **172** was observed. In order to promote the hydrogenation, higher hydrogen pressures and rigorous anhydrous and inert conditions were trialled; however, **172** was not formed. This is possibly due to differences in the hydrogenation equipment employed.



Scheme 68: *Reported procedures for the synthesis of SPINOL moieties.*

In 2019, Dou and co-workers developed a three step asymmetric synthesis of 3,3'-diarylated SPINOL units (Scheme **69a**).[168] They utilised a chiral rhodium catalyst for the asymmetric 1,4-conjugate addition of aryl boronic acids onto aldol product **175**, which was followed by a BF_3-promoted spirocyclisation of **176** to afford 3,3'-diarylated SPINOLs **177**. In several cases, when converted to chiral ligands, the SPINOL variants demonstrated higher enantioselectivities than the traditional SPINOL moieties. Future work will involve investigating these substituted SPINOL units on ferrocene moieties as chiral ligands (as shown in ligands **L-16l** and **L-16m**) (Scheme **69b**) for the enantioselective hydroheteroarylation of mono- and disubstituted alkenes.



Scheme 69: *Dou's reported methodology for the synthesis of SPINOL moieties* ***177*** *and potential ligands* ***(R)-L-16l*** *and* ***(R)-L-16m****.*

4.4 – Studies into the Mechanism

At this stage, a hydroarylation protocol for 1,1-disubstituted alkenes had been successfully developed to afford a range of structures encompassing all-carbon quaternary centres with promising levels of enantiopurity. Natural abundance ^{13}C kinetic isotope and deuterium labelling experiments were employed to gain greater insight into the mechanistic cycle.

4.4.1 – Determination of ^{13}C KIEs at Natural Abundance (Singleton Method)

The kinetic isotope effect (KIE) can be utilised for the elucidation of reaction mechanisms. It exploits the singularity that heavier isotopes react at a different rate compared to their lighter isotope counterparts. A KIE arises from a difference in vibrational energies between the isotopes at the ground state energy of a system, which is known as zero-point energy (ZPE). The different mass of the two isotopes is the main contributing factor to the change in vibrational energies and this is demonstrated by applying Hook's law (Equation 1) to a covalent bond. According to Hook's law, vibrational energy (E_n) is dependent on the frequency of the bond undergoing the reaction (ν) (Equation 2), which is inversely proportional to the square root of the reduced mass (μ) (Equation 3) of the two atoms either side of the bond (Equations 1–3).[169-173]

$$(1)\quad E_n = \left(n + \frac{1}{2}\right)h\nu \qquad (2)\quad \nu = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}} \qquad (3)\quad \mu = \frac{m_1 m_2}{m_1 + m_2}$$

n = principle quantum number, h = Planck's constant, c = speed of light,

k = force constant, m = mass

The isotope effect is most commonly studied for hydrogen and deuterium, because of the relatively large difference in mass between them, which gives large, easily measured KIE values. The frequency of vibration (υ) is inversely proportional to the reduced mass (μ) and hence the increase in mass results in a C–D bond vibrating slower than a C–H bond (Equation 2). This results in a lower zero-point energy for C–D bonds, which means that they have a higher activation energy. Consequently, a C–D bond is more stable and reacts at a slower rate than a C–H bond (Figure **6**). The KIE measured is always proportional to the difference in the Gibbs free energy (ΔZPE).[169-173]

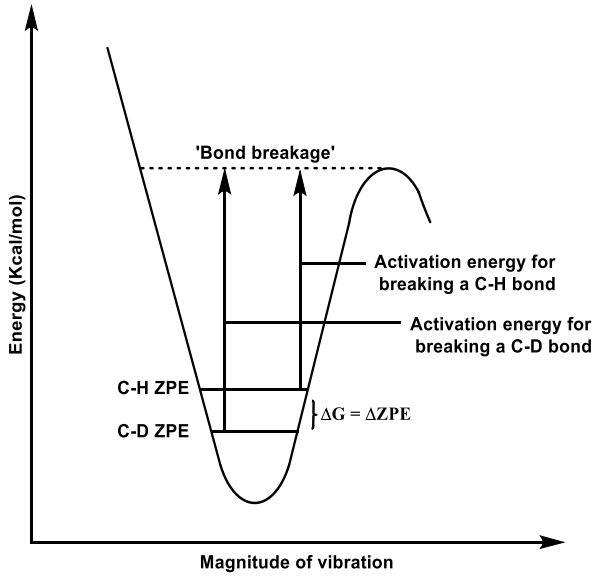


Figure 6: *Morse curve for the isotope effect between C–H and C–D bonds.*

The difference in the rate of reaction and hence the rate constants (k) for the isotopes allows the KIE to be measured through the following equation, where k_L is the rate constant for the lighter isotope and k_H the rate constant for the heavier isotope (Equation 4).

$$(4) \quad KIE = \frac{k_L}{k_H}$$

The Morse potential curve outlined in Figure 6 is only applicable for reactions that proceed by a simple mechanism, whereby the bond being monitored is fully broken at the transition state, i.e. homolytic cleavage. For more complex mechanistic pathways where the bond is partially broken at the transition state, the KIE depends on other factors, including the ΔZPE at the transition state; however, this topic will not be discussed further in this thesis.[169-173]

A KIE can be classified as either primary, or secondary. A primary KIE occurs when the labelled bond is broken, or formed during the first irreversible step, which is also the rate-determining step of the mechanistic cycle. Conversely, a secondary KIE is one in which no labelled bonds are broken or formed during the rate-determining step and it is always smaller than a primary KIE. Substantial

secondary KIEs are measured when there is a change in the type of bonding, hybridisation or steric environment at the isotopically labelled atom. However, whether these effects arise from bonding or non-bonding interactions such as solvation are not always clear. Standard KIEs are measured when k_L/k_H is greater than one. Additionally, inverse KIEs are observed when k_L/k_H is less than one.[169-173]

Heavier isotopes, including $^{12}C/^{13}C$, $^{14}N/^{15}N$, $^{16}O/^{18}O$ and $^{35}Cl/^{37}Cl$ have also been used to gain further insight into reaction mechanisms. However, the KIE of these heavier isotopes is much less pronounced than that for $^{1}H/^{2}D$ owing to the much smaller variation in mass, and hence the measurements are harder to conduct accurately.[174-176] For example, there is only an 8% change in mass when going from carbon-12 to carbon-13. This results in a minor change in the reduced mass; only small primary KIEs are measured and secondary KIEs are nearly completely negligible. Experimental measurements for these isotopes can be carried out using competition experiments between labelled and non-labelled species. Both species will react in the same manner, but at different rates, resulting in diminishment of the faster reacting species (the species containing the lighter isotope). The disadvantages of using labelled species is that the results often lack accuracy owing to the smaller KIEs measured and it is only applicable for a restricted number of systems. Additionally, labelled species are often difficult to synthesise, and are cost prohibitive owing to a labelled species being required for each KIE of interest.

An alternative method for measuring KIEs is to employ molecules containing isotopically labelled atoms in their natural abundance.[177] When any reaction proceeds, the unreacted starting material becomes enriched in the heavier, slower reacting isotope at the site of reactivity, shown by a significant KIE measurement. The variation in isotope arrangement is expressed by R/R_0 where R and R_0 are the amount of the minor isotope measured in the recovered and original starting material respectively. This ratio depends on how far to completion the reaction goes (F) and the measured KIE (Equation 5). As the reaction commences towards completion ($F \rightarrow 1$), R/R_0 approaches infinity, ensuring that the KIEs become sizeable and easily measured. The accuracy of the measured KIE depends upon the size of the KIE, the precision of analysis ($\Delta R/R_0$) and the uncertainty in percentage conversion (ΔF) (Equations 5–6).

$$(5)\quad R/R_0 = (1-F)^{\frac{1}{KIE}-1} \qquad (6)\quad KIE_{calcd} = \frac{\ln(1-F)}{\ln(1-F)R/R_0}$$

One method to measure natural abundance KIEs is to use isotope ratio mass spectrometry, which offers more precise results than competition experiments, particularly for ^{13}C KIEs.[178] However, the application requires the site of interest to degrade to a small molecule e.g. CO_2, which can be analysable by mass spectrometry, without fractionation of the isotopes. Another analytical tool for measuring KIEs is the use of ^{2}H NMR, although for heavier atoms, i.e. ^{13}C, NMR quantitation is often not precise enough.

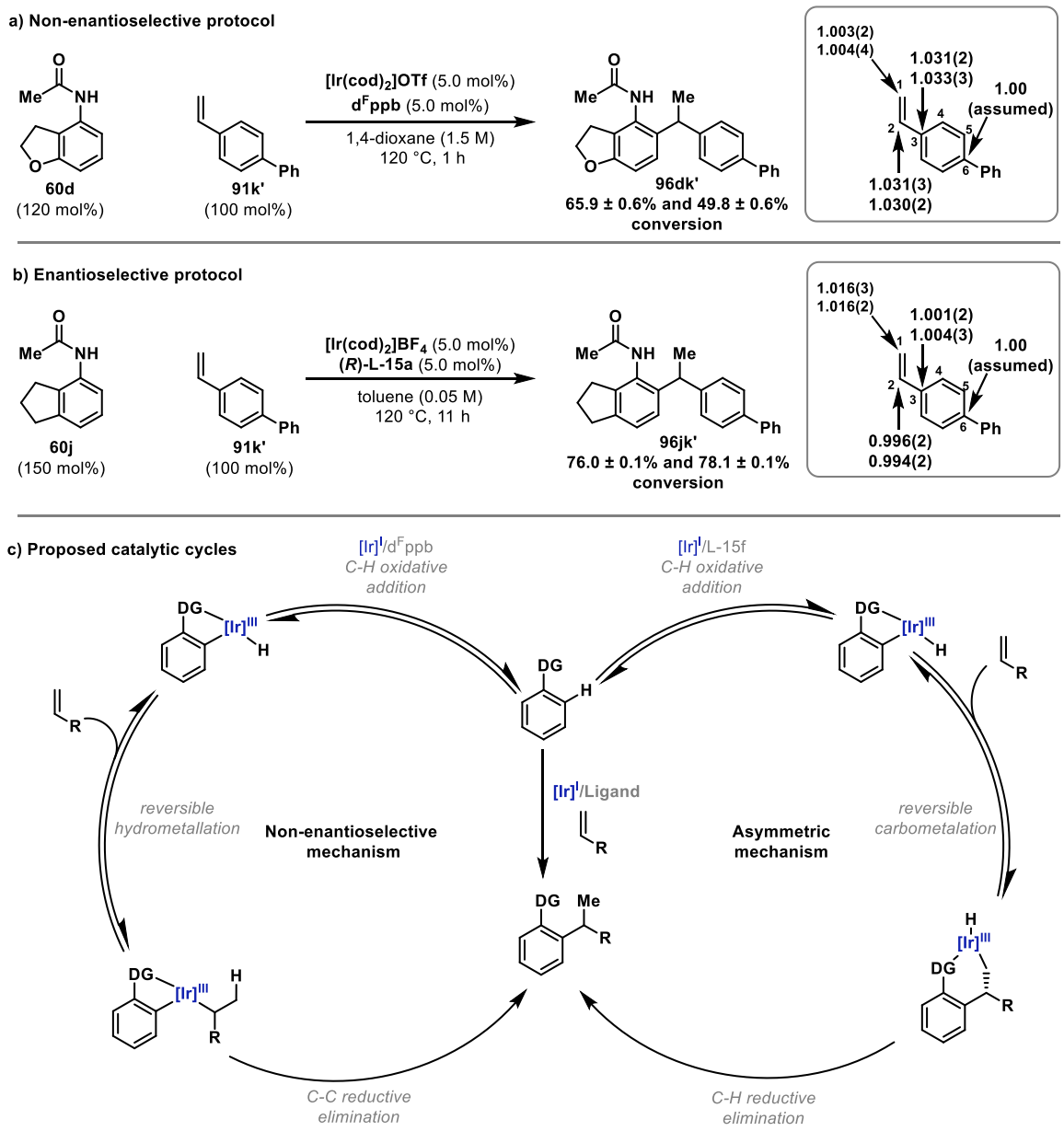
In 1995, Singleton and Thomas pioneered a general method for the determination of KIEs at natural abundance with high precision using ^{2}H and ^{13}C NMR analysis.[177] The reaction of interest was stopped at high conversion (>70% yield) and the unreacted starting material was isolated before analysis by ^{13}C NMR. The carbon signals of interest were integrated against an internal standard (a carbon atom in the molecule that can be assumed not to take part in the reaction mechanism i.e. KIE = 1) or if this is not possible, an external standard can be added. The integrations of the carbon signals allowed the determination of R/R_0 and subsequently the KIEs relative to the standard.

Despite the wide applicability of the Singleton method, some criteria need to be met for it to be successful: 1) the reaction must be scalable and clean to allow sufficient recovery of starting material for ^{13}C analysis in high purity and yield; 2) the reactant of interest must be the limiting reagent; 3) the reaction monitored must have an irreversible step; 4) the reaction mechanism must not alter during its progress. Following the initial report, the Singleton method has found application in determining a wide range of mechanistic pathways. In particular, the Singleton method has been instrumental in gaining a greater understanding of the Ir(I)-catalysed hydroarylation reactions carried out at Bristol.[179-180]

4.4.2 – Possible Mechanistic Pathways for the Hydroarylation of 1,1-Disubstituted Alkenes

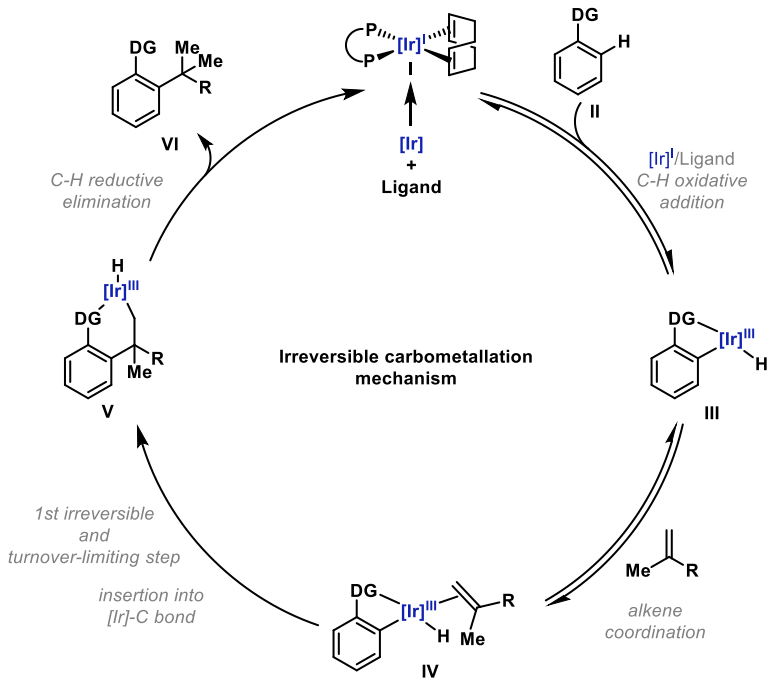
As described in previous chapters, the mechanistic pathway for the Ir(I)-catalysed hydroarylation of monosubstituted alkenes appears to be independent of the arene coupling partner, and in fact hinges upon the ligand. Using deuterium labelling experiments and ^{13}C natural abundance experiments, the non-enantioselective protocol previously developed at Bristol for the hydroarylation of monosubstituted alkenes was suggested to advance by reversible hydrometallation. This was followed by the first irreversible and rate-determining step: C–C reductive elimination (Scheme **70a**).[180] Significant KIEs were measured at C2 and C3 (1.031 and 1.032) for recovered styrene **91k'** in the non-enantioselective hydroarylation of styrene **91k'** with acetanilide **60d**. The significant KIE at C2 is consistent with C–C reductive elimination being the first irreversible step (Scheme **70c**) and is complementary of the results found by Singleton for Hartwig's methodology for the Pd-catalysed hydroamination of vinylarenes.[118, 181-183] The KIE at C3 was surprising and was attributed to the arene portion of the alkene potentially coordinating to the iridium at the stage of reductive elimination.

A carbometallation pathway is less commonly anticipated for hydroarylation processes, owing to the higher activation energy associated with olefin migratory insertion into metal–carbon over metal–hydrogen bonds.[184] Nevertheless, a carbometallation pathway was proposed by Dr. Grèlaud in the mechanistic studies for asymmetric hydroarylation of monosubstituted styrene **91k'** with acetanilide **60j** (Scheme **70c**). Surprisingly, a significant KIE was measured at C1 of recovered alkene **91k'** only (Scheme **70b**).[179] The measured KIEs led to the determination that carbometallation was reversible and that C–H reductive elimination was in fact the first irreversible step (Scheme **70c**).



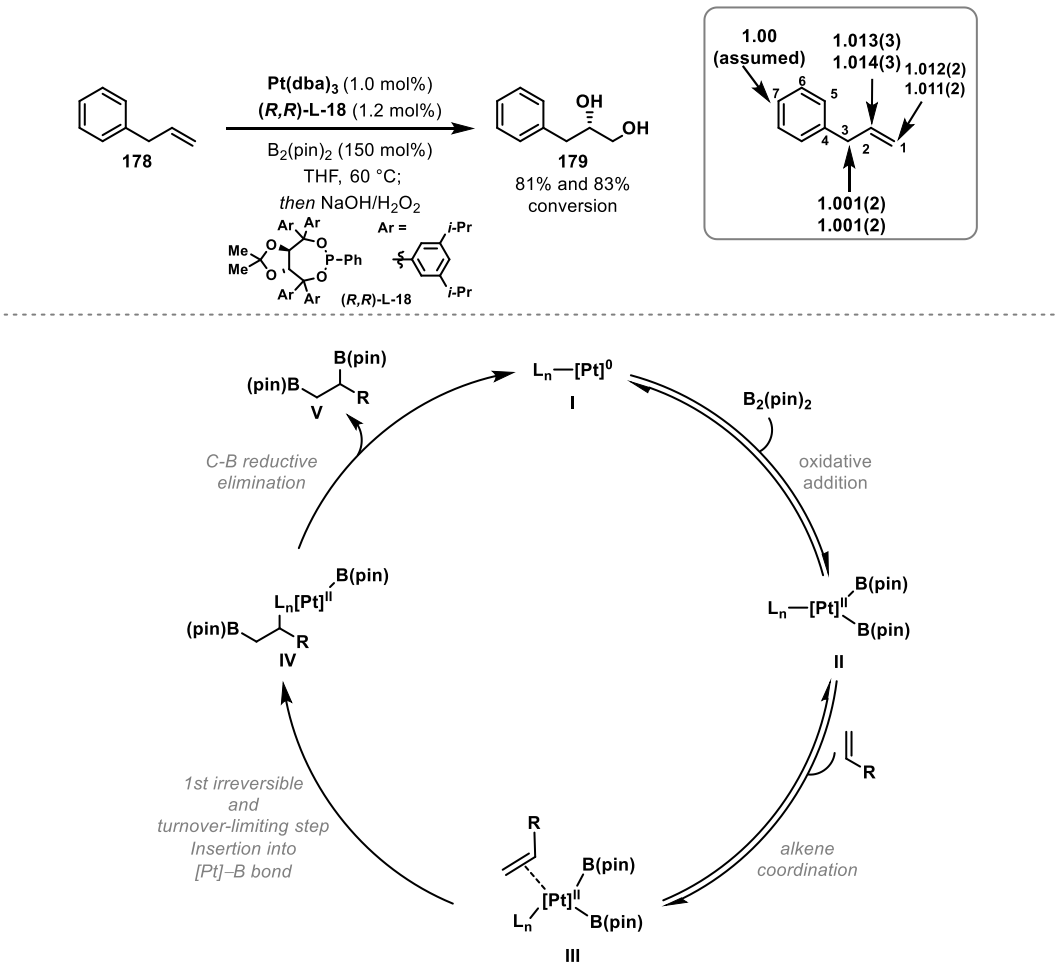
Scheme 70: *Proposed catalytic cycles for the hydroarylation of monosubstituted alkenes previously developed at Bristol; Standard deviations for the last digit are shown in parentheses.*

For the hydroarylation of 1,1-disubstituted alkenes, it was postulated that the reaction could proceed by either of the mechanisms discussed above (Scheme **70c**). Additionally, a third mechanistic pathway could be operative in which, following oxidative addition (**I** to **III**), the alkene inserts into the Ir(III)–C bond irreversibly to generate iridacycle **V**, which then undergoes C–H reductive elimination to afford hydroarylation product **VI** (Scheme **71**).[184-186]



Scheme 71: *Alternative carbometallation pathway possible for the hydroarylation of 1,1-disubstituted alkenes.*

Irreversible carbometallation has previously been proposed for alkene hydroarylation reactions, including those developed by Hartwig[106] and Romana.[103] In 2013, Morken and co-workers employed the Singleton method to investigate the mechanistic pathway of their Pt(0)-catalysed enantioselective diboration of monosubstituted alkenes (Scheme **72**).[187] They subjected allylbenzene to a Pt(0)-catalyst, $B_2(pin)_2$ and a chiral ligand to afford diboronated species **V**, which was then converted to diol **179** under oxidative conditions in good yield (78% yield) and enantiopurity (92% *e.e.*). To investigate the mechanistic pathway, the signals of interest in the ^{13}C spectra of recovered allylbenzene were integrated against internal standard C7. Significant KIEs were measured at both olefinic carbons of recovered alkene **178**, C1 and C2 (1.012 and 1.013), with negligible KIEs at all other positions. These KIE values suggest that both C1 and C2 are involved in the first irreversible step, and hence alkene insertion into the Pt–C bond is the rate determining and first irreversible step. The stereochemistry of the reaction is controlled in this step when the Pt-boron complex **II** adds across π-system of alkene **178**. This allowed Morken to propose the catalytic cycle in Scheme 72. Here, Pt(0)-catalyst **I** oxidatively adds into the diboron bond of $B_2(pin)_2$ and this is followed by alkene coordination and irreversible insertion into the Pt–B bond to give **IV**. C–B reductive elimination then gives **V**.



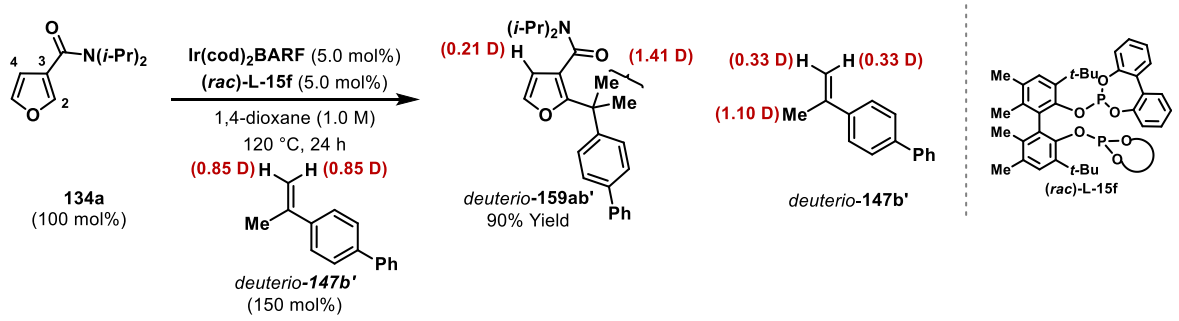
Scheme 72: *Morken and co-workers measured KIEs and suggested catalytic cycle for the diboration of alkenes. Standard deviations for the last digit are shown in parentheses.*

The work described by Singleton[181], Morken[187] and that previously carried out at Bristol[117, 179] provide an overview of the different mechanistic pathways that can occur for alkene difunctionalisation reactions and, therefore the mechanisms possible for the hydroarylation of 1,1-disubstituted alkenes. To decipher between possible reductive elimination and carbometallation pathways, deuterium exchange experiments were carried out, and natural abundance ^{13}C kinetic isotope effects (KIEs) were determined for the alkene coupling partner.

4.4.3 – Deuterium Labelling Experiments

The mechanism for the hydroarylation of 1,1-disubstituted alkenes was first probed through the use of a deuterium labelled alkene. β,β-Bisdeuterated alkene *deuterio*-**147b'** was prepared *via* Wittig olefination with a deuterated Wittig reagent. *Deuterio*-**147b'** was subjected to standard catalytic conditions with furan **134a** (Scheme **73**). ^{1}H and ^{2}H NMR analysis of *deuterio*-**159ab'** identified deuterium incorporation in both methyl groups (1.41 D, 71% deuterium) and minor deuterium incorporation at the C4-position of the furan (0.21 D, 21% deuterium), indicating that the carbonyl-group also directs into this position, albeit not preferentially over C2. Recovered alkene *deuterio*-**147b'**

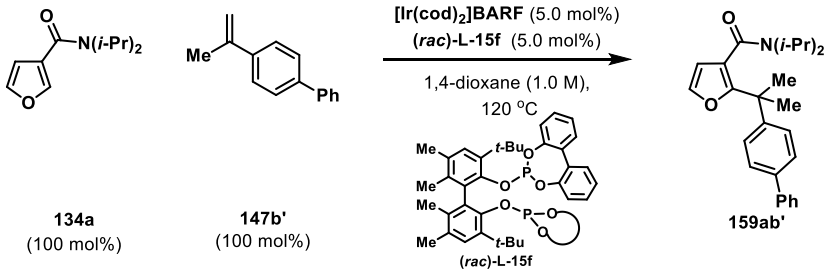
also demonstrated a scrambling of deuterium labels, with deuterium being observed in the methyl unit (1.1 D, 37% deuterium). Scrambling of the deuterium labels in product *deuterio*-**159ab'** and recovered *deuterio*-**147b'** indicates that both C–H oxidative addition and alkene hydrometallation are reversible.



Scheme 73: *A deuterium labelling study for the hydroarylation of deuterio-**147b'** with furan **134a**.*

4.4.4 – Determination of ^{13}C-KIEs for the Ir(I)-Catalysed Hydroarylation of 1,1-Disubstituted Alkenes with Furans

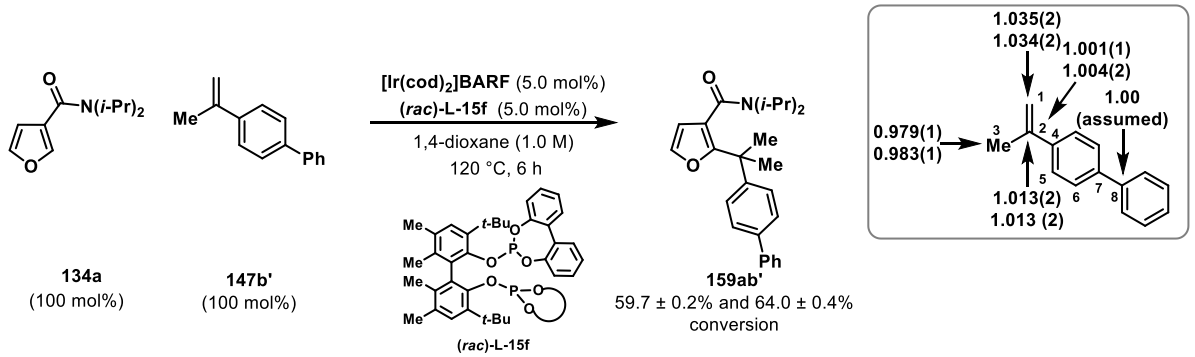
To fulfil the requirements of the Singleton method discussed in Section 4.4.1, furan derivative **134a** was chosen due to the efficiency in which the alkylation reaction proceeds. Alkene **147b'** was selected due to it being stable to column chromatography and non-volatile, making its recovery relatively facile. Another key requirement of the Singleton method is the substrate being examined must be the limiting reagent, hence, the reaction was repeated with one equivalent of alkene **147b'** and the reaction time was probed to identify when the reaction reached ~70% conversion (Table **28**). Fortunately, only small amounts of polymerised alkene **147b'** were observed (<2%), with almost complete recovery of alkene **147b'** achieved. The conversion was 60% after 4 hours (entry 1) and had reached 70% after 6 hours (entry 3), providing optimal conditions with which to proceed.



Entry	t	Yield[a] 159ab'	unreacted[a] 147b'
1	4 h	60%	40%
2	5 h	68%	32%
3	**6 h**	**70%**	**29%**

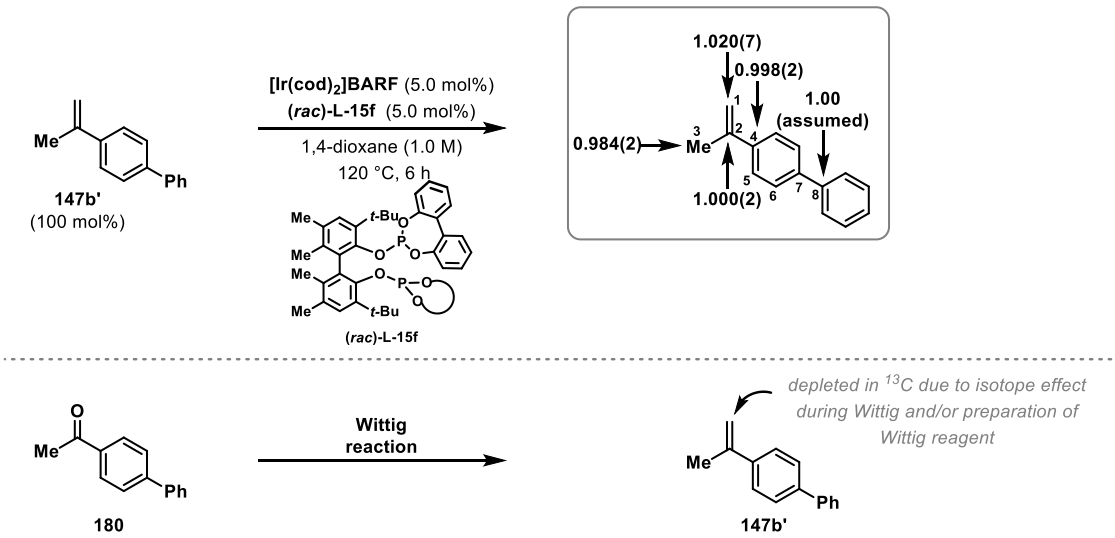
Table 28: *Selected optimisation results for the hydroarylation reaction of alkene **147b'** with furan **134a** for KIE measurements. [a] Conversion determined by ^{1}H NMR analysis of crude material against an internal standard.*

With optimal conditions in hand (Table **28**, entry 3), the reaction was successfully scaled from 0.1 mmol to 2.0 mmol and was carried out in repetition for validation. Each experiment was stopped after 6 hours, and unreacted alkene **147b'** was recovered by FCC. Recovered alkene **147b'** was analysed by quantitative ^{13}C NMR (*see* Section **7.6.5**) and olefinic carbons C1 and C2, methyl carbon C3 and *ipso*-carbon C4 (measured with C7 for which the KIE is assumed to be 1.000, due to overlapping signals) were integrated. The KIE for C8 was assumed to be 1.000 and hence was selected as the internal standard which the other carbons were integrated against. (Scheme **74**). A significant kinetic isotope effect was observed at C2 (1.013). Interestingly, an isotope effect was observed at C1 (1.035) and an inverse isotope effect was observed at C3 (0.981), with negligible KIE observed at C4/7 (~1.003).



Scheme 74: *^{13}C natural abundance KIEs measured for the hydroarylation of alkene **147b'** with furan **134a**; Standard deviations for the last digit are shown in parentheses.*

The isotope effect observed at C1 and C3 is attributed to isomerisation of the starting alkene. This was corroborated by subjecting alkene **147b'** to the standard Ir(I)-catalysed conditions in the absence of furan **134a** (Scheme **75**). Alkene **147b'** was recovered and analysed by quantitative ^{13}C NMR. Once again, a positive isotope effect was observed at C1, with a corresponding inverse isotope effect at C3, the average of which was 1.000 (Scheme **75**). Large ^{13}C-equilibrium isotope effects have been observed, but only at low temperature.[188] Therefore, it is envisaged that isotopic depletion at C1 occurs during the synthesis of alkene **147b'** from ketone **180**. Ir(I)-catalysed alkene isomerisation then reverts the uneven ^{13}C distribution between C1 and C3 back to a roughly even distribution due to the similar energy of ^{13}C at C1 and C3. The isotope effects are determined by integration of recovered alkene *vs* starting alkene and, therefore this appears as a positive isotope effect at C1 and a negative isotope effect at C3. Ir(I)-catalysed alkene isomerisation has previously been reported.[189-191] Further experiments carried out at Bristol have provided evidence to this effect. Alkene **147b'** was prepared by a process in which carbons C1 and C3 both originate from the same starting material (i.e. Grignard addition to an ester, followed by dehydrogenation). The relative ratio of ^{13}C at C1:C3 was different compared to the alkene obtained by the Wittig preparation method. This result supports that ^{13}C distribution at C1 and C3 is altered during the synthesis of alkene **147b'** from ketone **180**.

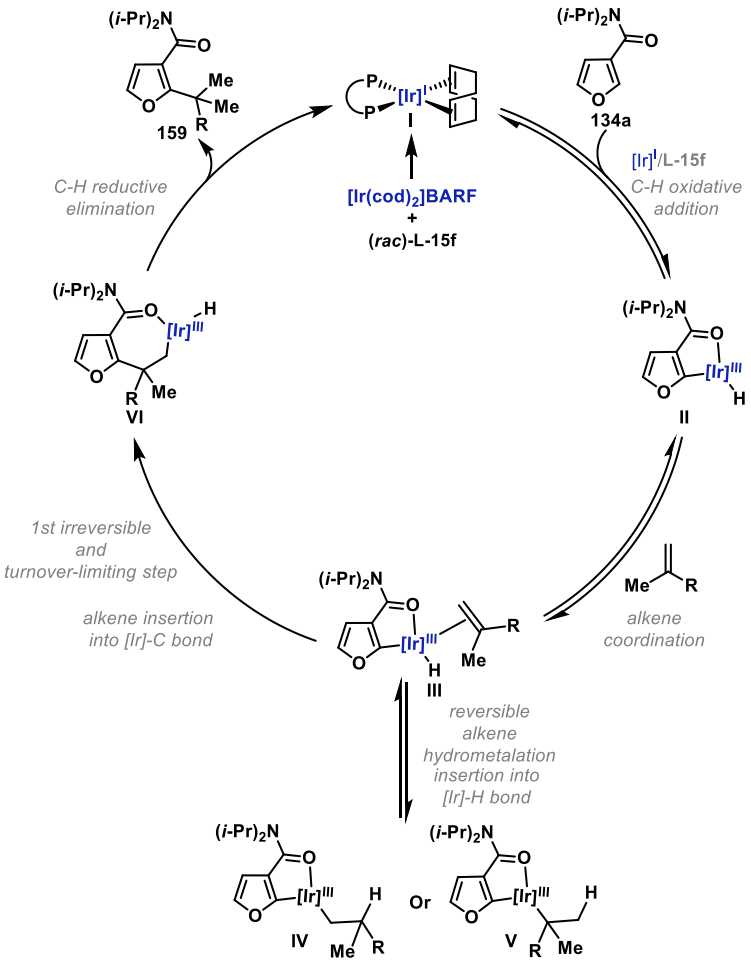


Scheme 75: *^{13}C natural abundance IEs measured for alkene **147b'** under the standard Ir(I)-catalysed conditions; Standard deviations for the last digit are shown in parentheses.*

Considering the isotope effects measured at C1 and C3 due to alkene synthesis, a significant KIE is measured at C1 and C2 (~0.016 and 0.013 respectively), indicating that both C1 and C2 are involved in the first irreversible step of the mechanistic cycle. The KIE values are consistent with carbometallation being the first irreversible step and mirror values obtained by Morken for alkene diboration (Scheme **72**).[187, 192] The proposed mechanism differs from that suggested for hydroarylation of monosubstituted alkenes with d^{F}ppb and ligand **(*S*)-L-15a** (Scheme **70**).

4.4.5 – Proposed Catalytic Cycle

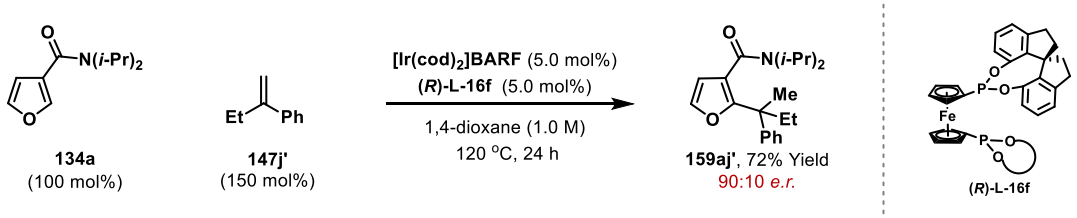
The mechanistic investigations above have led to the catalytic cycle proposed in Scheme 76. The process commences with the *in-situ* formation of active Ir(I)-catalyst **I**. Oxidative addition of **I** into the C–H bond at C2 of furan **134a** is directed by the carbonyl group to give Ir(III)-intermediate **II**. Alkene coordination to Ir(III)-intermediate **II** generates Ir(III)-intermediate **III**, from which reversible hydrometallation to branched and linear intermediates **V** and **IV** occurs. Hydroarylation of *deuterio*-**147b'** alkene with furan **134a** resulted in scrambling of the deuterium signals, which is consistent with a reversible hydrometallation step (*see* Scheme **74**). Next, the catalytic cycle could proceed through C–C reductive elimination from **V**. However, results from natural abundance ^{13}C KIE experiments disclosed that both C1 and C2 are involved in the first irreversible step, therefore, identifying carbometallation from Ir(III)-complex **III** as the productive pathway (Scheme **76**). A C–C reductive elimination pathway from **V** would have a significant KIE at the olefinic C2-position only.[180] It is probable that styrene more readily inserts into the Ir(III)–H bond over the Ir(III)–C bond (**V** *vs* **VI**); however, the reaction proceeds through a carbometallation pathway. This is most likely due to C–C reductive elimination from **V** requiring a higher activation energy than the insertion of alkene **147b'** into the Ir(III)–C bond to give **VI**.[186]



Scheme 76: *Proposed catalytic cycle for the hydroarylation of 1,1-disubstituted alkenes with furan* ***134a***.

4.5 – Summary and Conclusions

Through development of a second generation bisphosphite ligand, Ir(I)-catalysed hydroarylation of 1,1-disubstituted alkenes has been achieved, providing facile access to challenging all-carbon quaternary centres. The methodology has already proved extremely versatile with the Ir(I)-catalyst system being applicable for benzenoid, pyrrole and furan substrates. The desired products are produced in good to excellent yields (up to 94% yield) and overall the alkene scope is broad, considering the steric demands of the centre being formed. Both alkyl and aryl alkenes are applicable, but one limitation is that heteroatoms are not tolerated in the α-position. Significantly, an asymmetric protocol has been demonstrated using ferrocene-based bisphosphonite ligand **(*R*)-L-16f**. For example, furan **159aj'**, bearing a benzylic quaternary centre, was generated in good yield and enantiopurity (90:10 *e.r.*) (Scheme **77**). Further fine-tuning of the ligand may provide a versatile catalyst for enantioselective hydroarylations of 1,1-disubstituted alkenes.



Scheme 77: *Formation of quaternary stereocentre **159aj'** in good yield and enantiopurity.*

The mechanism was probed through deuterium labelling experiments and ^{13}C-KIE experiments based on the Singleton method. The results of these provide clear evidence for a catalytic cycle with a rate-determining step that is unique compared to Ir(I)-catalysed methodologies previously developed at Bristol.[116-117, 179] The significant KIEs measured at both olefinic carbon centres C1 and C2 provided evidence that carbometallation is the first irreversible step in the catalytic cycle. ^{13}C-KIE experiments also highlighted an interesting variation in the ^{13}C labels for alkene synthesis/isomerisation, showing an isotope effect at terminal olefin position C1 and at methyl unit C3.

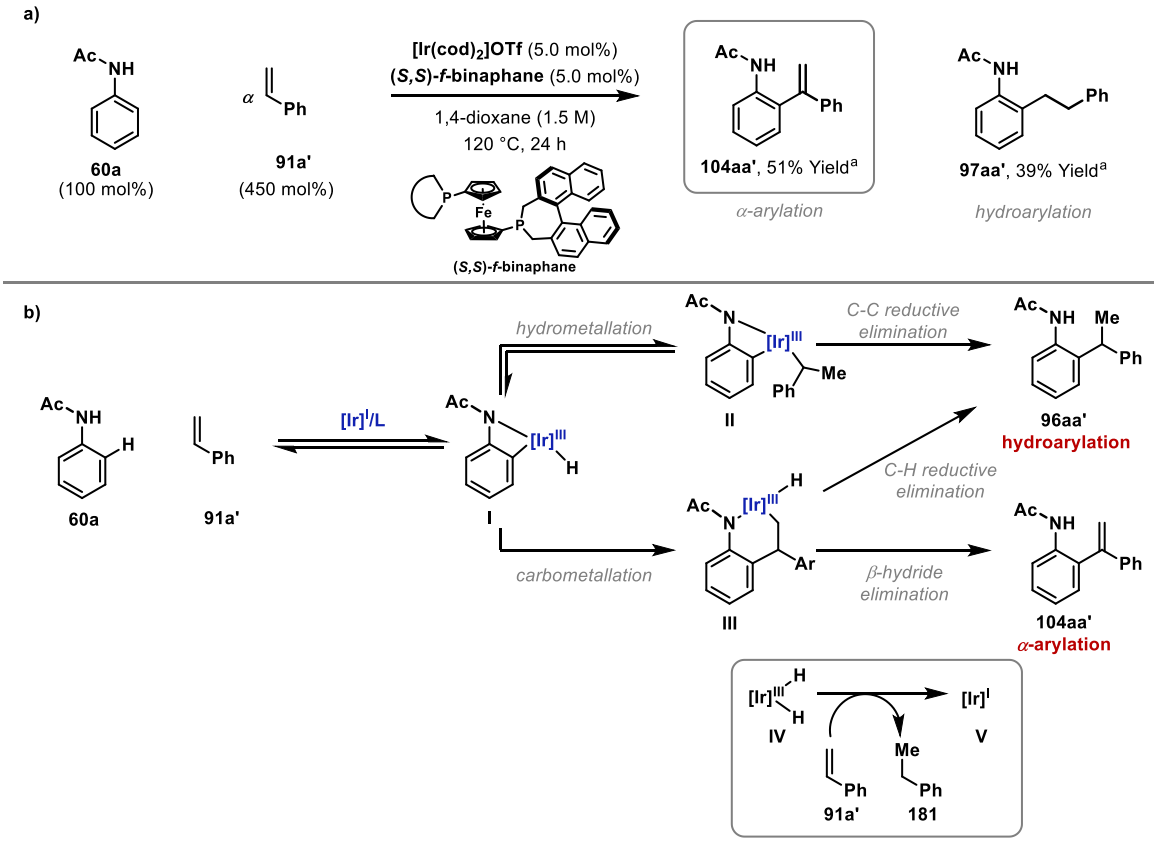
Chapter 5 – Iridium-Catalysed α-Selective Arylation of Styrenes by Dual C–H Functionalisation

Parts of this chapter have been adapted from a publication by Cooper et al.

(*Angew. Chem. Int. Ed*. **2018**, *57*, 14198)

5.1 – Reaction Discovery and Proposed Mechanism for the α-Arylation of Styrenes

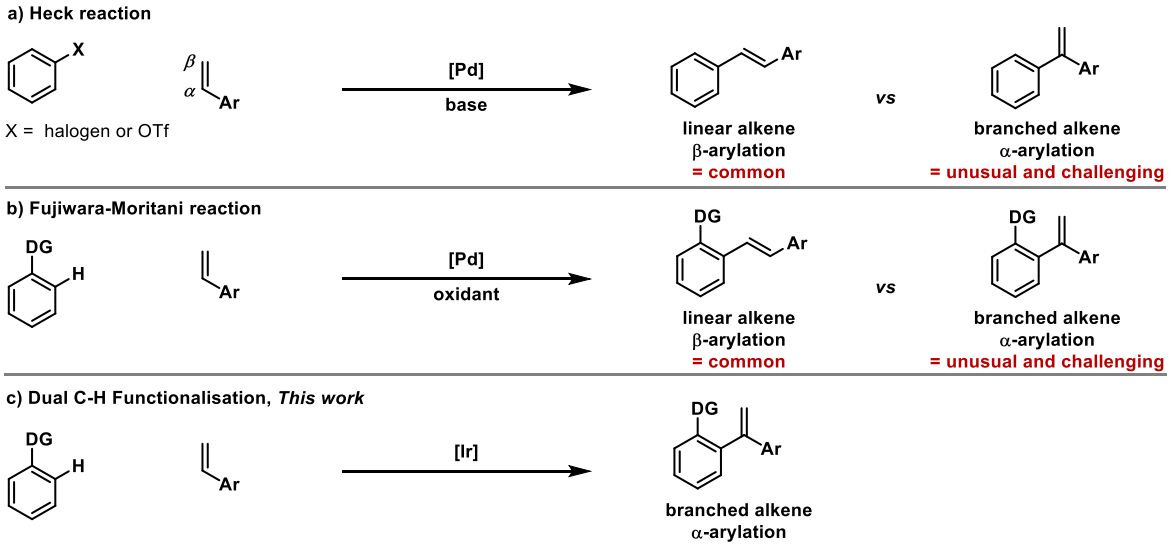
During the studies in Section 2.2.1, which involved the screening of commercially available chiral ligands for asymmetric styrene hydroarylation, α-arylated styrenes were observed in minor amounts (*see* Table **3**). For example, when attempting to perform an enantioselective styrene hydroarylation with acetanilide **60a** under Ir(I)-catalysis with ferrocene-based bisphosphine ligand (*S*,*S*)-*f*-binaphane, α-arylated styrene **104aa'** was generated in 51% yield, alongside 39% yield of linear hydroarylation product **97aa'** (Scheme **78a**). α-Arylated styrene **104aa'** was presumed to result from an oxidative Heck-type reaction, a proposed mechanism for which is shown in Scheme **78b**. It was suggested that modification of the Ir(I)-precatalyst with (*S*,*S*)-*f*-binaphane, promoted a carbometallative pathway from **I** to **III** (as supported by KIE experiments, *see* Section **4.4.4**).[179] Subsequent β-hydride elimination from **III**, gives **104aa'** and Ir(III)-dihydride species **IV**, which may be reduced to Ir(I) active catalyst **V** by excess styrene in the reaction mixture. The alkenylation process outlined (**60a** to **104aa'**) most likely requires a catalyst system that enforces access to an alkene carbometallation pathway, rather than a hydrometallation/reductive elimination pathway (**I** to **II** and **II** to **96aa'**), as suggested for non-enantioselective branch-selective styrene hydroarylation.[116] Similar 1,1-disubstituted alkenes have been observed in small amounts in Ir(I)-catalysed C–H alkylation reactions of unactivated alkenes with enamide directing groups.[193]



Scheme 78: *Observation of α-arylated styrene product **104aa'** and a proposed mechanism for its formation.* [a]*Yield determined by* ^{1}*H NMR analysis of crude material against an internal standard.*

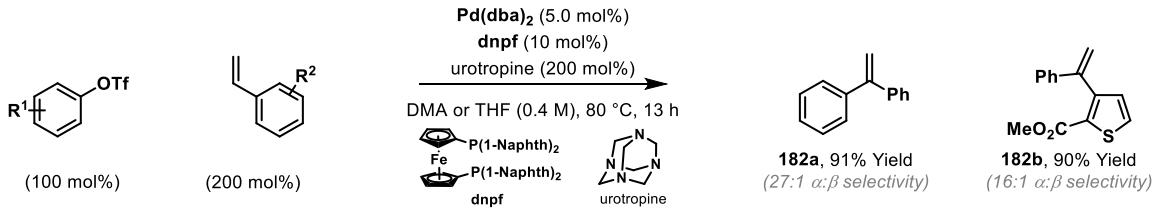
5.2 – Previously Developed Methodology for C–H Arylation of Alkenes

The dual C–H functionalisation method described above (Scheme **78a**) provides a regioisomeric product with respect to the Heck and Fujiwara-Moritani reactions.[194-195] The Heck reaction employs a Pd(0)-catalyst in the presence of a base to cross-couple activated alkenes with aryl halides or triflates. Here, arylation occurs selectively at the β-position, generating linear alkenes (Scheme **79a**).[194, 196-198] α-Arylation is much harder to achieve, with only a few examples reported and these often require highly activated alkenes.[199-203] The related Pd(0)-catalysed Fujiwara-Moritani reaction operates under oxidative conditions and often in the presence of a directing group (Scheme **79b**).[195, 204-215] This method for C–C bond formation is attractive as it achieves arylation of alkenes by dual C–H functionalisation, which eliminates the need to prepare aryl halide or triflate reagents. The regioselectivity of this method mirrors that of the Heck-reaction, giving predominantly β-arylated styrenes. The above discovery (Scheme **78a**) is therefore of potential importance, as it provides a facile method for the α-arylation of simple styrenes, whilst circumventing the need for halogenated coupling partners (Scheme **79c**).



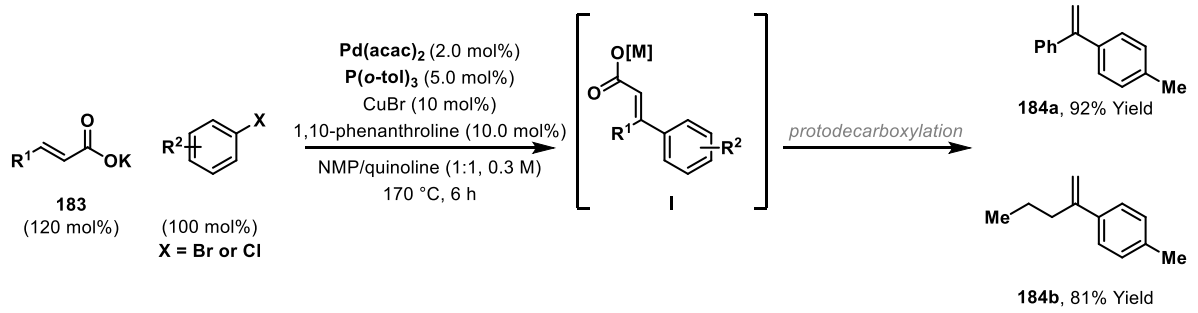
Scheme 79: *The Heck and Fujiwara-Moritani reaction.*

In 2013, Zhou and co-workers reported a general approach for a regioselective Heck-reaction that achieves α-arylation of styrenes with aryl triflates (Scheme **80**).[201-203] They utilised a Pd(0)-catalyst ligated with ferrocene-based bisphosphine dnpf. Here, the chemistry is reliant on the bulky naphthyl groups on dnpf, which sterically disfavour unwanted β-selective arylation. The protocol tolerates the coupling of styrenes and aliphatic alkenes with a range of arenes and heteroarenes to form 1,1-disubstituted alkenes (e.g. **182a** and **182b**).



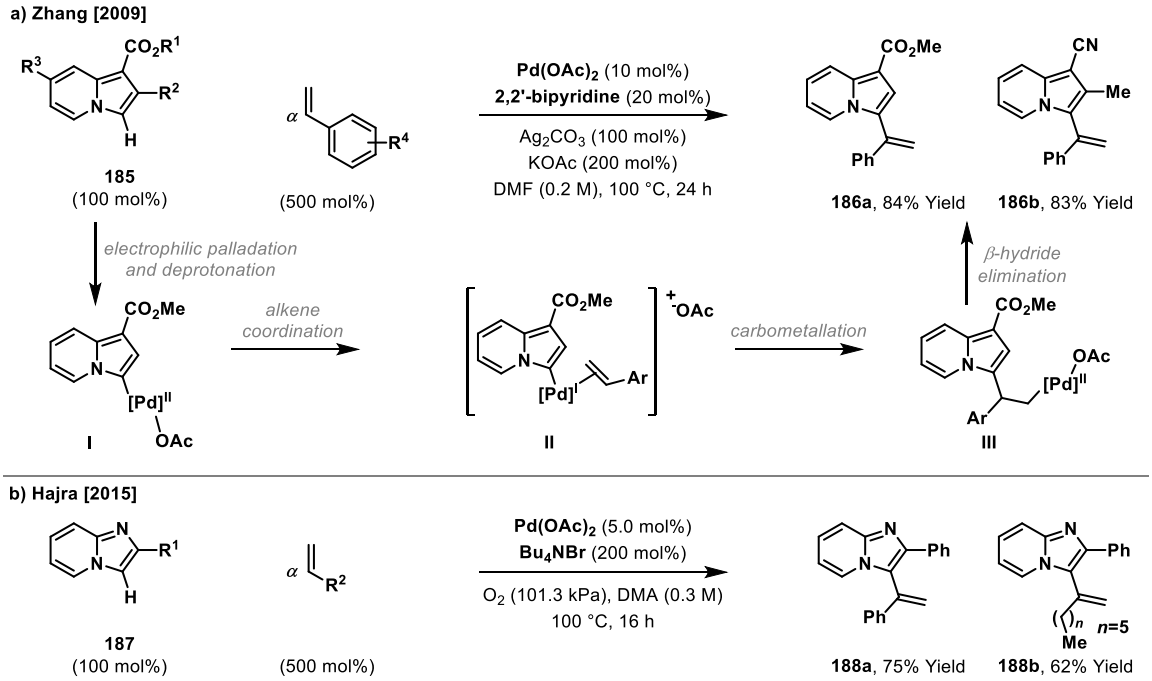
Scheme 80: *A general regioselective Heck reaction to generate 1,1-diarylated alkenes.*

Other methods which promote the α-selective arylation of styrenes utilise carboxylates as traceless directing groups.[216-217] For example, Goossen and co-workers utilised a Pd(0)-catalyst in conjugation with a Cu(I)-species to promote a regioselective Heck-type reaction (Scheme **81**). Styrene **183** bearing a traceless carboxylate directing group undergoes a Heck reaction with aryl halides to afford intermediate **I**. Subsequent Cu(I)-promoted protodecarboxylation affords 1,1-disubstituted alkenes, such as **184a** and **184b**, in excellent yields.



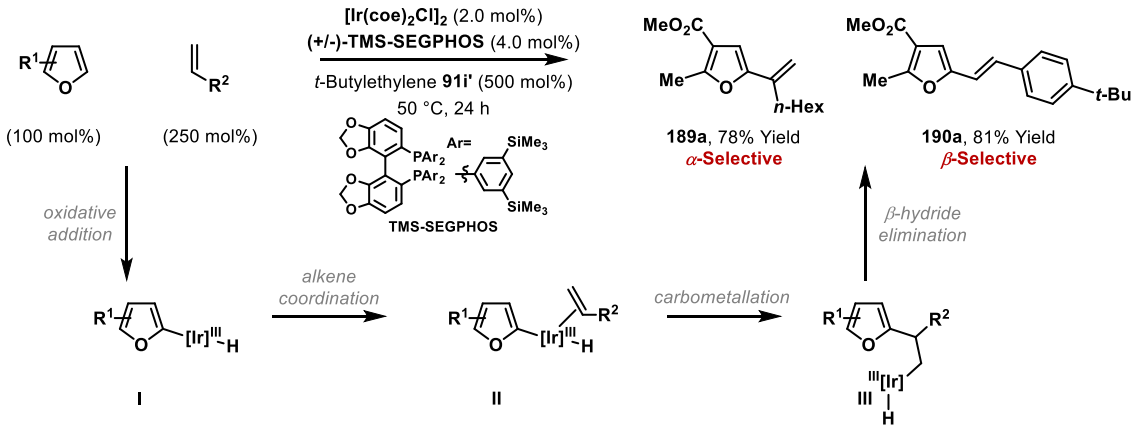
Scheme 81: *Carboxylate groups as traceless directing groups to promote α-arylation.*

The aforementioned methods involve prefunctionalised starting materials, resulting in time-consuming synthesis and waste. An alternative approach, whereby the α-selective arylation of alkenes is achieved by dual C–H functionalisation of the feedstock materials, offers an atom and step economical route to these motifs. However, to date, only a few processes that achieve α-selective arylation of styrenes by dual C–H functionalisation have been reported.[218-219] For example, in 2009, Zhang and co-workers reported the Pd(II)-catalysed oxidative cross-coupling of indolizine **185** with styrenes to afford α-heteroarylated products, such as **186a** and **186b**, in moderate to excellent yields (Scheme **82a**).[219] Zhang found that bidentate ligand, 2,2'-bipyridine, was crucial for achieving the desired α-arylation. The authors proposed an ionic pathway, in which, carbopalladation from **II** occurs to give **III**, followed by β-hydride elimination to afford the α-arylated styrenes selectivity. The resulting Pd(0)-species is oxidised to the active Pd(II)-catalyst by silver carbonate, thus completing the catalytic cycle. Later, Hajra and co-workers described Pd(II)-catalysed C–H alkenylation of imidazopyridines **187** (Scheme **82b**).[218] "Ligand-free" conditions were utilised under aerobic conditions to afford desired products, including **188a** and **188b**, in good yield, with water as the only by-product. Significantly, this protocol was also applicable for aliphatic alkenes. Zhang and Hajra's related methodologies are noteworthy for their high levels of selectivity, atom economy and simplicity. However, these protocols are limited to highly specific nitrogen-containing heteroaromatics.



Scheme 82: *α-Selective arylation of styrenes with N-heteroaromatics by dual C–H activation.*

A study with specific relevance to this work was reported by Hartwig and Sevov, who described Ir(I)-catalysed α-selective arylation of aliphatic alkenes with furan derivatives (Scheme **83**).[220] In this case an Ir(I)-catalyst ligated with wide bite angle bidentate TMS-SEGPHOS was utilised alongside *t*-butylethylene **91i'** as a sacrificial hydrogen acceptor. Alkenylated furans, such as **189a** were generated in high yields and selectivities. During evaluation of the scope, it was noted that arylation occurred selectively at the α-position with aliphatic alkenes, but β-arylation was observed with styrenes (e.g. **190a**). Similar to Zhang, Hartwig proposed that the mechanism proceeds by insertion of the alkene into the carbon–metal bond of **II** to give **III**, followed by β-hydride elimination. Evidence for this mechanistic pathway was provided by reactions with geometrically defined alkenes, kinetic studies and DFT calculations.

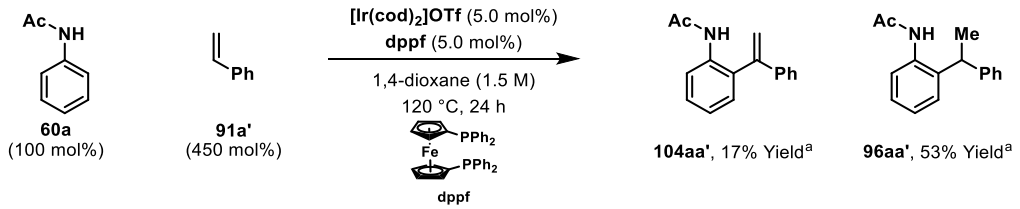


Scheme 83: *Hartwig and co-workers Ir(I)-catalysed olefination of furan derivatives with aliphatic and aromatic alkenes.*

Despite these recent advances, the development of a general method that achieves selective α-arylation of styrenes by dual C–H functionalisation is yet to be reported and would provide a regioisomeric alternative to the Fujiwara-Moritani and Heck reactions. To this end, optimisation studies into the recently discovered transformation began (Scheme **78a**).

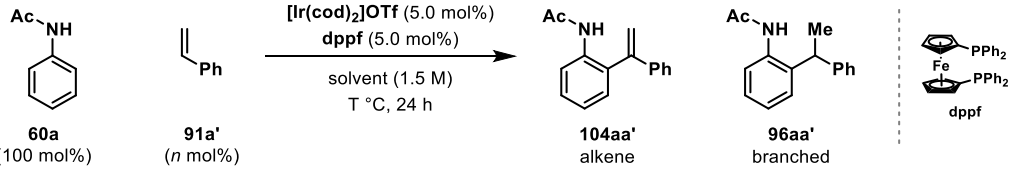
5.3 – Optimisation of the α-Selective Arylation of Styrenes

It was previously found that an Ir(I)-catalyst ligated with ligand (*S*,*S*)-*f*-binaphane provided significant quantities of α-arylated styrene **104aa'** (51% yield), alongside linear hydroarylation product **97aa'** (39% yield, Scheme **78a**). It was postulated that the ferrocene moiety of (*S*,*S*)-*f*-binaphane was vital to promoting a β-hydride elimination pathway, leading to **104aa'**. Evidence to this effect was provided by Zhou and co-workers, who found that ferrocene-based bisphosphine ligand dnpf promoted α-arylation of styrenes (Scheme **80**).[201-203] With this in mind, acetanilide **60a** and styrene **91a'** were subjected to an Ir(I)-catalyst ligated with cheaper 1,1'-bis(diphenylphosphino) ferrocene (dppf). Under these conditions, α-arylated styrene **104aa'** was formed in 17% yield, alongside branched hydroarylation side-product **96aa'** in 53% yield (Scheme **84**). Unlike with (*S*,*S*)-*f*-binaphane, none of linear regioisomer **97aa'** was observed under these conditions (*see* Scheme **78a**).



Scheme 84: *α-Selective arylation of styrene with acetanilide **60a** under Ir(I)/dppf catalysed conditions. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

Following this promising result for α-arylation of styrene with acetanilide **60a**, further optimisation studies were carried out utilising dppf and the key results are presented in Table 29. Initially, the effect of changing the solvent was investigated (entry 1–4); however, none of those trialled had a significant effect on the conversion to product **104aa'**. Notably, when water was used, the reaction still proceeded (entry 4, 15% yield), highlighting that the Ir(I)-catalyst system is relatively stable in aqueous conditions. Minor improvements were observed when increasing the temperature to 130 °C from 120 °C (entry 1 *vs* entry 5–6, 17% *vs* 23% and 22% yield). It was proposed that α-arylated product **104aa'** forms *via* β-hydride elimination from intermediate **III,** generating an Ir(III)-dihydride species, which is converted to the active Ir(I)-catalyst by excess styrene in the reaction mixture (Scheme **78b**). To increase the turnover of the Ir(I)-catalyst, the number of equivalents of styrene used was increased; however, no improvement to the yield of α-arylated product **104aa'** was observed (entry 7–8). Ketones readily accept hydrogen from transition metal catalysts to generate the corresponding alcohols.[221-223] Therefore the addition of various ketones (e.g. benzophenone, cyclobutanone and acetone) was investigated, although no increase in yield of product **104aa'** was observed. Running the reaction at different concentrations or reaction times, and the addition of alternative Ir(I)-sources (e.g. $[Ir(cod)_2]BARF$) did not have a beneficial effect. During this evaluation, alternative conditions were also screened with (*S,S*)-*f*-binaphane for the conversion of **60a** to **104aa'**, but no improvement in yield or selectivity was achieved.



Entry	solvent	T	*n*/mol%	Yield[a] 104aa'	Yield[a] 96aa'
1	1,4-dioxane	120 °C	450	17%	53%
2	1,2-DCB	120 °C	450	15%	46%
3	toluene	120 °C	450	19%	48%
4	water	120 °C	450	15%	40%
5	**1,4-dioxane**	**130 °C**	**450**	**23%**	**57%**
6	1,4-dioxane	140 °C	450	22%	54%
7	1,4-dioxane	130 °C	750	21%	60%
8	1,4-dioxane	130 °C	1000	22%	54%

Table 29: *Selected optimisation results for the α-arylation of styrene **91a'** with acetanilide **60a** under Ir(I)/dppf catalysed conditions. [a]Yield determined by ^1H NMR analysis of crude material against an internal standard.*

The Ir(I)-catalysed α-arylation of styrene using dppf as the ligand demonstrated poor efficiency and selectivity to hydroarylation side-product **96aa'** (Table **29**). To this end, over 70 commercially

available mono- and bidentate phosphine ligands were screened for the C–H alkenylation of acetanilide **60a** and the key results are reported in Table 30. 1,4-Bis(diphenylphosphino)butane (dppb) gave alkenylation product **104aa'**, albeit in poor yield (13%) and selectivity to branched **96aa'** and linear **97aa'** hydroarylation side-products (0.4:1:0.2, entry 1). However, an increase in the selectivity for alkenylation product **104aa'** was observed when electron-withdrawing substituents were added to the aryl substituents of the ligand (F, **L-19a** and CF_3, **L-19b**; entry 2, 1:1:0.3 and entry 3, 1:1:0.3 *vs* entry 1). In contrast to dppb derivatives, ferrocene-based bisphosphine ligands (entry 4–6) gave no linear regioisomer **97aa'**, and alkene **104aa'** was afforded in greater selectivity to branched hydroarylation side-product **96aa'** (4:1 *vs* 1:1).

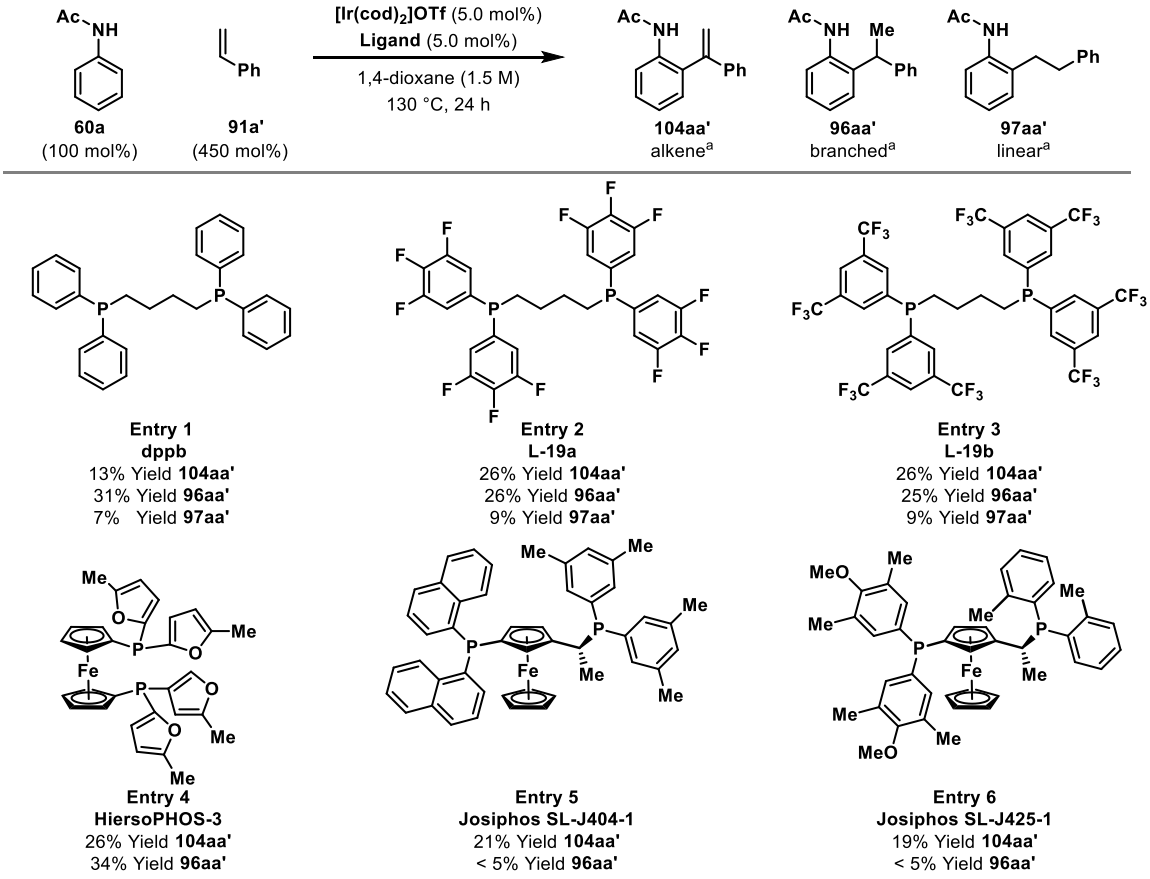


Table 30: *Selected results for α-arylation of styrene **91a'** with acetanilide **60a** under Ir(I)-catalysed conditions utilising commercially available ligands. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

5.3.1 – Design and Synthesis of Ferrocene-Based Bisphosphine Ligands

An achiral commercially available ligand, which gave alkenylated product **104aa'** selectively over hydroarylation side-products **96aa'** and **97aa'**, was not identified. However, it was noted that electron-deficient derivatives of dppb resulted in greater selectivity for α-arylation product **104aa'** over branched side-product **96aa'** (1:1 *vs* 0.4:1, Table **30**, entry 1–3). Additionally, ferrocene-based bisphosphine ligands did not result in linear hydroarylation side-product **97aa'** (Table **30**, entry 4–6). These

observations prompted the design and synthesis of dppf derivatives with electron-deficient aryl moieties (Table **31**). Electron deficient bisphosphine ligands **L-20a–d** were prepared in three steps from ferrocene.[201] Initially, ferrocene **191** was bis-lithiated with *n*-butyllithium and reacted with bis(diethylamino)chlorophosphine **192** under an inert and anhydrous atmosphere. Intermediate **193** was formed upon acidification with hydrochloric acid and reaction of **193** with various Grignard reagents gave ligands **L-20a–d**. These were isolated in low yields due to challenging purification. *Para*-cyano- and -methoxy reagents **194a** and **194b**, and *ortho*-substituted arene **194c** did not generate the desired bisphosphine ligand.

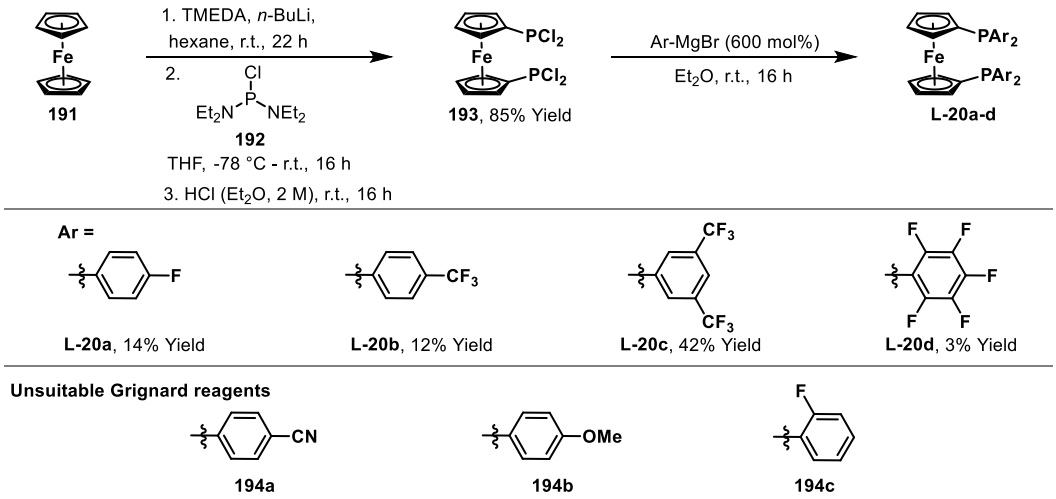
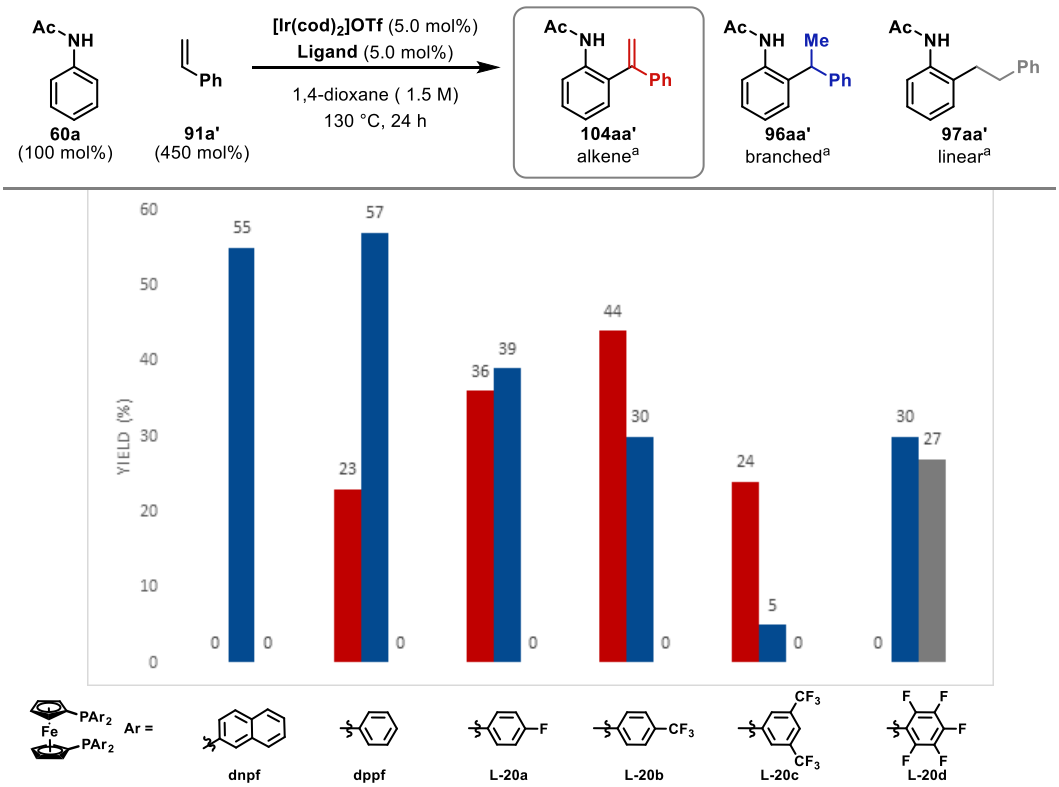


Table 31: *Synthesis of electron-deficient ferrocene-based bisphosphine ligands* ***L-20a–d****.*

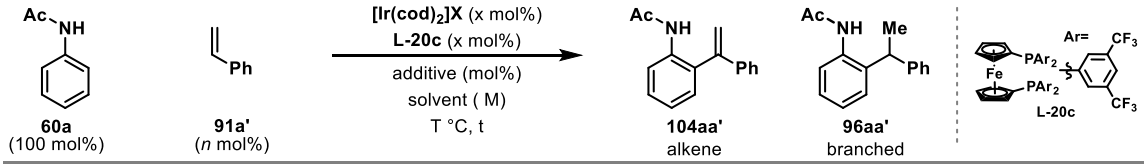
Ferrocene-based bisphosphine ligands **L-20a–d** were trialled under Ir(I)-catalysed conditions (Table **29**, entry 5) for the α-arylation of styrene **91a'** with acetanilide **60a** (Scheme **85**). In general, selectivity for alkenylation product **104aa'** *vs* hydroarylation side-product **96aa'** increased as the aryl moiety of the ligand became more electron-deficient (as observed with dppb derivatives; *see* Table **30**, entry 1–3). *Para*-trifluoromethyl ligand **L-20b** provided α-arylation product **104aa'** in the highest yield (44%), albeit in poor selectivity *vs* **96aa'** (1.5:1). Alternatively, when utilising bis-3,5-trifluoromethyl ligand **L-20c**, **104aa'** was generated in 24% yield and with good selectivity over **96aa'** (5:1). Conversely, pentafluorophenyl ligand **L-20d** generated only branched **96aa'** (30% yield) and linear **97aa'** hydroarylation products (27% yield). It was postulated that the highly electron-withdrawing nature of **L-20d** resulted in a switch in the mechanistic cycle from a β-hydride elimination to a reductive elimination pathway (*see* Scheme **78b**). Additionally, commercially available naphthyl substituted ligand **dnpf** was ineffective for C–H arylation and branched hydroarylation product **96aa'** was generated selectively (55% yield). Bis-3,5-trifluoromethyl ligand **L-20c** was chosen for further optimisation studies, due to the high selectivity it afforded for α-arylation product **104aa'** (5:1) over side-product **96aa'**.



Scheme 85: *α-Arylation of styrene **91a'** with acetanilide **60a** under Ir(I)-catalysed conditions utilising ferrocene-based bisphosphine ligands **L20a-d**. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

Having identified bis-3,5-trifluoromethyl bisphosphine ligand **L-20c** as the most selective, optimisation of the α-arylation of styrene **91a'** with acetanilide **60a** commenced (Table **32**). Conducting the reaction at a higher temperature and extending the reaction time to 48 h was beneficial to the yield of alkene **104aa'** (entry 2, 41% yield). Changing the solvent and using a greater number of equivalents of styrene did not improve conversion to product **104aa'** (entry 3–5). Running the reaction for longer (72 hours) resulted in an increase in the yield of alkenylation product **104aa'** to 60% (entry 6). Additionally, increasing the loading of Ir(I)-precatalyst and ligand to 7.5 mol% and decreasing the concentration were both beneficial to the yield of alkenylation product **104aa'** (entry 7). The proposed β-hydride elimination step to form alkene **104aa'** results in Ir(III)-dihydride species **IV** (*see* Scheme **78**, Section **5.1**). Turnover of this to the active Ir(I)-species is achieved by the reduction of excess styrene in the reaction mixture. This is supported by the presence of ethyl benzene **181** in the crude reaction mixture as observed by ^{1}H NMR and GCMS analysis (*see* Scheme **78**, Section **5.1**). To this end, external oxidants were investigated, to encourage more facile hydrogen removal, and hence increase the conversion to alkene **104aa**. Pinacolone[224] had a negligible effect (entry 8); however, by using 200 mol% *t*-butylethylene , alkene **104aa'** was generated in 74% yield and with a 10:2 selectivity over **96aa'** (entry 9). Hartwig and co-workers, previously demonstrated that *t*-butylethylene was an effective hydrogen-scavenger for the Ir(I)-catalysed α-arylation of aliphatic alkenes with furan

derivatives (Scheme **83**).[220] Alternative Ir(I)-sources, including $[Ir(cod)_2]BF_4$, $[Ir(cod)_2]OMe$ and $[Ir(cod)_2]BARF$, all resulted in lower or no conversion to **104aa'** (entry 10–12). Notably, when $[Ir(cod)_2]BARF$ or $[Ir(cod)_2]BF_4$ was utilised as the precatalyst, hydroarylation product **96aa'** was afforded with high selectivity over arylated product **104aa'**, presumably as a result of the lower coordinating abilities of the BARF/BF_4 counterions compared to triflate.



Entry	t	T	solvent (M)	*n* (mol%)	additive (mol%)	X (mol%)	Yield 104aa'[a]	Yield 96aa'[a]
1	24 h	120 °C	1,4-dioxane (1.5 M)	450	/	OTf (5.0)	24%	5%
2	48 h	130 °C	1,4-dioxane (1.5 M)	450	/	OTf (5.0)	41%	18%
3	48 h	130 °C	toluene (1.5 M)	450	/	OTf (5.0)	19%	32%
4	48 h	130 °C	DCB (1.5 M)	450	/	OTf (5.0)	34%	41%
5	48 h	130 °C	1,4-dioxane (1.5 M)	750	/	OTf (5.0)	43%	18%
6	72 h	130 °C	1,4-dioxane (1.5 M)	450	/	OTf (5.0)	60%	18%
7	72 h	130 °C	1,4-dioxane (0.5 M)	450	/	OTf (7.5)	65%	22%
8	72 h	130 °C	1,4-dioxane (0.5 M)	450	pinacolone (200)	OTf (7.5)	68%	21%
9	**72 h**	**130 °C**	**1,4-dioxane (0.5 M)**	**450**	***t*-butylethylene (200)**	**OTf (7.5)**	**74%[b]**	**15%**
10	72 h	130 °C	1,4-dioxane (0.5 M)	450	*t*-butylethylene (200)	BF_4 (7.5)	9%	46%
11	72 h	130 °C	1,4-dioxane (0.5 M)	450	*t*-butylethylene (200)	OMe (7.5)	0%	0%
12	72 h	130 °C	1,4-dioxane (0.5 M)	450	*t*-butylethylene (200)	BARF (7.5)	20%	88%

Table 32: *Selected optimisation results for the α-arylation of styrene **91a'** with acetanilide **60a** utilising ligand **L-20c**. [a]Yield determined by ^{1}H NMR analysis of crude material against an internal standard; [b]Isolated yield.*

5.4 – Reaction Scope

5.4.1 – Scope with Respect to the Directing Group

With bis-3,5-trifluoromethyl bisphosphine ligand **L-20c** now providing efficient conversion of acetanilide **60a** to alkenylation product **104aa'**, the scope with respect to the directing group was explored (Table **33**). A wide range of sterically varied anilide-based directing groups, including primary, secondary and tertiary alkyl groups were employed to generate desired α-arylated products **104ka'–104qa'** in good to excellent yields (57–81%), and with high selectivity over hydroarylation side-products **96ka'–96qa'** (4:1 to >20:1). In all cases, C–H alkenylation products **104ka'–104qa'** were easily separated from minor hydroarylation products **96ka'–96qa'** by FCC. Higher selectivity for alkenylation product **104** over hydroarylation product **96** was often observed with bulkier directing groups. For example, cyclohexyl anilide **60p** generated α-arylated product **104pa'** in excellent selectivity over **96pa'** (8:1 *vs* 5:1 for **104aa'**:**96aa'**). This protocol is currently limited to acetanilides where the R-group on the directing group is carbon-based and more electron rich urea or carbamate

directing groups are not tolerated **60r** and **60s** (Table **33**). Additionally, cyclopropanated and alkenylated acetanilides **60t** and **60u** were not viable, potentially due to competing alkene coordination or Ir(I) oxidative addition into the C–H/C–C bond of the cyclopropane unit. The lack of reactivity of *N*-methyl derivative **60v** could possibly be attributed to 1,3-strain occurring between the methyl group and the *ortho*- C–H bond (Figure **7**). Alternatively, C–H oxidative addition of the Ir(I)-catalyst into the methyl group could be competitive. This could potentially hinder the formation of 6-membered iridacycle **II** and therefore inhibit formation of **104va'**. Other classes of directing group were also examined, including ketones **89a** and **89b** and benzamide **90a**, but in all cases no conversion to the target products was observed. However, the lack of directing group tolerance is not considered a major restriction owing to the ease of installation and removal of the *N*-acetyl-based groups (*see* Section **5.5**, Scheme **88**).

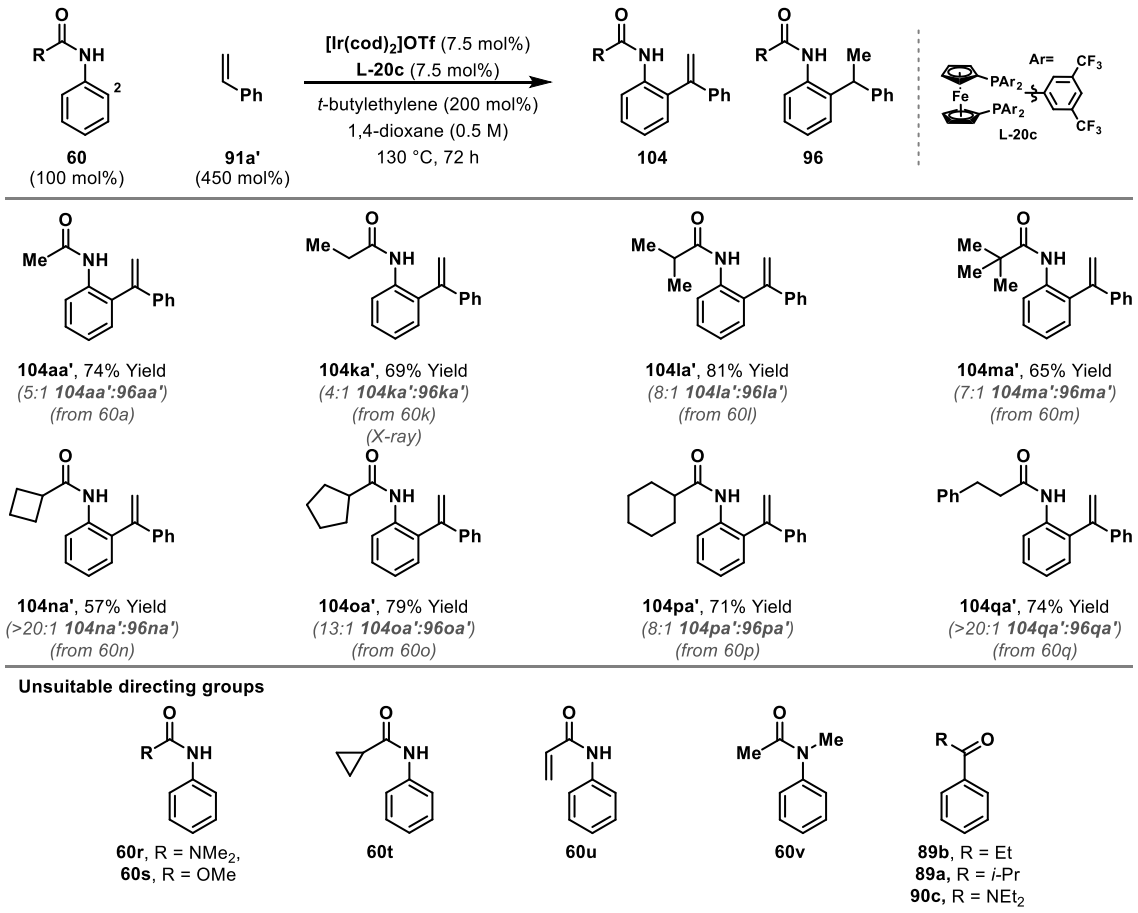


Table 33: *Scope of the directing group in the α-arylation of styrene with anilide substrates **60k–60q**.*

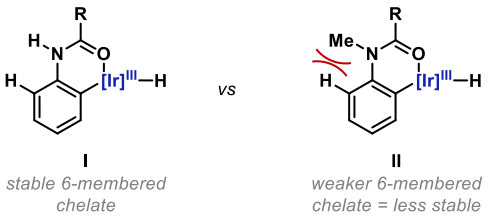
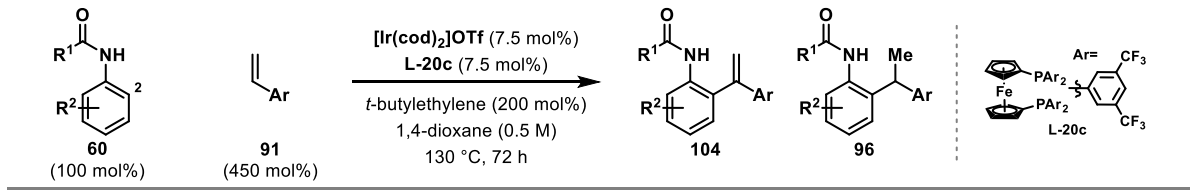


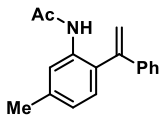
Figure 7: *Steric interaction in 6-membered iridacycle intermediate **II**.*

5.4.2 – Scope with Respect to the Anilide

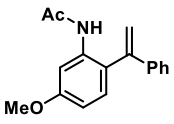
Having investigated the scope of the directing group, subsequent studies revealed that the C–H alkenylation process tolerates diverse substitution on the arene portion of the anilide coupling partner (Table **34**). Systems with substitution in the *meta*-position (e.g. **60c**, **60b**, **60w** and **60x**) underwent highly regioselective C–H alkenylation at the less hindered *ortho*-position and with good selectivity over hydroarylation side-products **96**. *Para*-substituted anilides (e.g. **60y**, **60z** and **60aa**) engaged efficiently; for example, the potentially labile C–Br bond of **60y** remained intact (61% yield), maintaining the possibility for further derivatisation. Additionally, **60z** with a *para*-ester group reacted selectively at the C2-position of the anilide, which highlights the greater coordinating ability of acetanilide functionality compared to the ester moiety. Systems with highly electron-withdrawing

groups, such as *para*-trifluoromethyl derivative **104ga'**, suffered from poorer yields (19%). However, by switching to acetanilide **60ab**, bearing a more sterically demanding directing group, and substituted styrene **91e'** (*p*-Tol), **104abe'** could be generated in acceptable yield (43%) and with excellent selectivity over **96abe'** (>20:1). This result suggests that a more electron rich alkene promotes a β-hydride elimination pathway over C–H reductive elimination (*see* Scheme **78b**, **III** to **104aa**). This may be a result of increased hyperconjugation from the more electron-rich π-system into the σ* orbital of the benzylic C–H bond, which would weaken the benzylic C–H bond and therefore promote β-hydride elimination. Anilide **60e** with a methyl in the *ortho*-position suffered from low selectivity (2:1) for alkenylation product **104ea'** over hydroarylation side-product **96ea'**. Nevertheless, derivative **104ael'** was produced in high selectivity (<20:1). Some limitations of the process include low selectivity when halogens are in the *meta*-position of the anilide (e.g. **104ia'**) and no reactivity for anilides with *ortho*-substituents other than a methyl-substituent, such as in **60ah**.

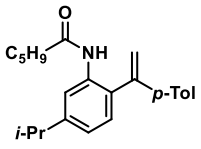




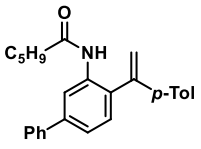
104ca', 77% Yield
*(5:1 **104ca':96ca'**)*
(from 60c and 91a')



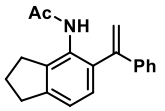
104ba', 65% Yield
*(5:1 **104ba':96ba'**)*
(from 60b and 91a')



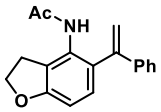
104we', 78% Yield
*(>20:1 **104we':96we'**)*
(from 60w and 91e')



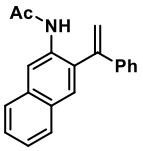
104xe', 70% Yield
*(>20:1 **104xe':96xe'**)*
(from 60x and 91e')



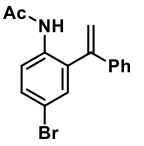
104ja', 83% Yield
*(5:1 **104ja':96ja'**)*
(from 60j and 91a')



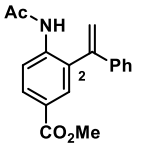
104da', 68% Yield
*(7:1 **104da':96da'**)*
(from 60d and 91a')



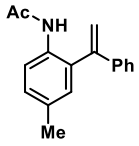
104fa', 72% Yield
*(5:1 **104fa':96fa'**)*
(from 60f and 91a')



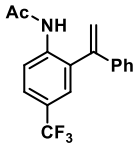
104ya', 61% Yield[a]
*(4:1 **104ya':96ya'**)*
(from 60y and 91a')



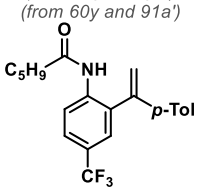
104za', 58% Yield
*(6:1 **104za':96za'**)*
(from 60z and 91a')



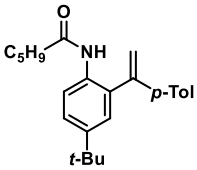
104aaa', 71% Yield
*(13:1 **104aaa':96aaa'**)*
(from 60aa and 91a')



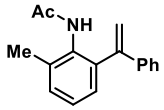
104ga', 19% Yield
*(>20:1 **104ga':96ga'**)*
(from 60g and 91a')



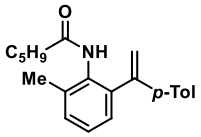
104abe', 43% Yield[a,b]
*(>20:1 **104abe':96abe'**)*
(from 60ab and 91e')



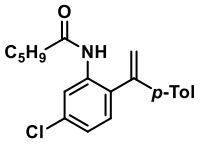
104ace', 94% Yield
*(20:1 **104ace':96ace'**)*
(from 60ac and 91e')



104ea', 56% Yield
*(2:1 **104ea':96ea'**)*
(from 60e and 91a')

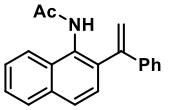


104ade', 50% Yield[a,b]
*(>20:1 **104ade':96ade'**)*
(from 60ad and 91e')

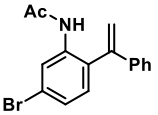


104aee', X = Cl, 34% Yield[a,b]
*(3:1 **104aee':96aee'**)*
(from 60ae and 91e')

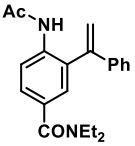
Arenes that gave poor yield/selectivity



104afa', 46% Yield[c]
*(1.5:1 **104afa':96afa'**)*
(from 60af and 91a')

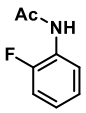


104ia', *25% Yield*[c]
*(2:1 **104ia':96ia'**)*
(from 60i and 91a')

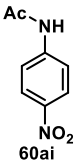


104aga', 14% Yield[c]
*(1:2 **104aga':96aga'**)*
(from 60ag and 91a')

Unsuitable arenes



60ah

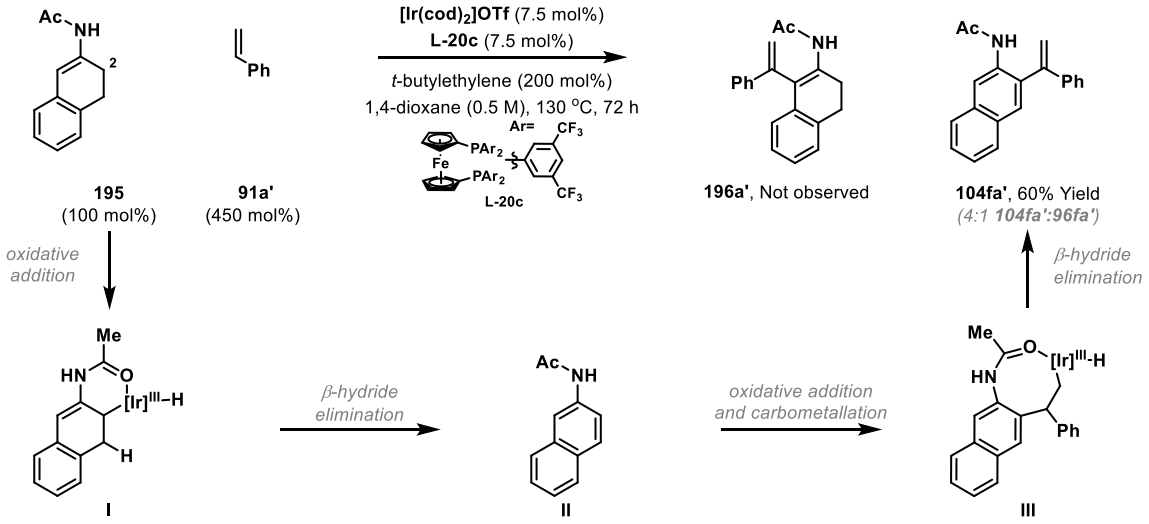


60ai

Table 34: *Scope of anilide substrates **60** in the α-arylation of styrene **91a'**. [a]10 mol% of Ir(cod)2OTf and ligand was used; [b]The reaction was run for 96 h; [c]Yield determined by [1]H NMR analysis of crude material against an internal standard.*

To expand the scope to non-aromatic coupling partners, dihydronaphthalene **195** was exposed to Ir(I)-catalysed conditions (Scheme **86**). No conversion to expected product **196a'** was observed, but

alkenylation product **104fa'** was isolated. Dehydrogenative aromatisation of dihydronaphthalene **195** was unexpected and is presumed to occur *via* carbonyl directed oxidative addition of the Ir(I)-catalyst into the C2–H bond to form **I**, followed by β-hydride elimination to form **II**. β-Hydride elimination then generates alkenylation product **104fa'** in 60% yield over the two steps. Here, dehydrogenative C–C bond formation is occurring in conjunction with dehydrogenative aromatisation (Scheme **86**). Ir(I)-catalysts have previously demonstrated dehydrogenative properties.[225] This result suggests that this directing group strategy promotes Ir(I) oxidative addition into activated sp^3 C–H bonds which could demonstrate greater significance.



Scheme 86: *Tandem dehydrogenation/C–H arylation of **195**.*

5.4.3 – Scope with Respect to the Alkene Coupling Partner

Following the above studies, anilide **60o** was selected to explore the scope of the alkene coupling partner, owing to the high selectivity for arylation product **104oa'** over **96oa'** (13:1, Table **33**). Electronically diverse substituents were well tolerated in the *para*-position; for example, fluorine-derivative **104on'** and *t*-Bu-derivative **104op'** were generated in excellent yields (75% and 80%) (Table **35**). However, the selectivity for arylation over hydroarylation decreased for trifluoromethyl derivative **104oo'** (4:1 *vs* >20:1 for **104oe'**), which suggests that highly electron-withdrawing substituents impede the β-hydride elimination pathway (*see* Scheme **78b**, **III** to **104aa'**). *Meta*-substituted styrenes **91r'** and **91s'** proceeded smoothly to give desired products **104or'** and **104os'** in good yields (70% and 64%). However, for *ortho*-substituted styrenes **91g'** and **91t'**, arylation proceeded in poorer yields (**104og'** and **104ot'**, 50% and 29%), likely due to the more congested centre during bond formation. More complex benzothiophene derivative **91u'** was utilised to give alkenylation product **104ou'** in a moderate yield; however, other vinyl heteroaromatics **91y'–91aa'** did not afford the target alkenylation products. This is potentially a result of the more strongly coordinating heteroatoms ligating to the Ir(I)-centre, which would deactivate the Ir(I)-catalyst. Additionally, styrene **91ab'** with a methyl in the β-position

was not tolerated. With the current Ir(I)-system, the C–H alkenylation process occurs efficiently with styrenes only. Alkyl alkenes such as, **91c'** and **91i'** including more activated enol ether **91ac'** and allene **197** were ineffective.

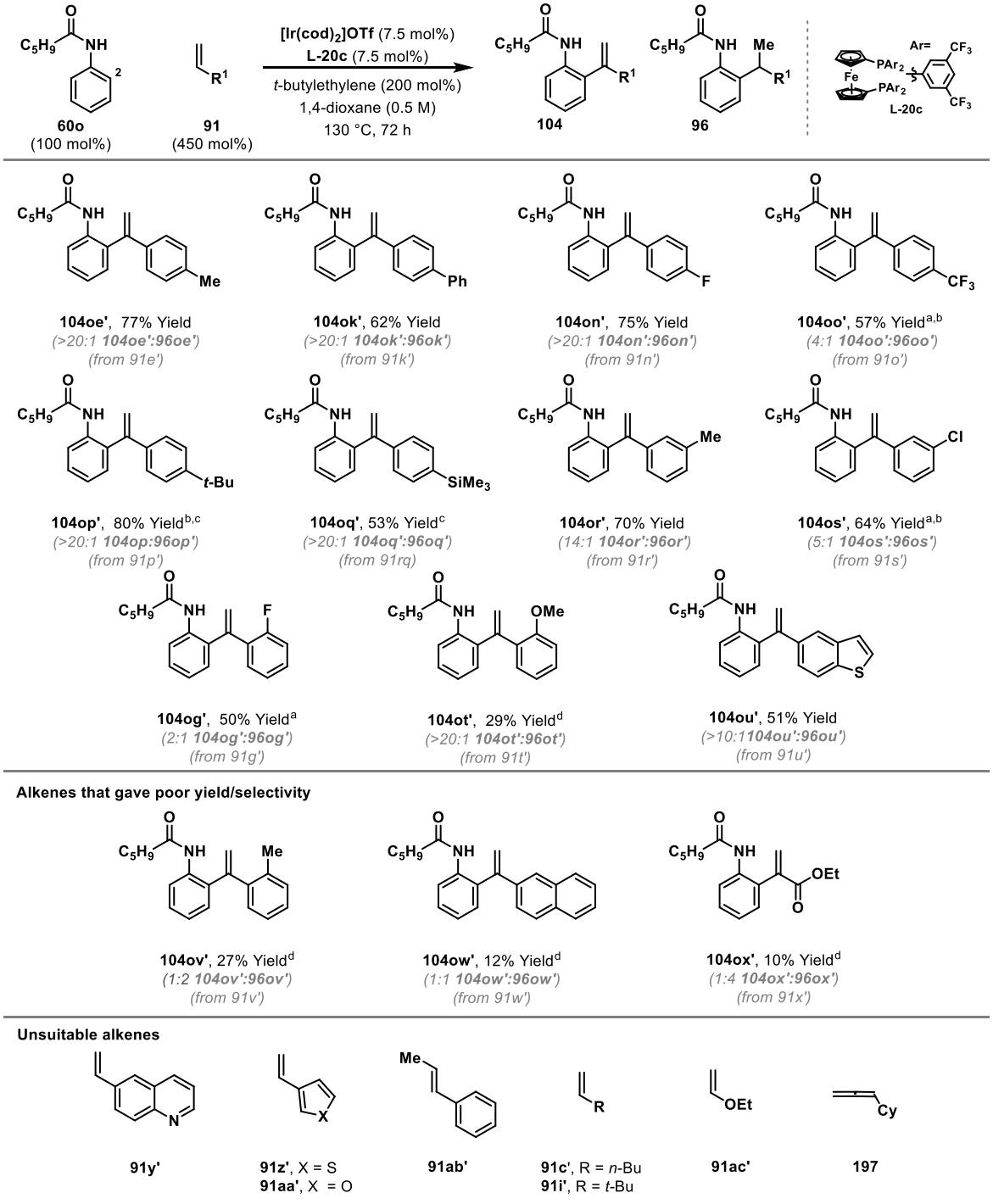
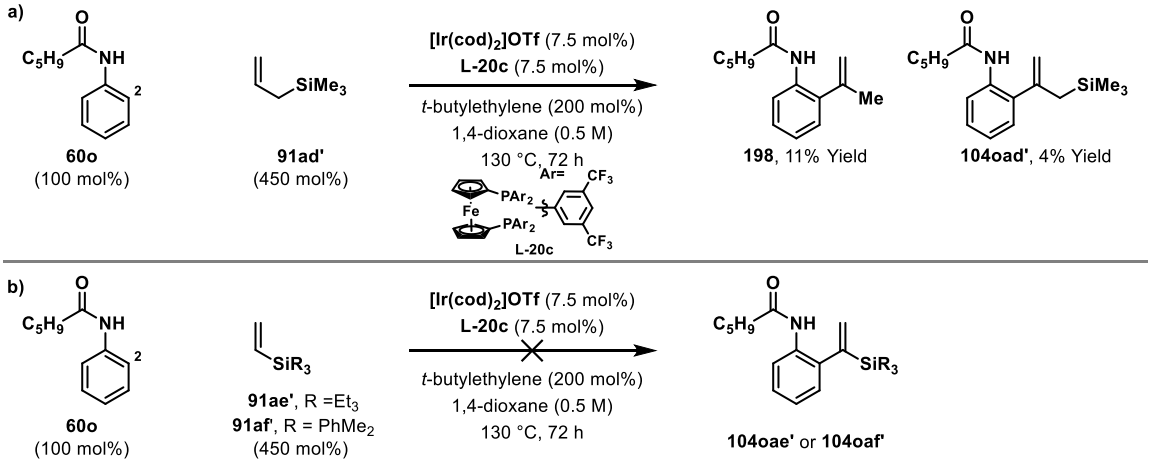


Table 35: *Scope of the α-arylation of various styrenes with anilide substrate* ***60o****.* [a]*10 mol% of Ir(cod)$_2$OTf and ligand used;* [b]*The reaction was run at 1.0 M;* [c]*The reaction was run for 96 h;* [d]*Yield determined by* ^{1}*H NMR analysis of crude material against an internal standard.*

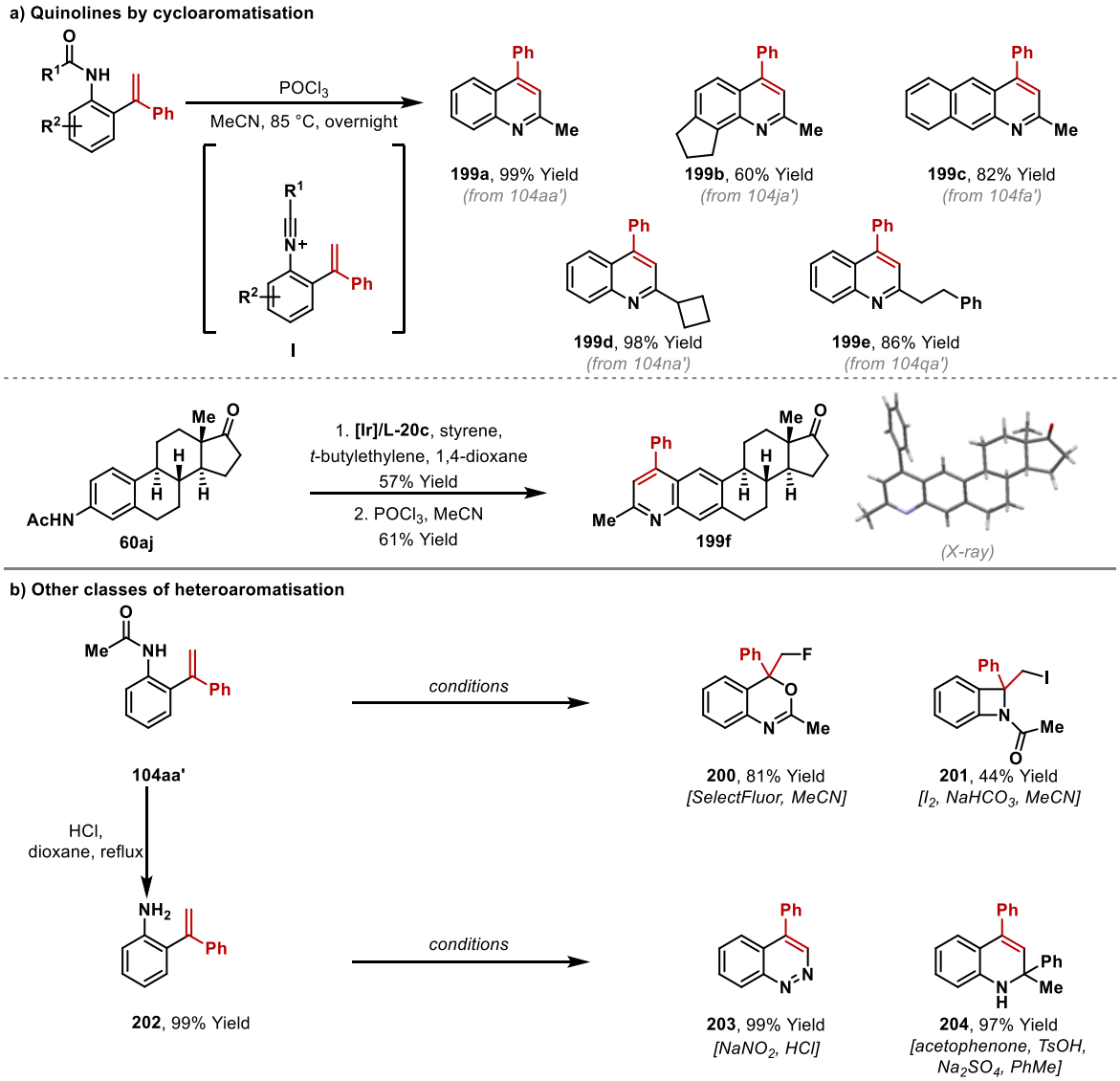
The α-arylation of various alkyl alkenes with acetanilide **60o** did not proceed under Ir(I)-catalysis. However, when allyltrimethylsilane **91ad'** was utilised, desilylated α-selective arylation product **198** was isolated in 11% yield, alongside small amounts of expected product **104oad'** (4% yield) (Scheme **87a**). It is proposed that **198** forms *via* protodesilylation of **104oad'**, which usually occurs under acidic conditions.[226] Increasing the reaction time, temperature, and precatalyst and ligand loadings all resulted in decreased conversion to **104oad'**. Towards achieving the α-selective arylation of aliphatic alkenes selectively, triethylvinylsilane **91ae'** and dimethylphenylvinylsilane **91af'** were investigated (Scheme **87b**). It was envisaged that protodesilylation would be prohibited, through removal of the β-hydrogen atom; however, targets **104oae'** and **104oaf'** were not observed.



Scheme 87: *α-Selective arylation of alkene **91ad'** with acetanilide **60o**.*

5.5 – Derivatisations of the α-Arylation Products

Anilide C–H alkenylation products **104** described in this chapter are useful moieties, especially in the synthesis of challenging bicyclic *N*-containing heteroaromatics. For example, when exposed to phosphorus(V) oxychloride, alkenylation products (**104aa'**, **104ja'**, **104fa'**, **104pa'** and **104qa'**) underwent efficient cycloaromatisation to afford quinoline systems **199a–199e** (Scheme **88a**).[227] This heteroaromatisation strategy offers a facile and effiecient method to afford complex polycyclic systems, including **199b** and **199c**. This methodology was also applicable to estrone derivative **60aj**, which afforded unusual quinoline **199f** in 35% yield over two steps (C–H alkenylation and cycloaromatisation) (Scheme **88a**). When alkene **104aa'** was exposed to Selectfluor[228] and iodine[229] fluorinated benzoxazine **200** and azetidine **201** were generated in 81% and 44% yield (Scheme **88b**). Under acidic conditions, hydrolysis of **104aa'** gave aniline **202** quantitatively. This then underwent facile transformation to a diazonium salt , which rapidly cyclised onto the alkene moiety to form cinnoline **203** in quantitative yield. Additionally, upon exposure to acetophenone, dihydroquinoline **204**, which comprises a tetrasubstituted stereocentre, was formed in excellent yield (97%) (Scheme **88b**).



Scheme 88: *Derivatisations of C–H alkenylation products **104**.*

5.6 – Ir(I)-Catalysed α-Arylation of Styrenes with Pyrrole Derivatives

Having successfully developed methodology for the α-selective arylation of styrenes with acetanilides, studies to expand the methodology to include more varied substrates began. To this end, several viable heteroaromatic coupling partners were exposed to the Ir(I)-catalysed conditions with styrene. When pyrrole **126a** was subjected to optimised conditions (Table **32**, entry 9) no reaction occurred. However, when pyrrole **126a** was exposed to alternative (*S*,*S*)-*f*-binaphane ligand (*see* Section **2.2.3**, Table **3**), under the conditions developed for styrene hydroarylation with pyrrole **126a** (Section **3.2.1**, Table **11**), C–H alkenylation product **128aa'** was generated in 74% yield and with high selectivity over branched side-product **127aa'** (Table **36**). This result indicates that ligand choice can manipulate the delicate balance between reductive elimination and β-hydride elimination pathways (*see* Scheme **78b**). A brief scope study of this protocol was conducted (Table **36**). Notably, decreasing the size of the directing group (**126b** *vs* **126c**) resulted in an improvement in selectivity for arylation product **128ba'**

over hydroarylation side-product **127ba'**, albeit in diminished yield (29%). This suggests that when utilising (*S*,*S*)-*f*-binaphane as the ligand, C–H reductive elimination is more facile with sterically demanding substituents on the directing group (*see* Scheme **78b**, **III** to **104aa'**). The procedure tolerates electronically diverse styrenes with substitution in the *para*- and *meta*-positions, affording products **128ap'**, **128an'**, **128ak'** and **128as'** in moderate to good yields (25–72%). Aliphatic alkenes were less efficient; however, unlike acetanilide derivatives, alkenylated pyrrole **128ac'** was generated in a low yield (14% by ^{1}H NMR analysis of crude material). For pyrrole **126e**, which is arylated at C3, C–H alkenylation occurred with complete selectivity for the less hindered position (C5 over C2), giving **128ea'** in a 50% yield. *N*-Methyl-pyrrole **150**, equipped with a directing group at C3, gave alkenylation product **205a'** in 59% yield, although it was generated with poor regioselectivity, with alkenylation occurring in both the C2- and C4-positions (1:1.7). All other heteroaromatics trialled (e.g. **126f**, **150b**, **150c**, **134a**, **131** and **145**) were unreactive under the Ir(I)-catalysed conditions.

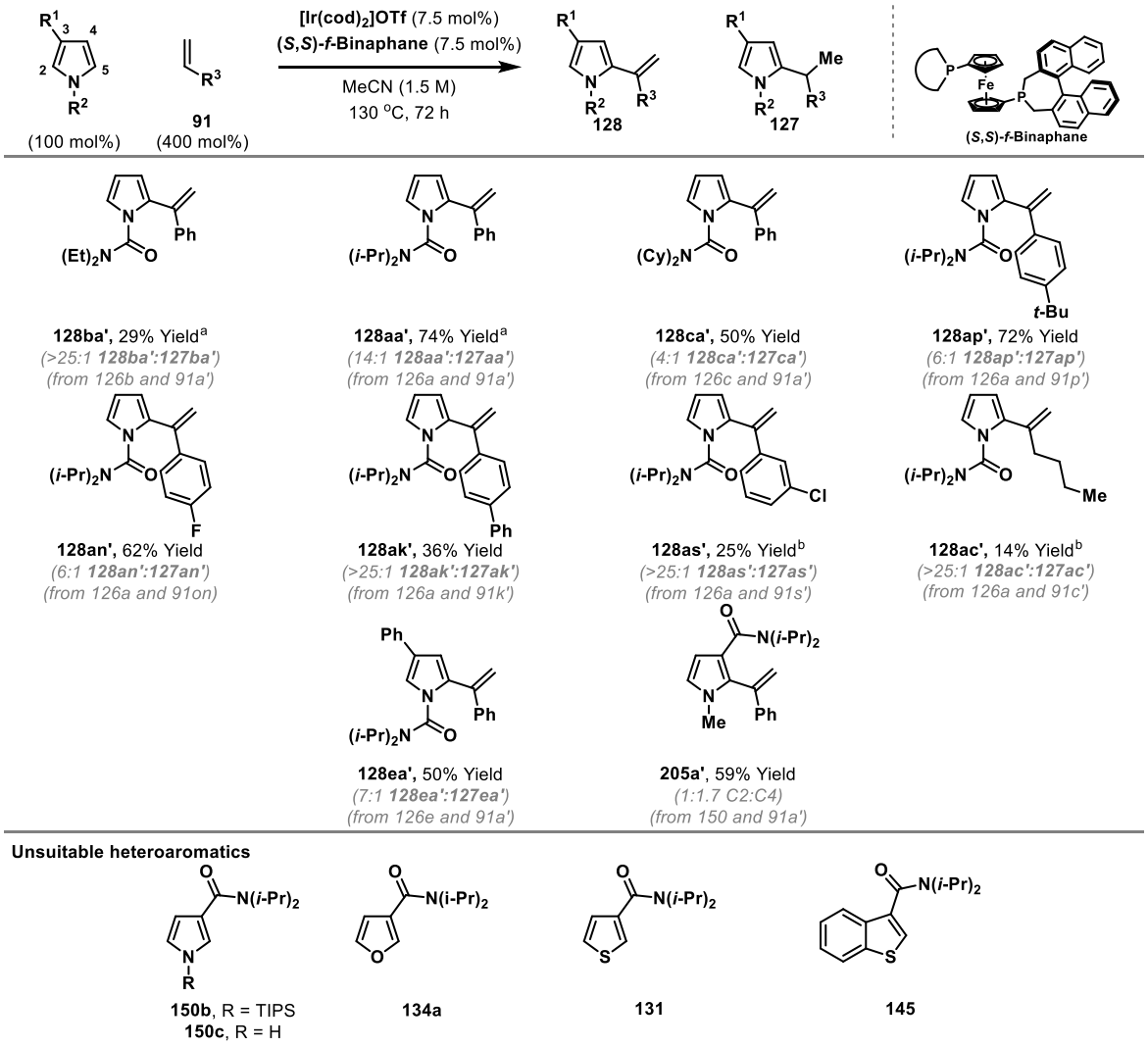
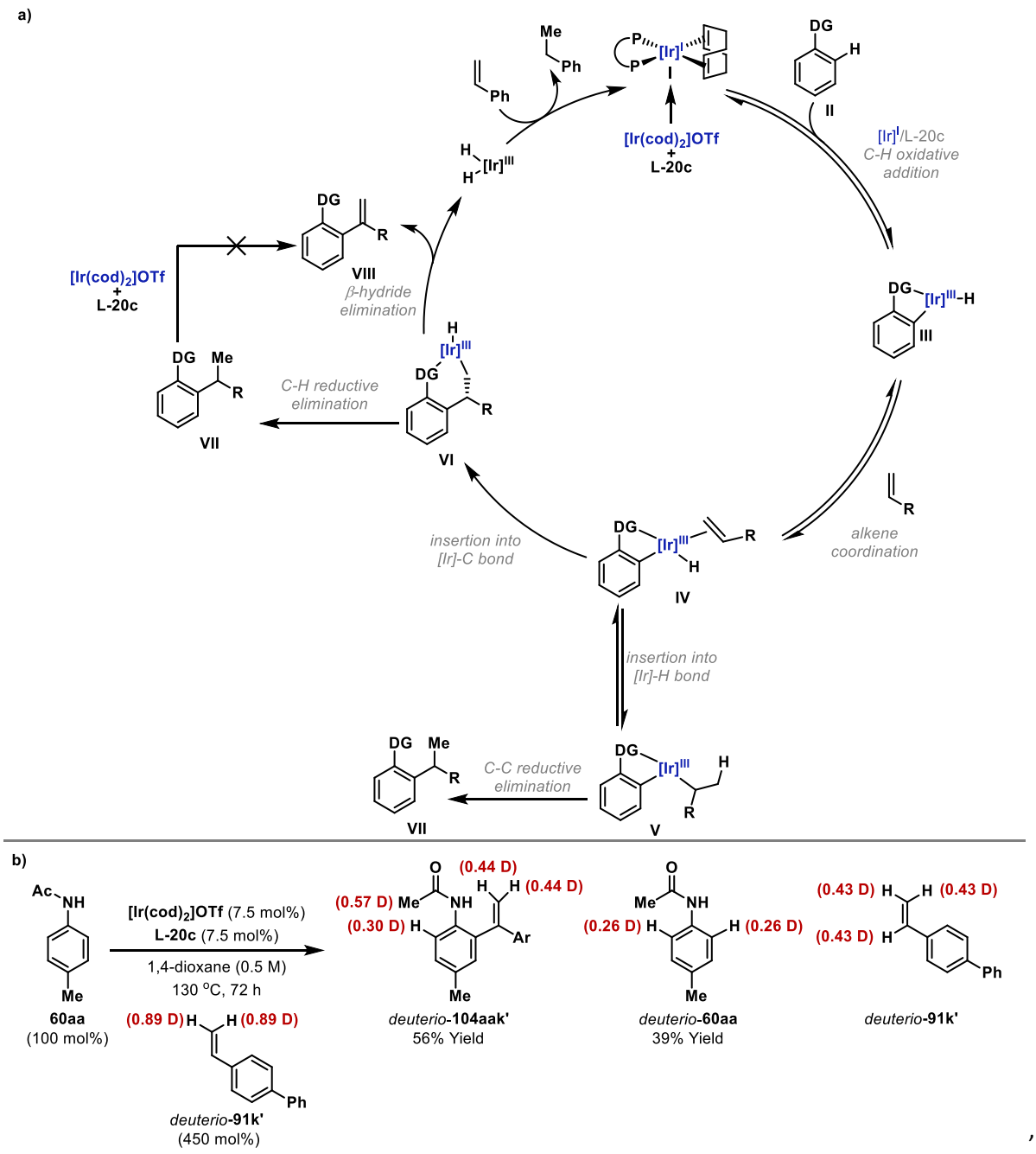


Table 36: *Extension of the C–H alkenylation process to pyrrole substrates. [a]The reaction was run for 48 h; [b]Yield determined by ^{1}H NMR analysis of crude material against an internal standard.*

5.7 – Studies into the Mechanism

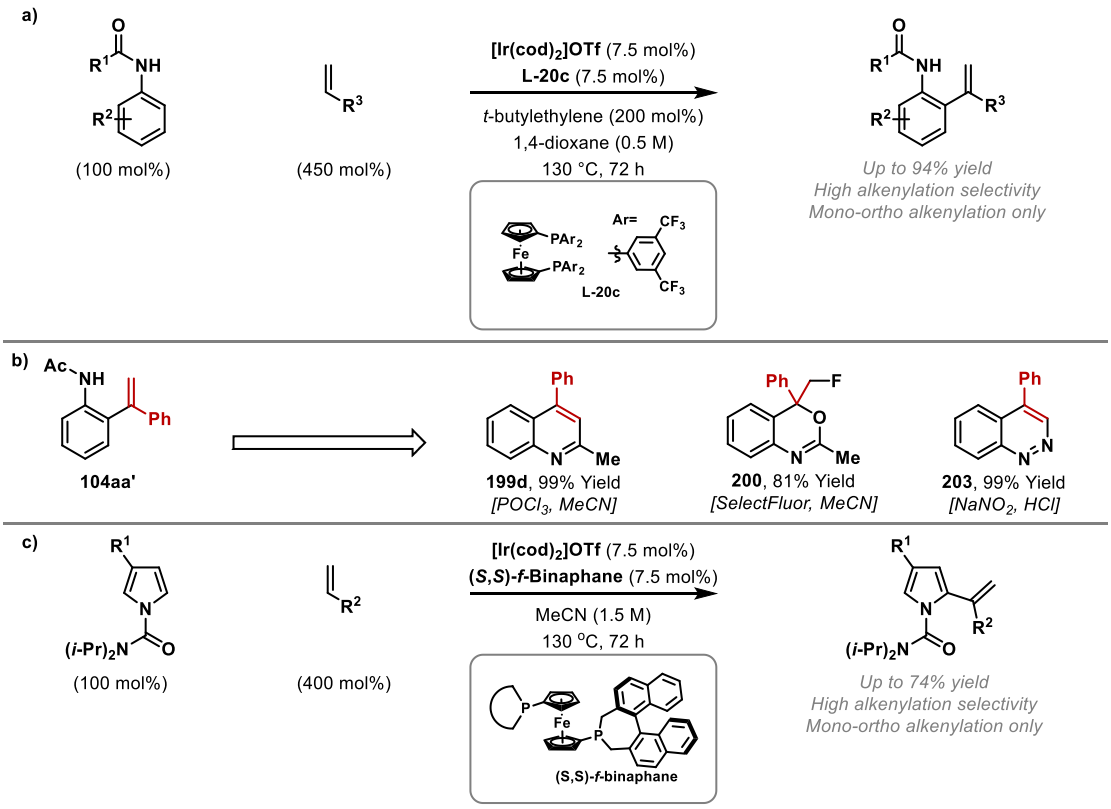
Methodology for Ir(I)-catalysed α-arylation of styrenes has been developed. To gain insight into the mechanistic cycle and to potentially develop a more versatile protocol, hydroarylation product **VII** was subjected to the C–H alkenylation conditions to monitor if dehydrogenation of **VII** occurred to generate product **VIII**. No conversion to alkene **VIII** was observed (Scheme **89a**), supporting the proposal that **VIII** is generated *via* a carbometallation pathway (**IV** to **VI** to **VII**, rather than by dehydrogenation of **VII**). To evaluate the proposed mechanism further, the arylation of *deuterio*-**91k'** with acetanilide **60aa** was conducted (Scheme **89b**). ^{1}H- and ^{2}H NMR analysis of *deuterio*-**104aak'** disclosed deuterium incorporation at the terminal position of the alkene (0.88 D, *44% deuteration*) and the remaining *ortho*-position (0.30 D, *30% deuteration*). This result is consistent with reversible migratory insertion of *deuterio*-**91k'** into the *ortho* Ir(I)–H bond (**IV** to **V**). Subsequent β-hydride or β-deuteride elimination from **V** then occurs, where the latter forms an Ir–D species which in turn can undergo reversible oxidative addition into **60aa** and *deuterio*-**91k'**. Additionally, deuterium incorporation was observed at the methyl of the directing group (0.57 D, *19% deuteration*), suggesting that Ir(I) can also promote enol tautomerisation. Deuterium incorporation in both *ortho*-positions of *deuterio*-**60aa** (0.52 D, *26% deuteration*) and the α-position of alkene *deuterio*-**91k'** (0.43 D, *43% deuteration*) also support reversible hydrometallation. Accordingly, with this ligand system, branched hydroarylation side-product **VII**, forms by C–C reductive elimination from **V** or C–H reductive elimination from **VI**.



Scheme 89: *Proposed mechanistic cycle and deuterium labelling study.*

5.8 – Summary and Conclusions

The design and synthesis of ferrocene-based bisphosphine ligand **L-20c** allowed efficient α-arylation of styrenes *via* dual C–H functionalisation. This protocol offers a regioselective alternative to the classical Pd(II)-catalysed Fujiwara-Moritani reaction and tolerates a wide range of electronically diverse acetanilides and styrene coupling partners (Scheme **90a**). The α-arylation products are synthetically useful and can undergo facile transformation to a range of diverse and interesting *N*-containing heteroaromatics (Scheme **90b**). By employing an alternative ferrocene-based bisphosphine ligand (*S*,*S*)-*f*-binaphane, the protocol was extended to pyrrole derivatives (Scheme **90c**).



Scheme 90: *α-Arylation of styrenes with acetanilide and pyrrole derivatives.*

Evidence gained through ^{13}C KIE's demonstrated that a carbometallative pathway was possible under Ir(I) catalysed conditions (*see* Section **4.4**). It is proposed that ferrocene-based bisphosphine ligand **L-20c** promotes a carbometallation pathway, followed by β-hydride elimination. This is in contrast to the reductive elimination pathways proposed for alkene hydroarylation (*see* Section **4.4**). Deuterium labelling experiments support reversible C–H oxidative addition and hydrometallation (*see* Scheme **89a**) and these results are in line with the original mechanism outlined in Scheme 78b. The properties associated with ferrocene-based bisphosphine ligands that promote β-hydride elimination after carbometallation are currently not fully understood. Further studies are required to gain greater insight into the mechanism and to expand the scope of the methodology.

Chapter 6 – Overall Summary and Conclusions

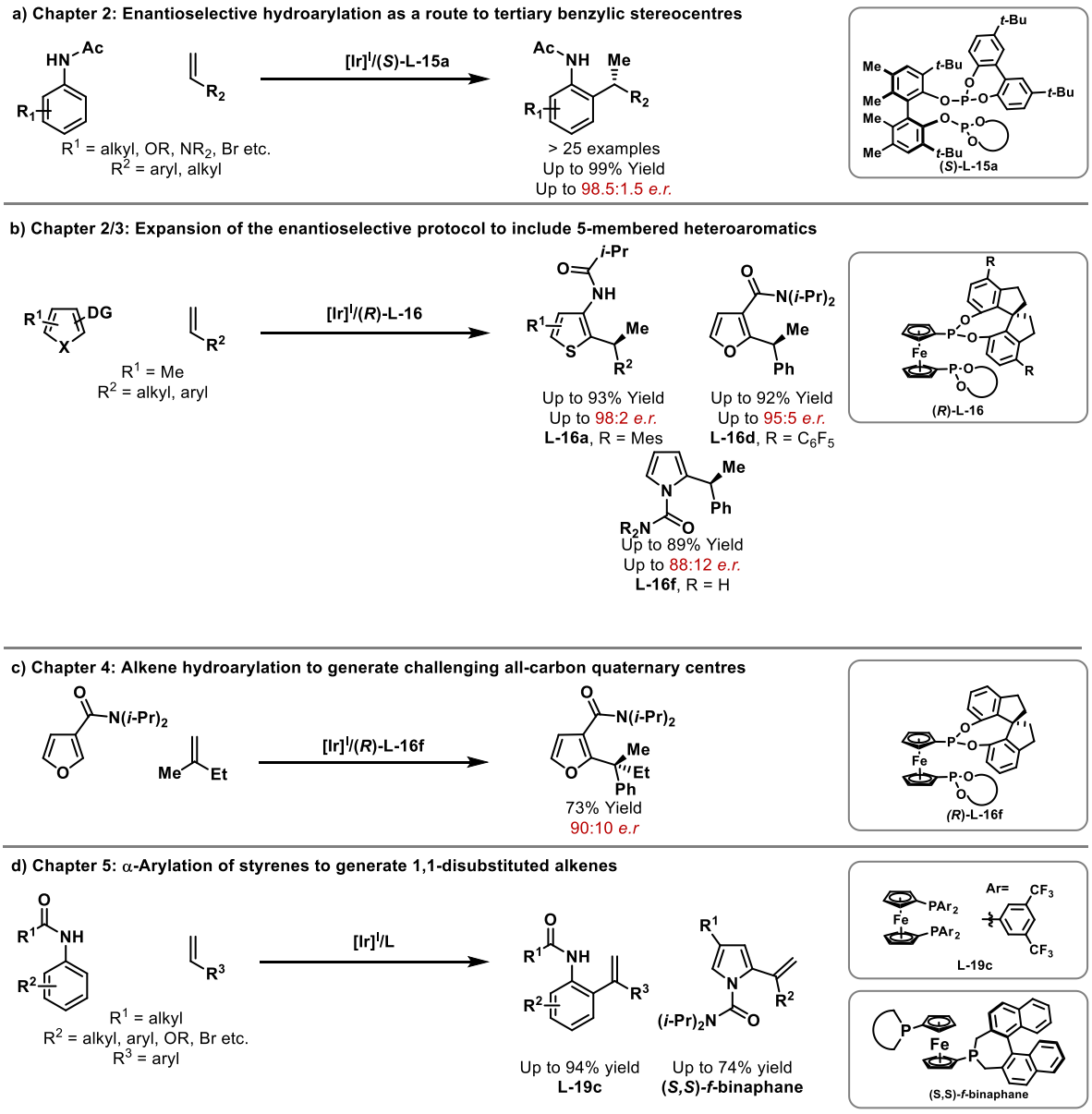
The research presented in this thesis has contributed to the development of a ligand-enabled, highly enantioselective protocol for branch-selective alkene hydroarylation with acetanilide substrates. An extensive screen of commercially available chiral ligands led to a cationic Ir(I)-complex modified with bisphosphite ligand **(*S*)-L-15a**, as designed by Dr. Simon Grélaud. The Ir(I)/**(*S*)-L-15a** system was applicable to the hydroarylation of a range of aryl and alkyl substituted alkenes to afford tertiary benzylic stereocentres in excellent yields and enantiopurity (Scheme **91a**). Development of ferrocene-based bisphosphonite ligand **(*R*)-L-16a** expanded the scope of the hydroarylation reaction to thiophene substrates (Scheme **91b**). These protocols provide an alternative to traditional cross-coupling reactions by circumventing the need for prefunctionalised starting materials. Therefore, an atom and step economical approach has been achieved. This work represents the first general and highly enantioselective protocol for branch-selective hydroarylation of unactivated aliphatic alkenes.

Additionally, in Chapter 3, the Ir(I)/**(*R*)-L-16d–f** catalysed enantioselective branch-selective hydroheteroarylation methodology was expanded to other heteroaromatics (pyrroles, furans), to achieve tertiary benzylic stereocentres in excellent yields and with promising levels of enantioselectivity (up to 95:5 *e.r.*) (Scheme **91b**). Investigations into a chiral ligand which would provide a general protocol for enantioselective branch-selective hydroheteroarylation is currently ongoing at Bristol.

Subsequent studies focused on expanding the Ir(I)/**L-15a** catalysed methodology to the hydroarylation of 1,1-disubstituted alkenes to access highly challenging benzylic all-carbon quaternary centres. This strategy allows the hydroarylation of a range of 1,1-disubstituted alkenes with aryl and heteroaromatic coupling partners. Studies towards an enantioselective protocol are ongoing; good enantioselectivity has been achieved for styrene hydroarylation with a furan substrate using ligand **(*R*)-L-16f** (90:10 *e.r.*) (Scheme **91c**). Deuterium labelling experiments and natural abundance ^{13}C-KIE experiments employing the Singleton method have provided evidence for a catalytic cycle in which carbometallation is the first irreversible and therefore turnover determining step. This contrasts both the non-enantioselective and enantioselective Ir(I)-catalysed hydroarylations of mono-substituted alkenes reported at Bristol. A general protocol to access sterically demanding all-carbon quaternary centres *via* hydroarylation of unactivated alkenes is yet to be reported.

Additionally, the synthesis of ferrocene-based electron-deficient bisphosphine ligand **L-20c** provided access to α-arylated styrenes *via* a dual C–H functionalisation pathway (Scheme **91d**). A carbometallative pathway, followed by β-hydride elimination was invoked to explain the α-arylated products obtained. This contrasts with the reductive elimination pathways proposed for alkene hydroarylation. This protocol is suitable for the hydroarylation of diverse styrenes with a range of substituted acetanilides. The products are synthetically useful as demonstrated by their rapid transformation to interesting *N*-containing heteroaromatics. Through re-evaluation of the ligand, this

protocol was expanded to include pyrrole coupling partners. This strategy offers a regioselective alternative to the classical Pd-catalysed Heck and Fujiwara-Moritani reactions to provide challenging α-arylated styrenes. The properties associated with ferrocene-based bisphosphine ligands that promote a β-hydride elimination pathway are currently not fully understood. Further studies are required to gain greater insight into the mechanism and to expand the scope of the methodology.



Scheme 91: *Enantioselective hydroarylation of mono-substituted alkenes and 1,1-difunctionalised alkenes with a range of arenes and heteroaromatics and α-arylation of styrenes by dual C–H functionalisation*

In summary, the judicious design and synthesis of several bisphosphine ligands has led to Ir(I)-catalysed methodology for the enantio- and branch-selective alkylation and branch-selective alkenylation of a range of aryl and heteroaromatic substrates. The design of new bisphosphine ligands

has provided access to mechanistic pathways and synthetic products in a step and atom economical manner, providing an alternative method to often labour-intensive established cross-coupling reactions.

Chapter 7 – Experimental

7.1 – General Experimental Details

All materials for which a synthetic route is not described or referenced were purchased from commercial sources (Acros, Sigma, Alfa Aesar, Fluorochem, Strem and TCI). All reagents requiring purification were purified using standard laboratory techniques according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966). Catalytic reactions were carried out in Young-type re-sealable tubes. Liquid styrene derivatives were distilled using a Hickman distilling head before use. All other commercially available alkenes were used as received without any further purification. Anhydrous solvents were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. Anhydrous 1,4-dioxane was purchased as anhydrous grade and stored over activated 4Å molecular sieves prior to use. All reactions were performed using dry solvents unless stated otherwise. Et_3N was distilled over CaH_2 and stored over activated 4Å molecular sieves under nitrogen. The removal of the solvents in vacuo was achieved employing rotary evaporators connected with diaphragm pumps (15 mmHg) or, for high-boiling solvents, oil pumps (0.1 mmHg). Materials were then dried on a high-vacuum line prior to analysis. Reactions requiring anhydrous conditions were performed under a nitrogen atmosphere, using Schlenk techniques and flame/oven-dried equipment. In particular, catalytic reactions were carried out in oven dried (minimum 2 hours) or flame dried Young-type re-sealable tubes. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40–63 μm, 230–400 mesh). Ligands were purified by chromatography on deactivated silica gel (stirred overnight with 10% w/w of Et_3N). Thin layer chromatography was performed using aluminium backed 60 F_{254} silica plates. Visualisation was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat. Proton nuclear magnetic resonance spectra (NMR) were recorded on a JEOL ECS 400, Varian 400-MR, Varian VNMR 500a, Varian VNMR 500b or Bruker Advance III HD 500 Cryo. ^1H NMR spectra were recorded at 400 MHz or 500 MHz as stated. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz as stated. In particular, ^{13}C NMR analyses for the determination of KIEs (Singleton method, Chapter 4) were performed using the Bruker 500 Cryo instrument exclusively. Chemical shifts (δ) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), septets (sept), multiplets (m) and broad (br.). Coupling constants (*J*) are quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data ($DEPT^{135}$, COSY, HSQC and HMBC and nOe experiments). Where compounds were isolated as a mixture of isomers (*e.g.* rotamers), they are referred as *A* and *B*. *In situ* yields were determined by employing 1,3,5-trimethoxybenzene as an internal standard. Mass spectra were recorded using a Brüker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS (ESI+ mode), Shimadzu GCMS QP2010+ (EI+ mode), a Bruker Ultraflex II (MALDI), Thermo Scientific Orbitrap Elite (APCI mode) and a Waters Synapt G2S (Nanospray). Infrared spectra were recorded on a Perkin Elmer

Spectrum Two FTIR spectrometer as thin films or solids compressed on a diamond plate. Melting points were determined using Reichert melting point apparatus and are uncorrected. Optical rotations were measured using a ADP440^{+} polarimeter at the concentration and temperature stated. Enantiomeric excess was determined using an Agilent 1290 Infinity chiral SFC as stated for each compound.

7.2 – General Procedures

General procedure A: for deuterium exchange experiments

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with substrate (0.143 mmol, 100 mol%), [Ir(cod)$_2$]BARF (5 mol%) and d^{F}ppb (5.61 mg, 5 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Deuterium oxide (77 μL, 3000 mol%) in 1,4-dioxane (1.5 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 100–150 °C for 24 h, before being cooled to ambient temperature and concentrated *in vacuo.* Purification of the residue by FCC afforded the corresponding *deuterio* compound.

General Procedure B: for the synthesis of silver salts

To a round-bottom flask charged with the relevant substrate (100 mol%) and THF (0.05 M) under nitrogen was added Ag_2O (50 mol%) and the solution was stirred at ambient temperature overnight. The solution was concentrated *in vacuo* to afford the product. *The silver salts were used without further purification.*

General Procedure C: for the hydroarylation of styrenes with benzamide and acetanilide substrates

To An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with substrate (100 mol%), [Ir] (5.0 mol%) and ligand (5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene (450 mol%) and anhydrous 1,4-dioxane (1.5 M concentration with respect to substrate) were added and the tube was fitted with a Young's tap. The reaction mixture was then heated at 100–130 °C for 24 h, before being cooled to ambient temperature and concentrated *in vacuo.* Purification of the residues by FCC afforded the title compounds.

General Procedure D: for the asymmetric hydroheteroarylation of alkenes with thiophenes

A flame-dried tube, fitted with a magnetic stirrer, was charged with thiophene substrate (0.1 mmol), [Ir(cod)$_2$]OTF (5.0 mol%) and **(*R*)-L-16a (**5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene derivative (120 mol%) in anhydrous 1,4-dioxane (0.5 M concentration with respect to substrate) was added. The tube was fitted with a Young's tap and heated to 90–100 °C for 24 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the pure products.

General Procedure E: for the protection of pyrroles

The title compounds was prepared following a literature procedure.[230] A round-bottomed flask was charged with 4-dimethylaminopyridine (10 mol%), suspended in CH_2Cl_2 (1.85 M with respect to the acetyl chloride), under nitrogen. Pyrrole (135 mol%) and triethylamine (100 mol%) were added dropwise. The solution was stirred at ambient temperature for 15 minutes, followed by dropwise addition of the acetyl chloride derivative (100 mol%). The resulting solution was stirred overnight. The reaction mixture was dissolved in diethyl ether and washed with saturated aq. $NaHSO_4$ solution, aq. $NaHCO_3$ and water, before being dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by FCC afforded the title compounds.

General Procedure F: for the carbamoyl protection of *N*-heteroaromatics

The title compounds were prepared following a modified literature procedure.[231] A flame-dried round-bottom flask was charged with NaH (60% in mineral oil, 120 mol%), suspended in THF (1.2 M) under nitrogen. The suspension was cooled to 0 °C and a solution of pyrrole or indole (100 mol%) in THF (0.9 M) was added dropwise over 10 minutes. The solution was stirred at 0 °C for 1 h, followed by dropwise addition of acetyl chloride derivative (110 mol%) in THF (0.8 M) over 10 minutes. The solution was then warmed to ambient temperature and stirred overnight. The reaction was quenched by the addition of saturated aq. NH_4Cl solution and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by FCC afforded the title compounds.

General Procedure G: for the carbamoyl protection of other heteroaromatics

The title compounds were prepared following a modified literature procedure.[232]A flame-dried round-bottom flask was charged with *N*,*N*-diisopropyl carbamoyl chloride (461 mg, 2.82 mmol) and toluene (1.5 mL), under nitrogen. A solution of substrate (2.56 mmol), toluene (1.0 mL) and triethylamine (0.428 mL, 3.07 mmol) were added dropwise over 10 minutes. The resulting solution was heated to 85 °C and stirred for 6 h. The solution was warmed to ambient temperature before being quenched with aq. HCl solution (5 M, 3.0 mL). The organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC or recrystallisation afforded the title compounds.

General Procedure H: for the carbamoyl protection of heteroaromatics from acids

The title compounds were prepared following a modified literature procedure.[233] An oven-dried flask was charged with the corresponding acid (7.80 mmol) and DMF (2 drops) in CH_2Cl_2 (15 mL) under nitrogen and the solution was cooled to 0 °C. Oxalyl chloride (0.739 mL, 8.74 mmol) was added dropwise over 5 minutes and the resulting solution was stirred for 2 h at 0 °C. The solvent was removed *in vacuo*, before the residue was dissolved in CH_2Cl_2 (15 mL), purged with nitrogen and cooled to 0 °C. Diisopropylamine (2.19 mL, 15.6 mmol) was added dropwise over 5 minutes, before the solution was warmed to ambient temperature and stirred overnight. The reaction mixture was quenched with aq. HCl

(1 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, washed with saturated aq. NaOH (10 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC afforded the title compounds.

General Procedure I: for the hydroarylation of styrene with heteroaromatics

A flame-dried tube, fitted with a magnetic stirrer, was charged with substrate (0.143 mmol), $[Ir(cod)_2]OTf$ (5.0 mol%) and d^Fppb (5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene derivative (450 mol%) in anhydrous 1,4-dioxane (1.5 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 120 °C for 24 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the title compounds.

General Procedure J: for the asymmetric hydroarylation of pyrroles

A flame-dried tube, fitted with a magnetic stirrer, was charged with substrate (0.143 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and **(*R*)-L-16c** or **(*R*)-L-16f** (7.5 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene derivative (450 mol%) in anhydrous MeCN (1.5 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 130 °C for 48 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the title compounds.

General Procedure K: for the asymmetric hydroarylation of furans

A flame-dried tube, fitted with a magnetic stirrer, was charged with substrate (0.1 mmol), $[Ir(cod)_2]BARF$ (5.0 mol%) and **(*R*)-L-16a** or **(*R*)-L-16d** (5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Alkene derivative (400 mol%) in anhydrous 1,2-DCB (0.5 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 90 °C for 48 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the title compounds.

General Procedure L: for the asymmetric hydroarylation of alternative furans

A flame-dried tube, fitted with a magnetic stirrer, was charged with **139** (0.143 mmol), $[Ir(cod)_2]BARF$ (5.0 mol%) and **(*R*)-L-16c** (5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene (400 mol%) in anhydrous 1,4-dioxane (1.0 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 100–120 °C for 24–48 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the title compounds.

General Procedure M: for the preparation of α-methyl styrene substrates

To a flame-dried flask was added methyltriphenylphosphonium bromide (120 mol%) in anhydrous THF (0.5 M) under nitrogen and the solution was cooled to 0 °C. Potassium *tert*-butoxide (120 mol%) was added portion-wise and the resulting solution was stirred at 0 °C for 1–2 h. The relative ketone was added dropwise and after stirring for 20 mins at 0 °C the solution was warmed to ambient temperature and stirred overnight. The solution was filtered with hexane and concentrated *in vacuo* to provide the crude product. Purification by FCC afforded the pure styrene.

General Procedure N: for the preparation of amide substrates from acyl chlorides

To a flame-dried flask was added acyl chloride (100 mol%) in dry CH_2Cl_2 (0.5 M) under nitrogen. The solution was cooled to 0 °C, before the dropwise addition of diethylamine (400 mol%). The reaction was warmed to ambient temperature and stirred overnight. The solution was washed with aq. HCl (2 M, 2 × 10 mL) and aq. $NaHCO_3$ (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude product. Purification of the residue by FCC afforded the pure amide.

General Procedure O: for the preparation of amide substrates from carboxylic acids

To a flame dried Schlenk tube was added carboxylic acid (100 mol%) in dry CH_2Cl_2 (0.8 M), under nitrogen. Thionyl chloride (240 mol%) was added and the tube was sealed and heated to reflux for 1 h. The resulting solution was cooled to ambient temperature and concentrated *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (0.5 M) and cooled to 0 °C, before the dropwise addition of diethylamine (400 mol%). The reaction was warmed to ambient temperature and stirred overnight. The solution was washed with aq. HCl (2 M, 2 × 10 mL), aq. $NaHCO_3$ (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude product. Purification of the residue by FCC afforded the pure amide.

General Procedure P: for the formation of quaternary centres on benzamide substrates

A flame-dried tube, fitted with a magnetic stirrer, was charged with substrate (0.1 mmol), $[Ir(cod)_2]$BARF (5.0 mol%) and **(*rac*)-L-15f** (5.0 mol%). The tube was taken into a glove box where styrene (400 mol%) and anhydrous 1,4-dioxane (1.0 M concentration with respect to substrate) was added. The tube was fitted with a Young's tap and removed from the glove box. The reaction mixture was then heated to 120 °C for 72 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the pure products.

General Procedure Q: for the formation of quaternary centres on 5-membered heteroaromatics

A flame-dried tube, fitted with a magnetic stirrer, was charged with substrate (0.1 mmol), $[Ir(cod)_2]$BARF (5.0 mol%) and **(*rac*)-L-15a (**5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene derivative (150–400 mol%) in anhydrous 1,4-dioxane (1.0 M concentration with respect to substrate) was added. The tube was fitted with a Young's tap and the reaction mixture was heated to 120 °C for 16–48 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC afforded the pure products.

General Procedure R: for the preparation of ligands L-20a–L-20d

An oven-dried multi-neck flask fitted with a condenser was charged with Mg turnings (500 mol%) and purged with nitrogen. One iodine bead was added, and the solids were suspended in dry Et_2O (4.50 mL/mmol of Mg). To activate the magnesium, the solution was heated to reflux with a heatgun. Once cooled to ambient temperature, the fluorinated aryl bromide (600 mol%) was added *via* syringe and the solution was heated at reflux for 1 h. The solution was cooled to ambient temperature, before 1,1'-bis(dichlorophosphino)ferrocene (100 mol%) dissolved in dry Et_2O (6.00 mL/mmol of 1,1'-bis(dichlorophosphino)ferrocene) was added dropwise. The solution was stirred overnight. Unreacted Grignard reagent was quenched by the addition of water (15 mL/mmol). The resulting solution was extracted with CH_2Cl_2 (3 × 25 mL/mmol). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 and filtered through Celite® to afford the crude product as an orange oil. Purification by FCC (hexane/EtOAc 0–5%) followed by recrystallisation with cyclohexane afforded the title compounds.

General Procedure S: for the preparation of alkene substrates

The title compounds were prepared following a modified literature procedure.[234] A resealable tube was charged with the corresponding bromo-reagent (2.40 mmol), vinyl boronic acid pinacol ester (0.448 mL, 2.64 mmol), $Pd(OAc)_2$ (21.6 mg, 0.096 mmol), SPhos (78.8 mg, 0.192 mmol) and K_3PO_4 (1.53 g, 7.21 mmol). The tube was purged with nitrogen before the addition of 1,4-dioxane (9.60 mL) and water (0.216 mL). The reaction tube was sealed and heated to 80 °C for 2 h. The resulting solution was filtered through celite® with EtOAc, before washing with H_2O (20 mL) and brine (20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residues by FCC afforded the title compounds.

General Procedure T: for the preparation of acetanilide substrates

The title compounds were synthesised following a modified literature procedure.[235] To an ice-cooled solution of aniline (100 mol%), EtOAc (0.6 M with respect to substrate), and triethylamine (105 mol%), was added acid chloride (105 mol%) dropwise. The reaction was warmed to ambient temperature and stirred overnight. The resulting mixture was dissolved in EtOAc, before being washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC or recrystallisation afforded pure acetanilide.

General Procedure U: for the branch-selective α-arylation of styrenes with acetanilide substrates

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with substrate (100 mol%), $[Ir(cod)_2]OTf$ (7.5–10 mol%) and **L-20c** (7.5–10 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene derivative (450 mol%) and *t*-butylethylene (200 mol%) in anhydrous 1,4-dioxane (0.5–1.0 M concentration with respect to substrate) were added and the tube was fitted with a

Young's tap. The reaction mixture was then heated at 130 °C for 72–96 h, before being cooled to ambient temperature and concentrated *in vacuo.* Purification of the residues by FCC afforded the title compounds. The alkenylation and hydroarylation products were easily separated by FCC. In some cases a second column was performed to remove an impurity associated with degradation of the ligand.

General Procedure V: for the synthesis of quinolines

The title compounds were prepared by a modified literature procedure.[227] A 3-necked, oven-dried flask, fitted with a condensor was charged with the corresponding alkene (100 mol%) and purged with nitrogen. MeCN (0.03 M with respect to alkene) and $POCl_3$ (1000 mol%) were added and the solution was heated at reflux and stirred overnight. The reaction was cooled to ambient temperature and diluted with water (2.0 mL). Aq. 1 M NaOH solution was added until pH 8 was reached and the resulting solution was extracted with EtOAc (3 × 5 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residues by FCC afforded the title compounds.

General Procedure W: for branch-selective Heck-like reaction on pyrrole substrates

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with pyrrole substrate (0.1 mmol), $[Ir(cod)_2]OTf$ (7.5–10 mol%) and (*S*,*S*)-*f*-Binaphane (7.5–10 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene derivative (400 mol%) in anhydrous MeCN (1.5 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated at 130 °C for 48–72 h, before being cooled to ambient temperature and concentrated *in vacuo.* Purification of the residues by FCC afforded the title compounds.

7.3 – Synthesis of Ir(I)-complexes

NaBARF

To a flame dried 3-neck round-bottom flask fitted with a condenser and dropping-funnel was added $NaBF_4$ (1.50 g, 13.7 mmol), Mg (2.20 g, 88.8 mmol), 1 iodine crystal and Et_2O (320 mL) under nitrogen. The solution was heated to reflux with a heat gun for 1 minute. The mixture was warmed to ambient temperature and 3,5-trifluoromethylbromobenzene (13.2 mL, 76.5 mmol) in Et_2O (100 mL) was added dropwise and then heated at reflux for 30 minutes. The reaction mixture was cooled to ambient temperature and aq. Na_2CO_3 (0.7 M, 430 mL) was added slowly. The resulting solution was stirred for an additional 30 minutes. The mixture was then filtered, and the filtrate was extracted with Et_2O (2 × 200 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (12.6 g, quantitative) as a light brown powder. ^{1}H NMR (400 MHz, Acetone-d_6): δ 7.88 – 7.76 (8H, m), 7.68 (4H, s). *The material was used in the next reaction without further purification.*

Bis(cyclooctadiene)iridium(I) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate ([Ir(cod)$_2$]BARF)

The title compound was prepared following a literature procedure.[116] To a solution of chloro(1,5-cyclooctadiene)iridium (I) dimer (110 mg, 0.163 mmol) and NaBARF (300 mg, 0.339 mmol) in CH_2Cl_2 (5 mL) was added 1,5-cyclooctadiene (0.375 mL, 3.06 mmol). The reaction mixture was stirred at ambient temperature for 2 hours and then filtered through Celite®. The solution was concentrated *in vacuo* and the residue was dried under vacuum (0.01 mmHg) to afford the title compound (406 mg, 94%) as a black solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (8H, s), 7.54 (4H, s), 4.99 (8H, s), 2.40 (8H, m), 2.25 (8H, m); ^{19}F NMR (377 MHz, $CDCl_3$): -62.2; ^{13}C NMR (101 MHz, $CDCl_3$): 161.8 (1:1:1:1 pattern, $^1J_{B\text{-}C}$ = 50.0 Hz), 134.9, 129.1 (qq, $^2J_{F\text{-}C}$ = 32.0 Hz, $^4J_{F\text{-}C}$ = 5.5 Hz), 124.7 (q, $^1J_{F\text{-}C}$ = 272.5 Hz), 117.7, 101.2, 30.5; ^{19}F NMR (377 MHz, $CDCl_3$): -62.2. *The spectroscopic proprieties for this compound were consistent with the data available in the literature.*[116]

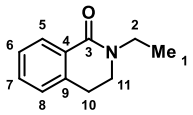
Ir(cod)$_2$OTF was synthesised by Dr. Giacomo Crisenza. [Ir(cod)$_2$]BF$_6$ and [Ir(cod)$_2$]PF$_6$ were synthesised by Dr. Simon Grélaud. [Ir(cod)(OMe)]$_2$ was purchased from commercial sources.

7.4 – Experimental Procedures and Data for the Studies in Chapter 2

7.4.1 – Substrate Synthesis

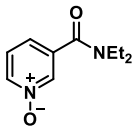
60a, ***60c***, ***90d***, ***91a***, ***101*** *and* ***103*** *were purchased from commercial sources (Sigma)*

2-Ethyl-3,4-dihydroisoquinolin-1(2*H*)-one (98)



The title compound was prepared following a literature procedure.[236] To a stirred suspension of NaH (60% in mineral oil, 377 mg, 9.43 mmol) in dry DMF (1.30 mL) was added a solution of 3,4-dihydroisoquinolin-1-(2H)-one (555 mg, 3.77 mmol) in dry DMF (3.80 mL) dropwise, followed by iodoethane (0.600 mL, 7.55 mmol). The resulting mixture was heated to 80 °C and stirred for 1 h. The reaction was cooled to 0 °C and quenched with water (10 mL), followed by extraction with diethyl ether (3 × 10 mL). The organic extracts were combined, washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 40%) afforded the title compound (565 mg, 85%) as a yellow oil. ν_{max}/cm^{-1}: 2974 (m), 2929 (m), 1639 (m), 1481 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 7.40 (1H, ddd, *J* = 7.5, 1.5, 1.5 Hz, C**7**-H), 7.33 (1H, ddd, *J* = 7.5, 1.5, 1.5 Hz, C**6**-H), 7.16 (1H, d, *J* = 7.5 Hz, C**8**-H), 3.63 (2H, q, *J* = 7.5 Hz, C**2**-H_2), 3.55 (2H, t, *J* = 6.5 Hz, C**11**-H_2), 2.99 (2H, t, *J* = 6.5 Hz, C**10**-H_2). 1.22 (3H t, *J* = 7.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2 (C**3**), 138.1 (C**9**), 131.6 (C**7**), 129.9 (C**4**), 128.3 (C**5**), 127.1 (C**6**), 126.9 (C**8**), 45.6 (C**11**), 42.3 (C**2**), 28.4 (C**10**), 12.9 (C**1**); HRMS: (ESI^+) calculated for $C_{11}H_{14}NO$ 176.1070. Found $[M+H]^+$ 176.1074.

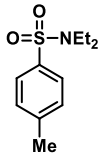
3-(*N*,*N*-Diethylcarbamoyl)pyridine 1-oxide (100)



The title compound was prepared following a literature procedure.[237] A flame-dried round-bottom flask was charged with *N*,*N*-diethylnicotinamide (0.377 mL, 2.24 mmol) and purged with nitrogen. MeCN (4 mL) and urea hydrogen peroxide (444 mg, 4.70 mmol) were added, followed by the dropwise addition of trifluoroacetic anhydride (0.623 mL, 4.48 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 4.5 hours. The reaction was quenched by the addition of saturated aq. sodium thiosulfate solution (4 mL) which resulted in the formation of a yellow precipitate. Aq. HCl solution (0.5 M, 8 mL) was then added to the stirred solution, which was then extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Purification of the residue by FCC (EtOAc/MeOH 20%) afforded

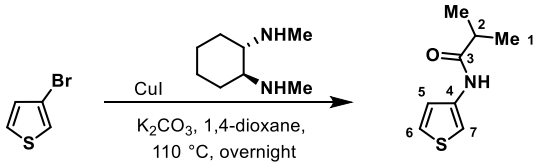
the title compound (255 mg, 59%) as a yellow powder. ν_{max}/cm^{-1}: 2875 (m), 1633 (s), 1434 (m), 1295 (m), 1254 (m), 1014 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 – 8.20 (2H, m), 7.31 (1H, m), 7.24 (1H, ddd, *J* = 8.0, 1.0, 1,0 Hz), 3.53 (2H, m), 3.27 (2H, m), 1.30 – 1.10 (6H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.6, 139.6, 137.29, 136.4, 126.2, 123.6, 43.5, 39.9, 14.5, 12.9; m.p. 55–57 °C ($CDCl_3$) (Lit.[238] 62–63 °C, EtOAc). *The spectroscopic proprieties for this compound were consistent with the data available in the literature.*[239]

_N,N_-Diethyl-4-methylbenzenesulfonamide (102)



The title compounds were prepared following a literature procedure.[240] A flame-dried round-bottom flask was charged with *p*-toluene sulfonyl chloride (1.00 g, 5.25 mmol) and purged with nitrogen. CH_2Cl_2 (15 mL) and trimethylamine (1.5 mL, 10.5 mmol) were added and the solution was cooled to 0 ℃. $HNEt_2$ (1.10 mL, 10.5 mmol) was added dropwise with vigorous stirring. The solution was stirred at 0 ℃ for 1 h before being warmed to ambient temperature and stirred over night. The reaction was quenched by the addition of aq. HCl solution (2 M, 12 mL). The organic layer was separated, washed with aq. saturated $NaHCO_3$ solution (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (0.70 g, 59%) as colourless needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (2H, d, *J* = 8.0 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 3.21 (4H, q, *J* = 7.0 Hz), 2.40 (3H, s), 1.11 (6H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.0, 137.5, 129.7, 127.1, 42.1, 21.6, 14.3, m.p. 57–58 °C ($CDCl_3$) (Lit.[241] 55–57 °C, *no recrystallisation solvent specified). The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[242]

_N_-(Thiophen-3-yl)isobutyramide (114a)

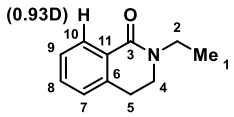


To a resealable tube was added isobutyramide (448 mg, 5.15 mmol), CuI (82.0 mg, 0.430 mmol) and K_2CO_3 (2.55 g 18.45 mmol) under nitrogen. 1,4-Dioxane (12 mL) was added followed by 3-bromothiophene (402 µL, 4.29 mmol) and diamine ligand (68.0 µL, 0.430 mmol). The tube was sealed and heated at 110 °C for 18 h. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite® and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (648 mg, 89%) as a colourless solid. ν_{max}/cm^{-1}: 3285 (s), 3099 (m), 2970 (s), 1657 (s), 1537 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (1H, ddd, *J* = 3.0, 1.5, 1.5 Hz, C**7**-H),

7.54 (1H, s, N-H), 7.21 (1H, ddd, *J* = 5.0, 3.0, 1.5 Hz, C**6**-H), 6.99 (1H, ddd, *J* = 5.0, 1.5, 1.5 Hz, C**5**-H), 2.50 (1H, heptd, *J* = 7.0, 1.5 Hz, C**2**-H), 1.25 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6 (C**3**), 135.8 (C**4**), 124.6 (C**6**), 121.1 (C**5**), 110.2 (C**7**), 36.3 (C**2**), 19.8 (C**1**); HRMS: (ESI^+) calculated for $C_8H_{12}NOS$ 170.0634. Found $[M+H]^+$ 170.0631. m.p. 137–139 °C.

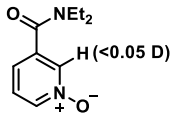
7.4.2 – Deuterium Labelling Experiments

*deuterio-**98***



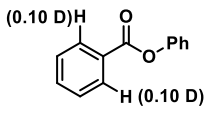
General procedure A: The reaction was run at 100 °C. Purification of the residue by FCC (hexane/EtOAc 70%) afforded *deuterio-**98*** as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 8.03 (0.07H, m, C**10**-H), 7.39 (1H, t, *J* = 7.5 Hz, C**8**-H), 7.32 (1H, d, *J* = 7.5 Hz, C**9**-H), 7.15 (1H, dd, *J* = 7.5, 1.5 Hz, C**7**-H), 3.62 (1.70H, q, *J* = 7.0 Hz, C**2**-H_2), 3.54 (2H, t, *J* = 6.5 Hz, C**4**-H_2), 2.98 (2H, t, *J* = 6.5 Hz, C**5**-H_2), 1.21 (3H, t, *J* = 7.0 Hz, C**1**-H_3); ^{2}H NMR (61 MHz, $CHCl_3$): δ 8.32 – 7.88 (0.93D, m, C**10**-H), 3.79 – 3.41 (0.30D, m, C**2**-H_2). *Deuterium incorporation was calculated by integration of both ^{1}H NMR and ^{2}D NMR signals.*

deuterio-**100**



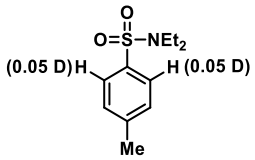
General Procedure A: The reaction was run at 120 °C. Purification of the residue by FCC (hexane/EtOAc 0–15%) afforded *deuterio*-**100** as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.20 (2H, m), 7.31 (1H, m), 7.24 (1H, dt, *J* = 8.0, 1.0 Hz), 3.53 (2H, d, *J* = 8.0 Hz), 3.27 (2H, d, *J* = 8.0 Hz), 1.30 – 1.10 (6H, m). *No deuterium incorporation was observed by ^{1}H or ^{2}D NMR analysis.*

deuterio-**101**



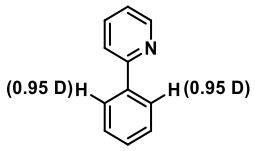
General Procedure A: The reaction was run at 150 °C. Purification of the residue by FCC (hexane/EtOAc 30%) afforded *deuterio*-**101** as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 – 8.18 (1.8H, m), 7.65 (1H, m), 7.57 – 7.48 (2H, m), 7.48 – 7.40 (2H, m), 7.30 (1H, m), 7.25 – 7.16 (2H, m); ^{2}H NMR (500 MHz, $CHCl_3$): δ 8.25 (0.2D, s). *Deuterium incorporation was calculated by integration of both ^{1}H and ^{2}D NMR signals.*

deuterio-**102**



General Procedure A: The reaction was run at 100 °C. Purification of the residue by FCC (hexane/EtOAc 50%) afforded *deuterio*-**102** as colourless needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1.90H, d, *J* = 8.0 Hz), 7.27 (2H, d, *J* = 8.0 Hz), 3.20 (4H, q, *J* = 7.0 Hz), 2.40 (3H, s), 1.10 (6H, t, *J* = 7.0 Hz); ^{2}H NMR (500 MHz, $CHCl_3$): δ 7.70 (0.10D, s). *Deuterium incorporation was calculated by integration of both ^{1}H and ^{2}D NMR signals.*

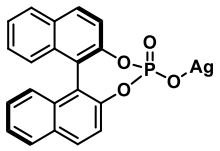
deuterio-**103**



General Procedure A: The reaction was run at 120 °C. Purification of the residue by FCC (hexane/EtOAc 30%) afforded *deuterio*-**103** as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (1H, ddd, *J* = 5.0, 2.0, 2.0 Hz,), 8.00 (0.10H, m), 7.79 – 7.69 (2H, m), 7.51 – 7.45 (2H, m), 7.42 (1H, m), 7.23 (1H, ddd, *J* = 7.0, 5.0, 2.0 Hz); ^{2}H NMR (500 MHz, $CHCl_3$): δ 8.01 (1.90D, s). *Deuterium incorporation was calculated by integration of ^{1}H NMR signals.*

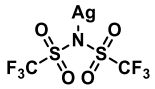
7.4.3 – Chiral Anions Synthesis

(((4*R*)-4-Oxidodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)oxy)silver ((*R*)-Ag-106b)



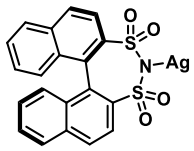
General Procedure B: The reaction was carried out with (*R*)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate (1.10 g, 3.19 mmol). The title compound (1.01 g, 69%) was afforded as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (2H, d, *J* = 9.0 Hz), 8.02 (2H d, *J* = 8.0 Hz), 7.47 – 7.41 (4H, m), 7.30 (2H, ddd, *J* = 8.0, 7.0, 1.5 Hz), 7.22 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (101 MHz, DMSO-d_6): δ 149.9 (d, *J* = 9.5 Hz), 131.9, 130.4, 129.9, 128.4, 126.1, 126.0, 124.5, 122.4, 121.7; ^{31}P NMR (162 MHz, DMSO-D_6): δ 6.56; m.p 261–263 °C (Et_2O) (Lit.[243] 261 °C, decaline). *The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[243]

1,1,1-Trifluoro-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide ((*R*)-Ag-108a)



General Procedure B: The reaction was carried out with trifluoromethanesulfonimide (100 mg, 0.356 mmol). The title compound (53.3 mg, 38%) was afforded as a black residue; ^{13}C NMR (101 MHz, CD_3CN): δ 117.4; ^{19}F NMR (377 MHz, CD_3CN): δ -80.11. *The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[244-245]

(3,3,5,5-Tetraoxido-4*H*-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dithiazepin-4-yl)silver ((*R*)-Ag-108b)



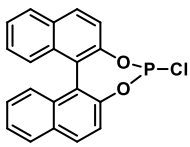
General Procedure B: The reaction was carried out with (*R*)-1,1'-binaphthyl-2-2'-disulfonimide (50.0 mg, 0.126 mmol) . The title compound (55.5 mg, 88%) was afforded as a silver solid. ν_{max}/cm^{-1}: 3073 (m), 2284 (m), 1584 (m), 1294 (s); ^{1}H NMR (400 MHz, CD_3CN): δ 8.17 – 8.04 (6H, m, ArC<u>H</u>), 7.58 (2H, ddd, J = 8.0, 7.0, 1.0 Hz, ArC<u>H</u>), 7.30 (2H, ddd, J = 8.0, 7.0, 1.0 Hz, ArC<u>H</u>), 7.15 (2H, ddd, J = 8.0, 1.0, 1.0 Hz, ArC<u>H</u>); ^{13}C NMR (101 MHz, CD_3CN): δ 140.7, 135.5, 134.3, 133.1, 130.0, 129.5, 128.7, 128.4, 127.9, 123.9; HRMS: (ESI^-) calculated for $C_{20}H_{12}NO_4S_2$ 394.0213. Found $[M]^-$ 394.0210; m.p. 287–290 °C (CD_3CN).

7.4.4 – Ligand Synthesis

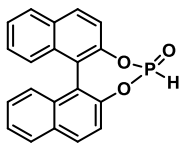
Commercial ligands were purchased from Strem or Sigma

D^{F}ppb was synthesised by Dr. Giacomo Crisenza

4-Chlorodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine



112

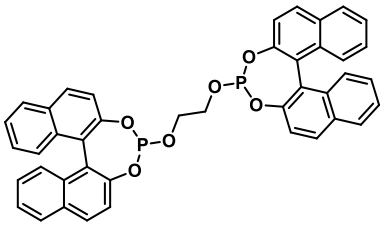


113

An oven-dried Schlenk tube fitted with a magnetic stirrer was charged with (*R*)-1,1'-bi(2-napthol) (2.00 g, 6.99 mmol). The tube was fitted with a rubber septum and purged with nitrogen. The solid was dissolved in dry and degassed toluene (40 mL) and the resulting solution was cooled to –78 °C. Distilled PCl_3 (0.671 mL, 7.69 mmol) and distilled trimethylamine (1.94 mL, 14.0 mmol) were added dropwise

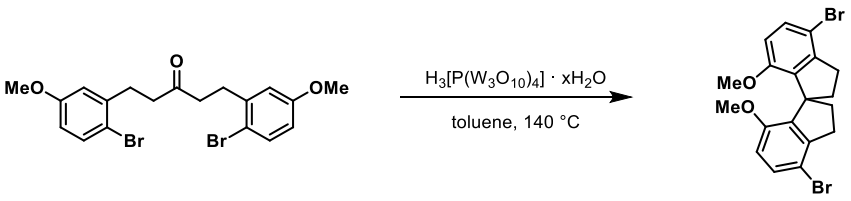
to the stirred solution. The resulting mixture was warmed to ambient temperature and stirred overnight. The resulting slurry was filtered through an oven-dried glass-fibre filter paper cannula and the salts were washed with dry and degassed toluene (3 × 10 mL). The solvent was removed under reduced pressure and the crude solid was washed with hexane (3 × 5 mL), filtered and dried under vacuum to furnish the title compound (1.43 g, 58%, 0.7:0.3 mixture of **112**:**113**) as an off-white powder. *Note: an inert atmosphere was maintained at all times;* ^{31}P NMR ($CDCl_3$, 162 MHz): 178.9 (**112**), 14.4 (**113**). *The phosphorus NMR data of these compounds were consistent with the data available in the literature.*[246-247] *The mixture was used in the next stage of the reaction without further purification.*

1,2-Bis(dinaphtho[2,1-d:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)ethane (L-14)



To an oven dried Schlenk tube was added **112/113** (250 mg, 0.510 mmol of **112**). The tube was fitted with a rubber septum and purged with nitrogen. Dry Et_2O (29 mL, freeze-pump-thawed) and ethylene glycol (14 µL, 0.260 mmol) was added. To the stirred solution was added distilled NEt_3 (0.160 mL, 1.12 mmol) dropwise at 0 °C. The solution was warmed to ambient temperature and stirred overnight. The resulting precipitate was collected by filtration through an oven dried sinter under nitrogen and washed with dry Et_2O (2 × 5 mL). The solvent was removed *in vacuo*. Analysis by ^{31}P NMR revealed the title product, alongside unassigned impurities. ^{31}P NMR ($CDCl_3$, 162 MHz): 141.5. *The phosphorus NMR data of the title compound is consistent with the data available in the literature. Note: an inert atmosphere was maintained at all times; Purification of the crude product was unsuccessful.*[248]

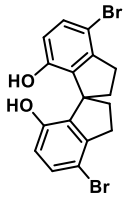
4,4'-Dibromo-7,7'-dimethoxy-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (165)



The title compound was synthesised following a literature procedure.[133] A solution of 1,5-bis(2-bromo-5-methoxyphenyl)pentan-3-one **164**[133] (5.73 g, 12.57 mmol) and phosphotungstic acid hydrate (5.44 g, 1.89 mmol) in toluene (75 mL) was heated at 140 °C under Dean-Stark conditions overnight. The resulting mixture was filtered through celite® with $CHCl_3$ and concentrated *in vacuo*. Purification of the reside by FCC (hexane/EtOAc 5%) afforded the title compound (6.05 g, 64%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.16 (2H, m), 6.52 (2H, d, *J* = 8.5 Hz), 3.52 (6H, s), 3.06 (2H, ddd,

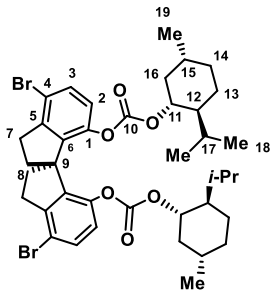
J = 16.0, 9.0, 3.5 Hz), 3.00 – 2.85 (2H, m), 2.37 – 2.26 (2H, m), 2.16 (2H, ddd, *J* = 12.5, 9.0, 3.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.8, 145.0, 138.2, 130.5, 111.0, 110.7, 62.1, 55.5, 38.1, 33.3; m.p. 155–157 °C ($CDCl_3$) (Lit.[133] 160–163 °C, *no recrystallisation solvent specified). The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[133]

4,4'-Dibromo-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol (166)



The title compound was synthesised following a literature procedure.[133] To a solution of 4,4'-dibromo-7,7'-dimethoxy-2,2',3,3'-tetrahydro-1,1'-spirobi[indene] (13.3 g, 30.3 mmol) in CH_2Cl_2 (120 mL) under nitrogen was added BBr_3 (73.0 mL, 72.7 mmol, 1 M in CH_2Cl_2) dropwise at -78 °C. The mixture was warmed to ambient temperature and stirred overnight. The mixture was then diluted with CH_2Cl_2 (145 mL), cooled to 0 °C and quenched by the slow addition of saturated aq. $NaHCO_3$ (290 mL). The organic layer was collected, washed with brine (120 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give crude 4,4'-dibromo-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol (11.4 g, 92%) as a colourless foam. *This material was used in the next step without further purification.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.5 Hz), 6.75 – 6.48 (2H, m), 4.53 (2H, s), 3.13 – 2.87 (4H, m), 2.46 – 2.13 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.1, 145.6, 132.7, 132.4, 116.7, 111.2, 77.5, 77.2, 76.8, 60.5, 36.9, 32.9; m.p. 153–155 °C (hexane) (Lit.[249] 148–149 °C, *hexane). The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[249]

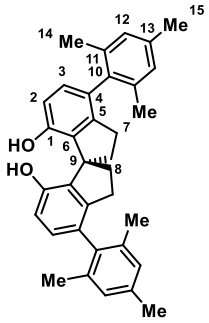
(*R*)-4,4'-Dibromo-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diyl bis((1*S*,2*R*,5*S*)-2-isopropyl-5- methylcyclohexyl) bis(carbonate) ((*R*)-168)



The title compound was synthesised following a literature procedure.[133] To a solution of NaOH (4.88 g, 122 mmol) in H_2O (82 mL) was added 4,4'-dibromo-2,2',3,3'-tetrahydro1,1'-spirobi[indene]-7,7'-diol (11.4 g, 27.8 mmol) and a solution of tetrabutylammonium bromide (4.13 g, 12.8 mmol) in $CHCl_3$ (82 mL). (1*R*)-(−)-menthyl chloroformate (17.9 mL, 83.4 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 20 minutes, before the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic phases were

combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by recrystallisation (hexane, hot) afforded the title compound (6.97 g, 36%) as a colourless solid. ν_{max}/cm^{-1}: 2954 (m), 2869 (m), 1754 (s), 1462 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (2H, d, *J* = 8.5 Hz, C**3**-H), 6.93 (2H, d, *J* = 8.5 Hz, C**2**-H), 4.33 (2H, ddd, *J* = 11.0, 11.0, 5.0 Hz, C**11**-H), 3.16 – 2.88 (4H, m, C**8**-H_2), 2.38 – 2.15 (4H, m, C**7**-H_2), 1.94 – 1.81 (2H, m, CH_2), 1.67 – 1.60 (6H, m, CH, CH_2), 1.47 – 1.33 (2H, m, C**12**-H), 1.31 – 1.21 (2H, m, CH), 1.03 – 0.76 (18H, m, C**18**-H_3, CH_2), 0.68 (6H, d, *J* = 7.0 Hz, C**19**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.5 (C**10**), 146.9 (C**1**), 145.5 (C**5**), 140.3 (C**6**), 131.3 (C**3**), 122.2 (C**2**), 116.4 (C**4**), 79.2 (C**11**), 61.8 C**9**), 46.7 (CH), 40.4 (CH_2), 37.9 (C**7**), 34.2 (CH_2), 33.0 (C**8**), 31.4 (C**12**), 25.8 (CH_2), 23.3 (CH_2), 22.2 (C**18**), 20.9 (C**18**), 16.3 (C**19**); HRMS (Nanospray) calculated for $C_{39}H_{51}O_6{}^{79}Br_2$ 773.2052 Found $[M+H]^+$ 773.2074; m.p. 101–102 °C (CH_2Cl_2); $[\alpha]^{24}_D$ = + 9.1 (c = 0.52, CH_2Cl_2).

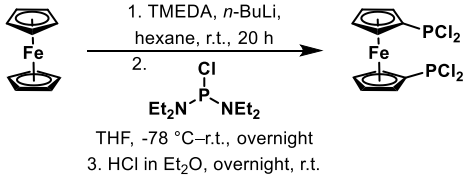
(*R*)-4,4'-Dimesityl-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol



To a round-bottom flask fitted with a condenser was added (*R*)-4,4'-dibromo-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diyl bis((1*S*,2*R*,5*S*)-2-isopropyl-5- methylcyclohexyl) bis(carbonate) (2.33 g, 3.00 mmol), $MesB(OH)_2$ (1.71 g, 10.5 mmol), $Pd(PPh_3)_4$ (208 mg, 0.180 mmol), Na_2CO_3 (1.27 g, 12.0 mmol), DME (20 mL), H_2O (8 mL) and EtOH (4 mL). The solution was heated at 100 °C for 16 h. The reaction mixture was cooled to ambient temperature and filtered through a pad of Celite® with CH_2Cl_2 and concentrated *in vacuo*. The residue was filtered through a pad of silica (hexane/EtOAc 20%) and concentrated *in vacuo*. The crude product was dissolved in THF/H_2O/EtOH (1:1:1, 90 mL) and KOH (3.00 g, 53.0 mmol) was added. The solution was heated at reflux for 1 h, before the being concentrated *in vacuo*. The mixture was acidified to pH=1 with aq. HCl (2 M) and extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the reside by FCC (toluene/EtOAc 2%) afforded the desired products (523 mg, 36%) as a colourless solid. ν_{max}/cm^{-1}: 3502 (m), 2938 (m), 2856 (m), 1472 (s), 1276 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (4H, s, C**12**-H), 6.93 (2H, d, *J* = 8.0 Hz, C**3**-H), 6.78 (2H, d, *J* = 8.0 Hz, C**2**-H), 4.67 (2H, br. s, OH) 2.75 – 2.61 (2H, m, C**7**-H_2), 2.62 – 2.50 (2H, m, C**7**-H_2), 2.34 (6H, s, C**15**-H_3), 2.31 – 2.23 (4H, m, C**8**-H_2), 1.99 (12H, br. s, C**14**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.0 (C**1**), 144.0 (C**6**), 137.1 (ArC), 136.7 (ArC), 136.4 (ArC), 136.0 (ArC), 130.9 (C**4**), 130.7 (ArC), 130.7 (C**3**), 128.2 (C**12**), 115.1 (C**2**), 58.5 (C**9**), 37.7 (C**8**), 30.7 (C**7**), 21.2 (C**15**), 20.6 (C**14**), 20.5 (C**14**); HRMS: (MALDI)

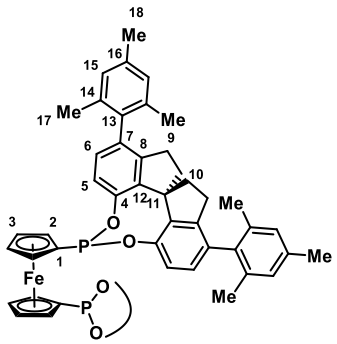
calculated for $C_{35}H_{36}O_2Na$ 511.2608. Found $[M+Na]^+$ 511.2617; m.p. 260 °C degradation (toluene); $[\alpha]^{21}_D$ = - 44.7 (c = 0.20, CH_2Cl_2).

1,1'-Bis(dichlorophosphino)ferrocene (193)



The title compound was prepared following a literature procedure.[201] Ferrocene (1.86 g, 10.0 mmol) was added to a round-bottomed Schlenk flask, purged with nitrogen and dissolved in dry and deoxygenated hexane (47 mL). Distilled tetramethylethylenediamine (3.15 mL, 21.0 mmol) was added dropwise to the stirred solution over 10 minutes at ambient temperature, followed by *n*-BuLi (1.60 M in hexanes, 13.8 mL, 22.0 mmol). The solution was stirred for 22 h, before the resulting suspension was cooled to -78 °C in an acetone/dry ice bath. *N*,*N*-Bis(diethylamino)chlorophosphine (4.40 mL, 21.0 mmol) dissolved in dry and deoxygenated THF (14 mL) was added dropwise to the stirred suspension. Once the addition had finished, the mixture was warmed to ambient temperature and stirred for 4 days. The reaction mixture was then cooled to -78 °C in an acetone/dry ice bath and treated with a solution of HCl in diethyl ether (2.00 M, 80.0 mL, 160 mmol). The solution was warmed to ambient temperature and stirred overnight. The resulting salts were filtered off through an oven-dried sinter funnel under a flow of nitrogen. The salts were washed with dry hexane (7 × 10 mL) and the filtrate was collected and concentrated *in vacuo*, affording the product (3.28 g, 85%) as an orange powder. *Note: an inert atmosphere was maintained at all times and the compound was stored in a glovebox.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 – 4.62 (8H, m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 163.3. *The title compound was used without further purification. The spectroscopic properties for this compound were consistent with the data available in the literature.*[201]

(*R*)-L-16a

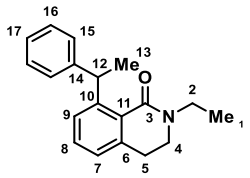


To a Schlenk tube was added (*R*)-4,4'-Dimesityl-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol (1.20 g, 2.46 mmol), ferrocene **193** (476 mg, 1.23 mmol), DMAP (30.0 mg, 0.246 mmol) and THF/CH_2Cl_2 (2:1, 36 mL) under nitrogen. The solution was cooled to 0 °C and NEt_3 (0.823 mL, 5.90 mmol) was

added dropwise. The solution was warmed to ambient temperature and stirred overnight. The mixture was filtered through a pad of Celite® with Et_2O and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 3%, SiO_2 deactivated with 10% of Et_3N) to afford the title ligand (1.09 g, 73%) as an orange solid. ν_{max}/cm^{-1}: 2946 (m), 2855 (m), 1468 (m), 1219 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 6.98 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 6.88 – 6.85 (4H, m, C**14**-<u>H</u>), 6.93 – 6.88 (4H, m, C**15**-H), 6.53 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 6.13 (2H, d, *J* = 8.0 Hz, ArC<u>H</u>), 4.68 – 4.63 (2H, m, ferrocene), 4.61 – 4.56 (2H, m, ferrocene), 4.36 – 4.31 (2H, m, ferrocene), 3.87 – 3.80 (2H, m, ferrocene), 2.71 – 2.57 (4H, m, C**9**-<u>H_2</u>), 2.42 – 2.25 (16H, m, C**9**-<u>H_2</u>, C**18**-<u>H_3</u>), 2.16 – 2.07 (4H, m, C**10**-<u>H_2</u>), 2.05 – 1.89 (28H, m, C**10**-<u>H_2</u>, C**17**-<u>H_3</u>); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.7 (Ar<u>C</u>), 145.1 (t, *J* = 4.9 Hz, C**4**), 143.6 (Ar<u>C</u>), 143.0 (Ar<u>C</u>), 142.5 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 137.4 (Ar<u>C</u>), 137.2 (Ar<u>C</u>), 136.7 (Ar<u>C</u>), 136.5 (Ar<u>C</u>), 136.2 (Ar<u>C</u>), 136.2 (Ar<u>C</u>), 136.0 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 134.3 (Ar<u>C</u>), 133.4 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 122.9 (Ar<u>C</u>H), 121.1 (Ar<u>C</u>H), 73.2 (ferrocene), 72.8 (ferrocene), 72.7 (t, *J* = 4.2 Hz, C**1**), 71.8 (ferrocene), 71.0 (ferrocene), 59.7 (C**11**), 38.3 (C**10**), 37.8 (C**10**), 30.2 (C**9**), 29.7 (C**9**), 21.2 (C**18**), 21.2 (C**18**), 20.7 (C**17**), 20.7 (C**17**), 20.3 (C**17**); ^{31}P NMR (162 MHz, $CDCl_3$): δ 158.8; HRMS: (Nanospray) calculated for $C_{80}H_{76}FeO_4P_2Na$ $[M+Na]^+$ 1241.4463. Found 1241.4426.

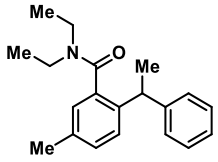
7.4.5 – Hydroarylation Reactions

2-Ethyl-8-(1-phenylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (99a')



General procedure C: The reaction was carried out with $[Ir(cod)_2]$BARF (5 mol%) and d^Fppb (5 mol%). The reaction mixture was heated at 100 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 50–60%) afforded the title compound (4.36 mg, 11%) as a colourless oil. ν_{max}/cm^{-1}: 2961 (m), 2928 (s) 1639 (s), 1597 (m), 1478 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.25 (4H, m, C**15**-<u>H</u>, C**16**-<u>H</u>), 7.24 – 7.20 (1H, m, C**8**-<u>H</u>), 7.16 – 7.09 (2H, m, C**9**-<u>H</u>, C**17**-<u>H</u>), 6.97 (1H, ddd, *J* = 7.5, 1.0, 1.0 Hz, C**7**-<u>H</u>), 5.81 (1H, q, *J* = 7.0 Hz, C**12**-<u>H</u>), 3.62 (2H, q, *J* = 7.0 Hz, C**2**-<u>H_2</u>), 3.54 – 3.41 (2H, m, C**4**-<u>H_2</u>), 3.00 – 2.82 (2H, m, C**5**-<u>H_2</u>), 1.63 (3H, d, *J* = 7.0 Hz, C**13**-<u>H_3</u>), 1.20 (1H, t, *J* = 7.0 Hz, C**1**-<u>H_3</u>); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.5 (C3), 149.5 (C**10**), 147.2 (C**14**), 139.5 (C**6**), 130.7 (C**8**), 128.3 (C**17**), 128.2 (C**15**), 128.1 (C**16**), 127.9 (C**11**), 125.6 (C**9**), 124.8 (C**17**), 45.6 (C**4**), 42.4 (C**2**), 38.9 (C**12**), 30.4 (C**5**), 22.2 (C**13**), 13.3 (C**1**); HRMS: (ESI^+) calculated for $C_{19}H_{21}NONa$ 302.1515. Found $[M+Na]^+$ 302.1520.

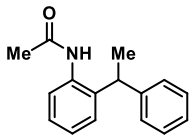
***N,N*-Diethyl-5-methyl-2-(1-phenylethyl)benzamide (93da')**



General procedure C: The reaction was carried out with $[Ir(cod)_2]BARF$ (5 mol%) and Walphos (SL-J005-1) (5 mol%). The reaction mixture was heated at 100 °C for 24 h. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (19.1 mg, 45%, 0.7:0.3 mixture of rotamers *A:B*, >25:1 branched:linear, 71:29 *e.r.*) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.03 (7H, m, *A*+*B*), 6.97 – 6.90 (1H, m, *A*+*B*), 4.37 (0.7 H, q, *J* = 7.0 Hz, *A*), 4.21 (0.3H, q, *J* = 7.0 Hz, *B*), 3.78 (0.3 H, dq, *J* = 14.0, 7.0 Hz, *B*), 3.61 (0.7 H, dq, *J* = 14.0, 7.0 Hz, *A*), 3.39 (0.3H, dq, *J* = 14.0, 7.0 Hz *B*), 3.34 – 3.10 (1.3H, m, *2A* + *B*), 2.70 (0.7H, dq, *J* = 14.0, 7.0 Hz, *A*), 2.35 (0.7H, dq, *J* = 14.0, 7.0 Hz, *A*), 2.30 (2.1H, s, *A*), 2.29 (0.9H, s, *B*) 1.60 (3H, d, *J* = 7.0 Hz, *A*+*B*), 1.28 (0.9H, dd, *J* = 7.0, 7.0 Hz, *B*), 1.16 (2.1H, dd, *J* = 7.0, 7.0 Hz, *A*), 1.10 (0.9H, dd, *J* = 7.0, 7.0 Hz, *B*), 0.83 (2.1H, dd, *J* = 7.0, 7.0 Hz, *A*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0 (*A*), 171.0 (*B*), 146.2 (*A*), 145.3 (*B*), 140.4 (*B*), 139.1 (*A*), 137.3 (*A*), 137.2 (B)135.7 (*B*), 135.6 (*B*), 130.5 (*B*), 129.9 (*A*), 129.5 (*A*), 128.4 (*B*), 127.9 (*A*), 127.8 (*A*), 127.7 (*B*), 127.3 (*A*), 126.2 (*A*), 126.1 (*A*), 126.0 (*B*), 43.1 (*B*), 42.6 (*A*), 40.8 (*A*), 40.2 (*B*), 38.8 (*B*), 38.7 (*A*), 22.9 (*A*), 21.2 (*B*), 21.2 (*B*), 21.0 (*A*), 14.2 (*B*), 13.6 (*A*), 13.0 (*B*), 12.9 (*A*). *The spectroscopic proprieties were consistent with the data available in literature.*[116]

SFC Conditions: (DAICEL CHIRALPAK-IC column (25 cm), CO_2:MeOH 99:1 – 98:2, over 20 mins, 5 mL/min, 140 bars, 60 °C). Retention times: 22.3 minutes (minor), 27.1 minutes (major), e.r. = 71:29.

***N*-(2-(1-Phenylethyl)phenyl)acetamide (96aa')**

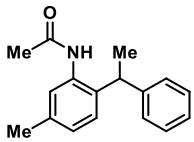


General Procedure C: The reaction was carried out with $[Ir(cod)_2]OTf$ (5 mol%) and (*R*)-DM-SEGPHOS (5.17 mg, 5 mol%). The reaction mixture was heated at 130 °C for 24 h. Purification of the residue by FCC (toluene/EtOAc 10%–30%) afforded the title compound (7.2 mg, 21%, 9:1 mixture of rotamers *A:B*, 3.5:1 branched:linear, 76.5:23.5 *e.r.*) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (0.9H, d, *J* = 7.5 Hz, *A*), 7.43 (0.9H, d, *J* = 7.5 Hz, *A*), 7.47 – 6.88 (7.2H, m, *A*+*B*), 6.72 (1H, s, *A*+*B*), 4.36- 4.23 (0.1H, m, B), 4.16 (0.9H, q, *J* = 7.0 Hz, *A*), 1.94 (2.7H, s, *A*), 1.63 (3.3H, d, *J* = 7.0 Hz, *A*+*B*);^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 145.4, 136.6, 135.4, 129.3, 127.4, 127.3, 127.3, 126.9, 125.6, 125.0, 41.0, 24.1, 21.8. *The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[117]

*Characteristic signals for the linear regioisomer **97aa'***: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 – 2.81 (4H, m), 1.94 (3H, s).

SFC Conditions: (DAICEL CHIRALPAK-IC column (25 cm), CO_2:MeOH 99:1 – 97:3, 1% every 15 mins, 2 mL/min, 140 bars, 40 °C). Retention times: 47.6 minutes (minor), 49.0 minutes (major), e.r. = 76.5:23.5.

***N*-(5-Methyl-2-(1-phenylethyl)phenyl)acetamide (96ca')**



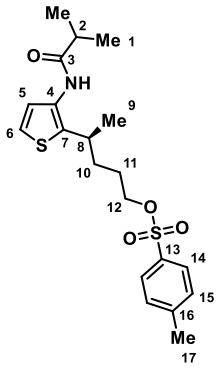
General procedure C: The reaction was carried out with $[Ir(cod)_2]OTf$ (5 mol%) and (*S*,*S*)-BDPP (5 mol%). The reaction mixture was heated at 120 °C for 24 h. Purification of the residue by FCC (toluene/EtOAc 10–30%) afforded the title compound (25.8 mg, 71%, 0.9:0.1 mixture of rotamers *A:B*, 1:1 branched:linear, 62.5:37.5 *e.r.*) as a colourless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (0.9H, s, *A*), 7.42 – 7.10 (6.2H, m, *A*+*B*), 7.04 (1H, d, *J* = 8.0 Hz, *A*), 6.73 (1H, br. s, *A*+*B*), 4.30 – 4.20 (0.1H, m, *B*), 4.13 (0.9H, q, *J* = 7.0 Hz, *A*), 2.34 (3H, s, *A*+*B*), 1.94 (2.7H, s, *A*), 1.75 (0.3H, s, *B*), 1.61 (3H, d, *J* = 7.0 Hz, *A*+*B*); ^{13}C NMR (101 MHz, $CDCl_3$, *major rotamer signals only*): δ 168.3, 145.7, 137.1, 135.1, 133.7, 129.2, 127.3, 127.3, 126.9, 126.4, 125.6, 40.7, 24.3, 21.9, 21.3; m.p. 116–118 °C (hexane/CH_2Cl_2), (Lit. 117–119 °C, hexane/CH_2Cl_2). *The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[117]

*Characteristic signals for the linear regioisomer **97ca':*** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 – 2.79 (4H, m), 2.31 (3H, s), 1.94 (3H, s).

SFC Conditions: (DAICEL CHIRALPAK-IC column (25 cm), CO_2:MeOH 99:1 – 97:3, 1% every 15 mins, 2 mL/min, 140 bars, 40 °C). Retention times: 43.7 minutes (minor), 46.2 minutes (major), e.r. = 63:38.

*Note: for alkenylation products see Section **7.7***

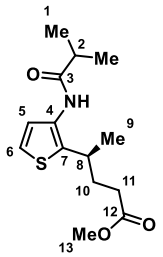
4-(3-Isobutyramidothiophen-2-yl)pentyl 4-methylbenzenesulfonate (115al')



General Procedure D: The reaction was run at 90 °C. Purification of the residue by FCC (hexane/EtOAc 30–40%) afforded the title compound (33.9 mg, 82% , 92:8 *e.r.*) as a yellow oil. ν_{max}/cm^{-1}: 3276 (m), 2965 (m), 1658 (s), 1354 (s), 1174 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.5 Hz, C**14**-H), 7.34 (2H, d, *J* = 8.5 Hz, C**15**-H), 7.29 – 7.23 (1H, m, C**5**-H), 7.11 (1H, s, N-H), 7.08 (1H, d, *J* = 5.5 Hz, C**6**-H), 4.04 – 3.95 (2H, m, C**12**-H_2), 3.02 (1H, p, *J* = 7.0 Hz, C**8**-H), 2.54 – 2.50 (1H, m, C**2**-H), 2.45 (1H, s, C**17**-H_3), 1.74 – 1.53 (4H, m, C**10**-H_2, C**11**-H_2), 1.31 – 1.11 (9H, m, C**1**-H_3, C**9**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5 (C**3**), 145.0 (C**16**), 137.5 (C**7**), 132.9 (C**13**), 131.0 (C**4**), 130.0 (C**15**) 127.9 (C**14**), 124.9 (C**5**), 121.2 (C**6**), 70.6 (C**12**), 35.9 (C**2**), 34.8 (C**10**), 31.7 (C**8**), 26.6 (C**11**), 23.0 (C**9**), 21.8 (C**17**), 19.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{28}NO_4S_2$ 410.1454. Found $[M+H]^+$ 410.1453; $[\alpha]^{22}_D$ = - 17.3 (c = 0.20, CH_2Cl_2).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 85:15, 2 mL/min, 140 bars, 60 °C). Retention times: 13.8 minutes (minor), 15.0 minutes (major), e.r. = 92:8.

Methyl 4-(3-isobutyramidothiophen-2-yl)pentanoate (115aj')



General Procedure D: The reaction was run at 100 °C. Purification of the residue by FCC (hexane/EtOAc 30–40%) afforded the title compound (8.40 mg, 30%, 96:4 *e.r.*) as a colourless oil. ν_{max}/cm^{-1}: 3289 (m), 2966 (m), 1734 (s), 1659 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, s, N-H), 7.55 (1H, d, *J* = 5.5 Hz, C**5**-H), 7.09 (1H, d, *J* = 5.5 Hz, C**6**-H), 3.72 (3H, s, C**13**-H_3), 3.12 (1H, h, *J* = 7.0 Hz, C**8**-H), 2.66 (1H, hept, *J* = 7.0 Hz, C**2**-H), 2.41 (1H, ddd, *J* = 16.0, 8.0, 4.5 Hz, C**11**-H_2), 2.23 (1H, ddd, *J* = 16.0, 8.0, 4.5 Hz, C**11**-H_2), 1.90 – 1.74 (2H, m, C**10**-H_2), 1.33 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 1.25 (6H, d, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5 (C**3**, C**12**), 134.3 (C**7**), 132.3 (C**4**), 124.3 (C**5**), 121.1 (C**6**), 52.1 (C**13**), 35.9 (C**2**), 34.7 (C**10**), 31.4 (C**11**), 30.9 (C**8**), 22.0 (C**9**), 19.9

(C**1**), 19.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{14}H_{22}NO_3S$ 284.1315. Found $[M+H]^+$ 284.1316; $[\alpha]^{25}_D$ = + 21.5 (c = 0.20, CH_2Cl_2).

SFC Conditions: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 99:1 to 96:4 over 20 minutes, 2 mL/min, 140 bars, 60 °C). Retention times: 12.4 (minor), 12.9 minutes (major), e.r. = 96:4.

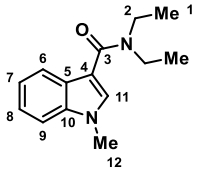
7.5 – Experimental Procedures and Data for the Studies in Chapter 3

7.5.1 – Substrate Synthesis

116 *was purchased from commercial sources (Sigma).*

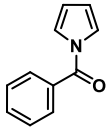
91c', ***91d'*** *and* ***91h'*** *were purchased from commercial sources (Sigma, Acros).*

_N,N_-Diethyl-1-methyl-1_H_-indole-3-carboxamide (119)



The title compound was prepared following a literature procedure.[250] A 50 mL round-bottomed flask was charged with *N,N*-diethyl-1-methyl-1H-indole-3-carboxamide (175 mg, 1.00 mmol), CH_2Cl_2 (20 mL) and DMF (50 μL) under nitrogen. Oxalyl chloride (0.254 mL, 3.00 mmol) was added dropwise to the stirred solution over ten minutes and the resulting mixture was stirred at ambient temperature for 1.5 hours, before being heated to reflux for 1 hour. The reaction was cooled to ambient temperature, before being concentrated *in vacuo.* The residue was taken up in CH_2Cl_2 (20 mL) and cooled to 0 ℃, before diethylamine (0.310 mL, 3.00 mmol) was added dropwise. The resulting solution was warmed to ambient temperature and stirred overnight. The reaction mixture was washed with aq. HCl solution (1 M, 10 mL) and the organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo.* Purification of the residue by FCC (CH_2Cl_2/MeOH 10%) afforded the title compound (182 mg, 79%) as an orange oil; ν_{max}/cm^{-1}: 2970 (m), 2932 (m), 1603 (s), 1532 (s), 1243 (s), 1100 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz, C**6**-H), 7.32 (1H, ddd, *J* = 8.0 Hz, 1.0, 1.0 Hz, C**9**-H), 7.30 (1H, s, C**11**-H), 7.27 (1H, m, C**8**-H), 7.19 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**7**-H), 3.80 (3H, s, C**12**-H_3), 3.58 (4H, q, *J* = 7.0 Hz, C**2**-H_2), 1.22 (6H, t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 (C**3**), 136.5 (C**10**), 129.5 (C**11**), 126.8 (C**5**), 122.5 (C**8**), 121.0 (C**7**), 120.7 (C**6**), 111.4 (C**4**), 109.6 (C**9**), 41.4 (C**2**), 33.2 (C**12**), 14.0 (C**1**); HRMS: (ESI^+) calculated for $C_{14}H_{18}N_2ONa$ 253.1311. Found $[M+Na]^+$ 253.1316.

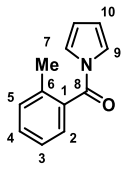
1-Benzoyl-1_H_-pyrrole (121a)



General Procedure E: The reaction was carried out with benzoyl chloride (0.860 mL, 7.40 mmol). Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (927 mg, 73%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.73 (2H, m), 7.60 (1H, m), 7.54 – 7.47 (2H,

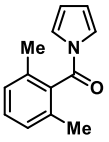
m), 7.31 – 7.27 (2H, m), 6.35 (2H, dd, *J* = 2.5, 2.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 133.4, 132.4, 129.6, 128.6, 121.4, 113.3. *The spectroscopic proprieties for this compound were consistent with the data available in the literature.*[251]

(1*H*-Pyrrol-1-yl)(*σ*-tolyl)methanone (121b)



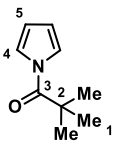
General Procedure E: The reaction was carried out with *σ*-toluoylchloride (0.480 mL, 3.70 mmol). Purification of the residue by FCC (toluene) afforded the title compound (380 mg, 55%) as a colourless oil. ν_{max}/cm^{-1}: 1699 (s), 1465 (s), 1399 (m), 1324 (s), 1309 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (1H, ddd, *J* = 7.5, 1.5, 1.5 Hz, C**3**-H), 7.38 (1H, dd, *J* = 7.5, 1.5 Hz, C**2**-H), 7.30 (2H, m, C**4**-H, C**5**-H), 7.17 – 7.12 (2H, m, C**9**-H), 6.35 – 6.28 (2H, m, C**10**-H), 2.34 (3H, s, C**7**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (C**8**), 136.6 (C**1**), 133.8 (C**6**), 131.0 (C**4**), 130.9 (C**3**), 127.9 (C**2**), 125.6 (C**5**), 120.8 (C**9**), 113.6 (C**10**), 19.5 (C**7**); HRMS: (ESI$^+$) calculated for $C_{12}H_{11}NONa$ 208.0733. Found $[M+Na]^+$ 208.0736.

(2,6-Dimethylphenyl)(1*H*-pyrrol-1-yl)methanone (121c)



General Procedure E: The reaction was carried out with 2,6-dimethylbenzoyl chloride (224 mg, 1.33 mmol). Purification of the residue by FCC (hexane/EtOAc 20%) afforded the title compound (175 mg, 73%) as colourless needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, br. s), 7.27 (1H, t, *J* = 7.5 Hz), 7.09 (2H, d, *J* = 7.5 Hz), 6.48 (1H, br. s), 6.39 (1H, br. s), 6.22 (1H, br. s), 2.21 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 134.9, 134.7, 129.9, 127.7, 121.2, 118.6, 114.1, 113.8, 19.3; m.p. 61–63 °C ($CDCl_3$) (Lit.[252] 59 °C, *no recrystallisation solvent specified). The spectroscopic properties of this compound were consistent with the data available in the literature.*[252]

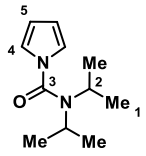
1-(*t*-Butylcarbonyl)pyrrole (123)



General Procedure E: The reaction was carried out with trimethylacetyl chloride (0.911 mL, 7.40 mmol). Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (667 mg, 60%) as a colourless liquid. ν_{max}/cm^{-1}: 2981 (m), 2936 (m), 1702 (s), 1460 (s); ^{1}H NMR (400 MHz,

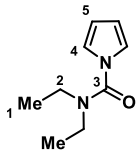
$CDCl_3$): δ 7.46 – 7.42 (2H, m, C**4**-H), 6.30 – 6.22 (2H, m, C**5**-H), 1.46 (9H, s, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0 (C**3**), 120.7 (C**4**), 112.0 (C**5**), 40.8 (C**2**), 28.7 (C**1**); HRMS: (APCI) calculated for $C_9H_{13}NO$ 152.1070. Found $[M+H]^+$ 152.1069.

***N,N*-Diisopropyl-1*H*-pyrrole-1-carboxamide (126a)**



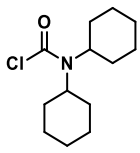
General Procedure F: The reaction was carried out with diisopropylcarbamic chloride (2.26 g, 0.139 mol). Purification of the residue by FCC (hexane/EtOAc 20%) afforded the title compound (2.46 g, quantitative) as colourless needles. ν_{max}/cm^{-1}: 2971 (m), 2934 (m), 1679 (s), 1430 (s), 1332 (s), 1318 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 – 6.95 (2H, m, C**4**-H), 6.24 – 6.19 (2H, m, C**5**-H), 3.83 (2H, hept, J = 6.5 Hz, C**2**-H), 1.37 (12H, d, J = 6.5 Hz, C**1**-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8 (C**3**), 120.2 (C**4**), 110.1 (C**5**), 48.7 (C**2**), 21.2 (C**1**); HRMS: (ESI^+) calculated for $C_{11}H_{19}N_2O$ 195.1492. Found $[M+H]^+$ 195.1492; m.p. 73–75 °C ($CDCl_3$).

***N,N*-Diethyl-1*H*-pyrrole-1-carboxamide (126b)**



General Procedure F: The reaction was carried out with diethylcarbamic chloride (0.415 mL, 3.28 mmol). Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (480 mg, 97%) as a colourless oil. ν_{max}/cm^{-1}: 2979 (m), 2940 (m), 1675 (s), 1421 (s), 1288 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (2H, dd, J = 2.5, 2.5 Hz, C**4**-H), 6.23 (2H, dd, J = 2.5, 2.5 Hz, C**5**-H), 3.44 (4H, q, J = 7.0 Hz, C**2**-H_2), 1.24 (6H, t, J = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.4 (C**3**), 120.4 (C**4**), 110.5 (C**5**), 42.6 (C**2**), 13.4 (C**1**); HRMS: (ESI^+) calculated for $C_9H_{15}N_2ONa$ 189.099834. Found $[M+Na]^+$ 189.098978.

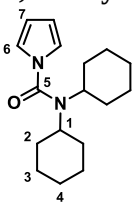
Dicyclohexylcarbamic chloride



The title compound was prepared following a literature procedure.[253] To a solution of triphosgene (451 mg, 1.52 mmol) in dry toluene (5 mL) under nitrogen, was added dicyclohexylamine (1.00 mL, 5.02 mmol) at -5 °C over 5 minutes. After stirring for 1 h the solution warmed to ambient temperature and

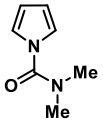
stirred for 24 h. The solids were removed by filtration and washed with toluene (3 ×10 mL). The filtrate was concentrated *in vacuo* to afford the title compound (775 mg, 70%) as a colourless solid which was used in the next step without further purification.

***N*,*N*-Dicyclohexyl-1*H*-pyrrole-1-carboxamide (126c)**



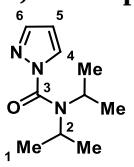
General Procedure F: The reaction was carried out with dicyclohexylcarbamic chloride (400 mg, 1.49 mmol). Purification of the residue by FCC (hexane/EtOAc 10–20%) afforded the title compound (346 mg, 85%) as a colourless solid. ν_{max}/cm^{-1}: 2929 (m), 2853 (m), 1676 (s) 1424 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 – 6.64 (2H, m, C**6**-H), 6.59 – 5.94 (2H, m, C**7**-H), 3.39 – 3.26 (2H, m, C**1**-H), 2.08 – 1.93 (4H, m, Cy), 1.86 – 1.57 (10H, m, Cy), 1.36 – 1.06 (6H, m, Cy); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0 (C**5**), 120.2 (C**6**), 110.1 (C**7**), 58.2 (C**1**), 31.3 (C**2**), 26.2 (C**3**), 25.4 (C**4**); HRMS: (ESI+) calculated for $C_{17}H_{27}N_2O$ 275.2118. Found [M+H]+ 275.2119; m.p. 96–98 °C ($CDCl_3$).

***N*,*N*-Dimethyl-1*H*-pyrrole-1-carboxamide (126d)**



General Procedure F: The reaction was carried out with dimethylcarbamic chloride (1.51 mL, 16.4 mmol). Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (1.92 g, 93%) as colourless needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (2H, dd, *J* = 3.0, 2.0 Hz), 6.22 (2H, dd, *J* = 3.0, 2.0 Hz), 3.09 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.9, 120.7, 110.6, 38.7; m.p. 56–57 °C ($CDCl_3$) (Lit.[254] 70–72 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[254]

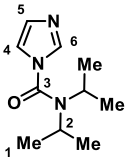
***N*,*N*-Diisopropyl-1*H*-pyrazole-1-carboxamide (129)**



General procedure G: The reaction was carried out with pyrazole. Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (490 mg, 98%) as a colourless oil. ν_{max}/cm^{-1}: 2974 (m), 1686 (s), 1438 (s), 1343 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (1H, dd, *J* = 3.0, 1.5 Hz, C**6**-H), 7.63 – 7.56 (1H, m, C**4**-H), 6.33 (1H, dd, *J* = 3.0, 1.5 Hz, C**5**-H), 4.21 – 4.02 (2H, m, C**2**-H), 1.38 (12H,

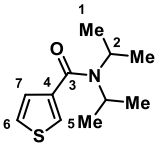
d, *J* = 7.0 Hz, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.7 (C**3**), 141.1 (C**4**), 131.4 (C**6**), 106.7 (C**5**), 48.9 (C**2**), 20.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{10}H_{17}N_3ONa$ 218.1264. Found $[M+Na]^+$ 218.1265.

***N,N*-Diisopropyl-1*H*-imidazole-1-carboxamide (130)**



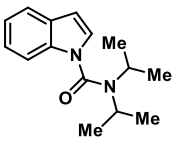
General procedure G: The reaction was carried out with imidazole. Purification of the residue by recrystallisation (hexane/EtOAc 10%) afforded the title compound (409 mg, 82%) as colourless crystals. ν_{max}/cm^{-1}: 3115 (m), 2974 (m), 1678 (s) 1433 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.71 (1H, m, C**6**-H), 7.18 – 7.11 (1H, m, C**5**-H), 7.08 – 7.03 (1H, m, C**4**-H), 3.75 (2H, hept, *J* = 7.0 Hz, C**2**-H), 1.36 (12H, d, *J* = 7.0 Hz, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.7 (C**3**), 136.4 (C**6**), 129.5 (C**4**), 117.7 (C**5**), 49.1 (C**2**), 20.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{10}H_{18}N_3O$ 196.1444. Found $[M+H]^+$ 196.1444; m.p. 64–66 °C (hexane/EtOAc).

***N,N*-Diisopropylthiophene-3-carboxamide (131)**



General Procedure H: The reaction was carried out with 3-thiophene-carboxylic acid. Purification of the residue by FCC (hexane/EtOAc 50%) afforded the title compound (497 mg, 30%) as a colourless solid. ν_{max}/cm^{-1}: 3086 (m), 2967 (m) 1623 (s), 1441 (s), 1319 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.36 (1H, m, C**7**-H), 7.34 – 7.28 (1H, m, C**6**-H), 7.13 (1H, dd, *J* = 5.0, 1.5 Hz, C**5**-H), 3.82 (2H, ap. br. s, C**2**-H), 1.50 – 1.18 (12H, m, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6 (C**3**), 139.3 (C**4**), 126.6 (C**5**), 125.7 (C**6**), 124.2 (C**7**), 45.6 (C**2**), 21.0 (C**1**); HRMS: (ESI+) calculated for $C_{11}H_{17}NOSNa$ 234.0923. Found $[M+Na]^+$ 234.0923; m.p. 77–79 °C (hexane/EtOAc).

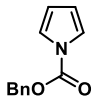
***N,N*-Diisopropyl-1*H*-indole-1-carboxamide (132)**



General Procedure E: The reaction was carried out with diisopropylcarbamic chloride (768 mg, 4.70 mmol). Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (851 mg, 82% yield) as colourless needles. ν_{max}/cm^{-1}: 2971 (m), 2939 (m) 1677 (s), 1428 (s), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.65 (1H, m, C**10**-H), 7.62 – 7.58 (1H, m, C**7**-H), 7.31 – 7.23 (1H, m, C**9**-H), 7.21 – 7.14 (2H, m, C**4**-H, C**8**-H), 6.57 (1H, dd, *J* = 3.5, 1.0 Hz, C**5**-H), 3.80 (2H, hept, *J* = 6.5 Hz, C**2**-H), 1.40 (12H, d, *J* = 6.5 Hz, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8 (C**3**), 136.0 (C**11**), 129.0

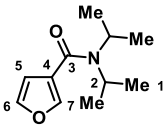
(C**6**), 125.4 (C**4**), 123.3 (C**9**), 121.4 (C**8**), 120.9 (C**7**), 112.9 (C**10**), 104.8 (C**5**), 48.7 (C**2**), 21.3 (C**1**); HRMS: (ESI$^+$) calculated for $C_{15}H_{21}N_2O$ 245.1648. Found $[M+H]^+$ 245.1640; m.p. 84–86 °C (hexane/EtOAc).

Benzyl 1*H*-pyrrole-1-carboxylate (133)



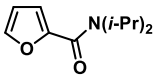
General Procedure E: The reaction was carried out with benzoyl chloroformate (1.40 mL, 10.0 mmol). Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (158 mg, 8%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.34 (5H, m), 7.30 (2H, dd, *J* = 3.0, 2.0 Hz), 6.25 (2H, dd, *J* = 3.0, 2.0 Hz,), 5.38 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.5, 135.0, 128.9, 128.9, 128.6, 120.3, 112.7, 69.0. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[255]

***N*,*N*-Diisopropylfuran-3-carboxamide (134a)**



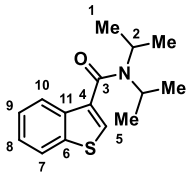
General Procedure H: The reaction was carried out with 3-furoic acid. Purification of the residue by FCC (hexane/EtOAc 30–50%) afforded the title compound (1.10 g, 72%) as an off-white solid. ν_{max}/cm^{-1}: 2971 (m), 2932 (m), 1618 (s), 1437 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.59 (1H, m, C**7**), 7.42 – 7.33 (1H, m, C**6**), 6.54 – 6.46 (1H, m, C**5**), 4.35 – 3.33 (2H, m, C**2**), 1.34 (12H, s, C**1**); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4 (C**3**), 142.7 (C**6**), 142.1 (C**7**), 123.5 (C**4**), 109.9 (C**5**), 47.5 (C**2**), 21.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{11}H_{18}NO_2$ 196.1332. Found $[M+H]^+$ 196.1338; m.p. 43–45 °C (hexane/EtOAc) (Lit.[256] 44–45 °C, hexane).

***N*,*N*-Diisopropylfuran-2-carboxamide (139)**



General Procedure H: The reaction was carried out with 2-furoic acid. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (1.27 g, 84%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.34 (1H, m), 6.82 (1H, d, *J* = 3.5 Hz), 6.43 (1H, dd, *J* = 3.5, 2.0 Hz), 4.37 – 3.55 (2H, m), 1.56 – 1.13 (12H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.4, 149.7, 143.0, 114.1, 111.0, 48.2, 21.0. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[257]

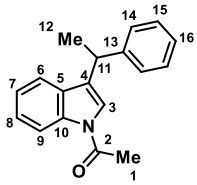
***N,N*-Diisopropylbenzo[*b*]thiophene-3-carboxamide (145)**



General Procedure H: The reaction was carried out with 1-benzothiophene-3-carboxylic acid. Purification of the residue by FCC (hexane/EtOAc 10–50%) afforded the title compound (1.50 g, 74%) as colourless cubes. ν_{max}/cm^{-1}: 2993 (m), 2963 (m), 1622 (s), 1440 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.82 (1H, m, C**10**-H), 7.80 – 7.73 (1H, m, C**7**-H), 7.43 – 7.34 (3H, m, C**5**-H, C**8**-H, C**9**-H), 3.84 – 3.67 (2H, m, C**2**-H), 1.82 – 1.17 (12H, m, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (C**3**), 139.8 (C**11**), 137.4 (C**6**), 134.6 (C**4**), 125.0 (ArCH), 124.8 (ArCH), 123.0 (ArCH), 122.9 (C**7**), 122.6 (C**10**), 50.1 (C**2**), 47.2 (C**2**), 21.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{15}H_{19}NOS$ 262.1260. Found $[M+H]^+$ 262.1256; m.p. 162–164 °C ($CDCl_3$).

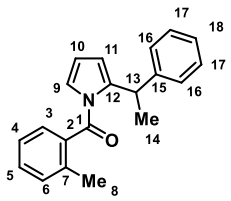
7.5.1 – Hydroarylation Reactions

1-(3-(1-Phenylethyl)-1*H*-indol-1-yl)ethan-1-one (118a')



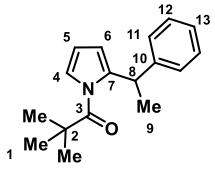
General procedure I: The reaction was carried out in the absence of a ligand. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (34.0 mg, 90%, 0.8:0.2 mixture of rotamers *A:B*) as a yellow oil. ν_{max}/cm^{-1}: 2966 (m), 1681 (s), 1450 (s), 1360 (s), 1213 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (1H, s, C**9**-H, *A*+*B*), 7.34 – 7.09 (9H, m, ArC-H, *A*+*B*), 4.30 (0.8H, q, *J* = 7.0 Hz, C**11**-H, *A*), 4.28-4.20 (0.2H, m, C**11**-H, *B*) 2.64 (2.4H, s, C**1**-H$_3$, *A*), 2.61 (0.6H, s, C**1**-H$_3$, *B*) 1.71 (2.4H, d, *J* = 7.0 Hz, C**12**-H, *A*), 1.68 (0.6H, d, *J* = 7.0 Hz, C**12**-H, *B*); ^{13}C NMR (101 MHz, $CDCl_3$, *major rotamer signals only*): δ 168.6 (C**2**), 145.1 (C**13**), 136.4 (C**10**), 130.2 (C**5**), 128.7 (C**15**), 127.6 (C**4**), 127.5 (C1**4**), 126.6 (C**8**), 125.3 (C**16**), 123.5 (C**7**), 121.8 (C**3**), 120.0 (C**6**), 116.7 (C**9)**, 36.9 (C**11**), 24.2 (C**1**), 22.0 (C**12**); HRMS: (EI) calculated for $C_{18}H_{17}NO$ 263.1310. Found [M] 263.1344. *Selective irradiation of signals for C**11**-H of rotamer A in a 1D gradient nOe experiment revealed a negative peak for the respective signals of rotamer B.*

2-(1-Phenylethyl)-1*H*-pyrrol-1-yl)(*o*-tolyl)methanone (122ba')



General procedure I: Purification of the residue by FCC (toluene) afforded the title product (10.8 mg, 26%) as a colourless oil. ν_{max}/cm^{-1}: 3027 (m), 2929 (m), 1708 (s), 1492 (m), 1319 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, m, C**6**-H), 7.27 – 7.20 (2H, m, C**17**-H), 7.19 – 7.11 (6H, m, C**4**-H, C**5**-H, C**8**-H, C**16**-H, C**18**-H), 6.52 (1H, dd, *J* = 3.5, 1.5 Hz, C**9**-H), 6.33 (1H, ddd, *J* = 3.5, 1.5, 1.5 Hz, C**11**-H), 6.12 (1H, dd, *J* = 3.5, 1.5 Hz, C**10**-H), 4.97 (1H, q, *J* = 7.0 Hz, C**13**-H), 1.98 (3H, s, C**8**-H_3), 1.60 (3H, d, *J* = 7.0 Hz, C**14**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8 C**1**), 146.0 (C**15**), 140.7 (C**12**), 136.3 (C**2**), 135.2 (C**7**), 130.7 (C**5**), 130.6 (C**6**), 128.3 (C**17**), 127.9 (C**4**), 127.7 (C**16**), 126.1 (C**3**), 125.6 (C**18**), 123.7 (C**9**), 112.6 (C**11**), 110.8 (C**10**), 38.6 (C**13**), 22.6 (C**14**), 19.2 (C**8**); HRMS: (ESI^+) calculated for $C_{20}H_{19}NONa$ 312.1359. Found $[M+Na]^+$ 312.1357.

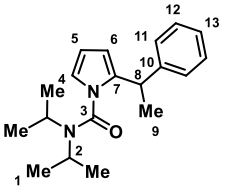
2,2-Dimethyl-1-(2-(1-phenylethyl)-1*H*-pyrrol-1-yl)propan-1-one (124a')



General procedure I: Purification of the residue by FCC (toluene) afforded the title product (3.00 mg, 8%) as a colourless oil. ν_{max}/cm^{-1}: 3027 (m), 2971 (m), 1711 (s), 1286 (s), 1214 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (2H, t, *J* = 7.5 Hz, C**12**-H), 7.14 (1H, ddd, *J* = 4.5, 3.0, 1.5 Hz, C**4**-H), 7.12 (1H, m, C**13**-H), 7.06 – 7.01 (2H, m, C**11**-H), 6.27 – 6.22 (1H, m, C**6**-H), 6.16 (1H, m, C**5**-H), 4.72 (1H, q, *J* = 7.0 Hz, C**8**-H), 1.53 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 1.10 (9H, s, C**1**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.4 (C**3**), 146.5 (C**10**), 140.6 (C**7**), 128.2 (C**12**), 127.7 (C**11**), 126.0 (C**13**), 120.8 (C**4**), 110.2 (C**6**), 109.4 (C**5**), 41.8 (C**2**), 38.4 (C**8**), 28.6 (C**1**), 22.4 (C**9**); HRMS: (ESI^+) calculated for $C_{17}H_{21}NONa$ 278.1515. Found $[M+Na]^+$ 278.1509.

Characteristic signals for the linear regioisomer **125a'**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 – 6.23 (1H, m), 6.03 – 5.96 (1H, m), 3.20 – 3.13 (2H, m), 2.94 – 2.85 (2H, m), 1.46 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 142.1, 137.4, 128.7, 128.4, 125.9, 120.6, 110.9, 110.3, 41.9, 35.8, 31.7, 29.0.

***N,N*-Diisopropyl-2-(1-phenylethyl)-1*H*-pyrrole-1-carboxamide (127aa')**

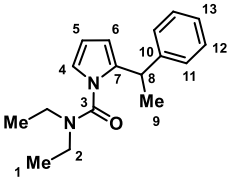


General Procedure J: The reaction was carried out with **(*R*)-L-16f** (R = H) at 120 °C. Purification of the residue by FCC (hexane/EtOAc 0–3%) afforded the title compound (32.2 mg, 75%, 88:12 *e.r.*) as a colourless oil. ν_{max}/cm^{-1}: 2969 (m), 2931 (m), 1681 (s), 1432 (s), 1329 (s); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.27 – 7.21 (2H, m, C**12**-H), 7.16 (1H, m, C**13**-H), 7.14 – 7.10 (2H, m, C**11**-H), 6.71 (1H, br. s, C**4**-H), 6.15 – 6.11 (1H, m, C**6**-H), 6.09 (1H, m, C**5**-H), 4.36 (1H, q, *J* = 7.5 Hz, C**8**-H), 3.42 – 3.33 (2H, m, C**2**-H), 1.51 (3H, d, *J* = 7.5 Hz, C**9**-H_3), 1.21 (6H, d, *J* = 7.0 Hz, C**1**-H_3), 0.90 (6H, ap. s, C**1**-H_3); ^{13}C NMR (126 MHz, DMSO-d_6, 100 °C): δ 151.6 (C**3**), 145.7 (C**10**), 137.3 (C**7**), 128.4 (C**12**), 127.3 (C**11**), 126.1 (C**13**), 119.3 (C**4**), 107.8 (C**5**), 106.7 (C**6**), 36.2 (C**8**), 22.05 (C**9**), 19.5 (C**1**); HRMS: (ESI^+) calculated for $C_{19}H_{26}N_2ONa$ 321.1937. Found $[M+Na]^+$ 321.1939; $[\alpha]^{25}_D$ = - 0.7 (c = 0.31, $CHCl_3$).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:IPA 95:5, 3 mL/min, 150 bars, 25 °C). Retention times: 10.2 minutes (minor), 11.5 minutes (major), e.r. = 88:12.

*Note C**2** is not observed by ^{13}C NMR analysis*

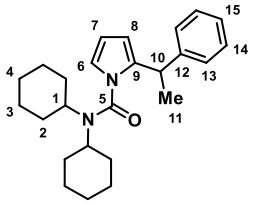
***N,N*-Diethyl-2-(1-phenylethyl)-1*H*-pyrrole-1-carboxamide (127ba')**



General Procedure J: The reaction was carried out with **(*R*)-L-16f** (R = H) at 120 °C. Purification of the residue by FCC (hexane/EtOAc 0–10%) afforded the title compound (34.9 mg, 90%, 86.5:13.5 *e.r.*) as a colourless oil. ν_{max}/cm^{-1}: 3026 (m), 2971 (m), 1681 (s) 1421 (s), 1286 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.16 (2H, m, C**12**-H), 7.16 – 7.06 (3H, m, C**11**-H, C**13**-H), 6.67 – 6.59 (1H, m, C**4**-H), 6.24 – 6.18 (1H, m, C**6**-H), 6.15 – 6.11 (1H, m, C**5**-H), 4.46 (1H q, *J* = 7.5 Hz, C**8**-H), 3.12 – 2.69 (4H, m, C**2**-H_2), 1.56 (3H, d, *J* = 7.5 Hz, C**9**-H_3), 0.88 (6H t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.3 (C**3**), 146.1 (C**10**), 138.4 (C**7**), 128.3 (C**12**), 127.8 (C**11**), 126.2 (C**13**), 119.7 (C**4**), 108.2 (C**5**), 107.6 (C**6**), 41.5 (C**2**), 37.2 (C**8**), 21.9 (C**9**), 12.7 (C**1**); HRMS: (ESI+) calculated for $C_{17}H_{23}N_2O$ 271.1805. Found [M+H]+ 271.1813; $[\alpha]^{25}_D$ = - 9.3 (c = 0.40, $CHCl_3$).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:IPA 95:5, 3 mL/min, 150 bars, 25 °C). Retention times: 10.2 minutes (minor), 11.5 minutes (major), e.r. = 87:13.

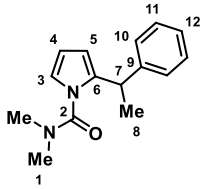
***N,N*-Dicyclohexyl-2-(1-phenylethyl)-1*H*-pyrrole-1-carboxamide (127ca')**



General Procedure J: The reaction was carried out with **(*R*)-L-16c** (R = Ph) at 130 °C. Purification of the residue by FCC (hexane/Et_2O 7.5%) afforded the title compound (47.1 mg, 87%, 75:25 *e.r.*) as an orange oil. ν_{max}/cm^{-1}: 2927 (m), 2854 (m), 1679 (s) 1426 (s), 1309 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.17 (2H, m, C**14**-H), 7.16 – 7.07 (3H, m, C**13**-H, C**15**-H), 6.62 – 6.56 (1H, m, C**6**-H), 6.25 – 6.19 (1H, m, C**7**-H), 6.14 – 6.09 (1H, m, C**8**-H), 4.50 (1H, q, *J* = 7.0 Hz, C**10**-H), 2.88 – 2.67 (2H, m, C**1**-H), 2.50 – 2.14 (2H, m, Cy), 1.93 – 0.59 (18H, m, Cy), 1.53 (3H, d, *J* = 7.0 Hz, C**11**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0 (C**5**), 146.6 (C**12**), 138.4 (C**9**), 128.4 (C**14**), 127.8 (C**13**), 126.1 (C**15**), 119.2 (C**6**), 108.0 (C**8**), 107.2 (C**7**), 59.7 (C**1**), 56.3 (C**1**), 37.0 (C**10**), 31.2 (Cy), 30.4 (Cy), 29.8 (Cy), 29.0 (Cy), 26.4 (Cy), 26.2 (Cy), 25.9 (Cy), 25.6 (Cy), 25.3 (Cy), 22.2 (C**11**); HRMS: (ESI+) calculated for $C_{25}H_{34}N_2NaO$ 401.2563. Found $[M+Na]^+$ 401.2571; $[\alpha]^{25}_D$ = - 4.3 (c = 0.50, $CHCl_3$).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:IPA 80:20, 2 mL/min, 150 bars, 25 °C). Retention times: 10.0 minutes (major), 10.7 minutes (minor), e.r. = 75:25.

***N,N*-Dimethyl-2-(1-phenylethyl)-1*H*-pyrrole-1-carboxamide (127da')**

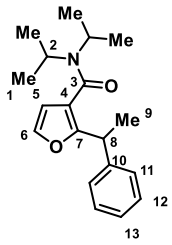


General Procedure J: The reaction was carried out with **(*R*)-L-16c** (R = Ph) at 130 °C. Purification of the residue by FCC (hexane/EtOAc 0–10%) afforded the title compound (23.3 mg, 65%, 74:26 *e.r.*) as colourless plates. ν_{max}/cm^{-1}: 2971 (m), 2935 (m), 1682 (s), 1423 (s), 1286 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.21 (2H, m, C**11**-H), 7.18 – 7.09 (3H, m, C**10**-H, C**12**-H), 6.62 (1H, dd, *J* = 3.0, 1.5 Hz, C**3**-H), 6.22 – 6.15 (1H, m, C**5**-H), 6.15 – 6.11 (1H, m, C**4**-H), 4.39 (1H, q, *J* = 7.0 Hz, C**7**-H), 2.49 (6H, br. s, C**1**-H_3), 1.58 (3H, d, *J* = 7.0 Hz, C**8**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0 (C**2**), 145.9 (C**9**), 138.3 (C**6**), 128.2 (C**11**), 127.8 (C**10**), 126.3 (C**12**), 119.8 (C**3**), 108.5 (C**4**), 107.1 (C**5**), 37.5 (C**1**), 37.2 (C**7**), 21.3 (C**8**); HRMS: (ESI^+) calculated for $C_{15}H_{18}N_2ONa$ 265.1311. Found $[M+H]^+$ 265.1315; m.p. 94–96 °C ($CDCl_3$); $[\alpha]^{24}_D$ = - 8.0 (c = 0.19, $CHCl_3$).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:IPA 95:5, 3 mL/min, 150 bars, 25 °C). Retention times: 10.8 minutes (minor), 11.3 minutes (major), e.r. = 74:26.

*Note: for alkenylation products see Section **7.7***

***N,N*-Diisopropyl-2-(1-phenylethyl)furan-3-carboxamide (135aa')**

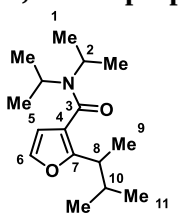


General Procedure K: The reaction was carried out with **(*R*)-L-16d** (R = C_6H_5). Purification of the residue by FCC (hexane/EtOAc 10–15%) afforded the title compound (24.4 mg, 82%, 95:5 *e.r.*) as a yellow oil. ν_{max}/cm^{-1}: 2269 (m), 1938 (m), 1623 (s), 1440 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.26 (4H, m, C**11**-H, C**12**-H), 7.25 (1H, d, *J* = 2.0 Hz, C**6**-H), 7.20 – 7.14 (1H, m, C**13**-H), 6.24 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.40 (1H, q, *J* = 7.5 Hz, C**8**-H), 4.04 – 3.73 (1H, m, C**2**-H), 3.62 – 3.19 (1H, m, C**2**-H), 1.64 (3H, d, *J* = 7.5 Hz, C**9**-H_3), 1.55 – 1.31 (6H, m, C**1**-H_3), 1.20 – 0.75 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7 (C**3**), 157.1 (C**7**), 144.2 (C**10**), 140.3 (C**6**), 128.6 (C**12**), 127.5 (C**11**), 126.5 (C**13**), 117.8 (C**4**), 109.3 (C5), 46.0 (C**2**), 38.0 (C**8**), 20.7 (C**1**), 19.5 (C**9**); HRMS: (ESI^+) calculated for $C_{19}H_{26}NO_2$ 300.1958. Found $[M+H]^+$ 300.1957; $[\alpha]^{25}_D$ = + 6.3 (c = 0.50, $CHCl_3$).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 92.5:7.5, 2 mL/min, 140 bars, 60 °C). Retention times: 7.1 minutes (major), 7.7 minutes (minor), e.r. = 95:5.

General Procedure J: The reaction was carried out with H_8-BINAP. *Characteristic peaks for linear regioisomer **136aa'**:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.40 (d, *J* = 1.9 Hz, 1H), 2.94 – 2.83 (m, 4H).

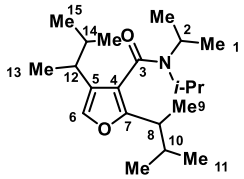
***N,N*-Diisopropyl-2-(3-methylbutan-2-yl)furan-3-carboxamide (135ad')**



General Procedure K: The reaction was carried out with **(*R*)-L-16a** (R = Mesityl). Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (20.0 mg, 75%, 72:28 *e.r.*) as a yellow oil. ν_{max}/cm^{-1}: 2964 (m), 2931 (m), 1624 (s), 1438 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (1H, d, *J* = 2.0 Hz, C**6**-H), 6.23 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.20 – 3.36 (2H, m, C**2**-H), 2.83 – 2.73 (1H, m, C**8**-H), 1.94 – 1.80 (1H, m, C**10**-H), 1.68 – 1.01 (12H, m, C**1**-H_3), 1.23 (3H, d, *J* = 7.0 Hz, C**9**-H), 0.92 (3H, d, *J* = 6.5 Hz, C**11**-H_3), 0.79 (3H, d, *J* = 6.5 Hz, C**11**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0 (C**3**), 159.0 (C**7**), 139.8 (C**6**), 117.9 (C**4**), 108.9 (C**5**), 50.2 (C**2**), 46.2 (C**2**), 38.9 (C**8**), 33.1 (C**10**), 21.1 (C**1**), 20.9 (C**11**), 20.6 (C**11**), 16.5 (C**9**); HRMS: (ESI^+) calculated for $C_{16}H_{28}NO_2$ 266.2115. Found $[M+H]^+$ 266.2118; $[\alpha]^{25}_D$ = - 26.3 (c = 0.20, $CHCl_3$).

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 88:2, 2 mL/min, 140 bars, 60 °C). Retention times: 15.0 minutes (major), 16.5 minutes (minor), e.r. = 72:28

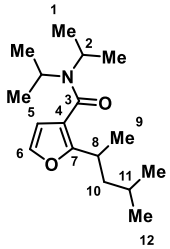
***N,N*-Diisopropyl-2,4-bis(3-methylbutan-2-yl)furan-3-carboxamide (137ad')**



General Procedure K: The reaction was carried out with **(*R*)-L-16a** (R = Mesityl). Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (4.00 mg, 12%, 0.6:0.4 mixture of rotamers *A:B*) as a colourless oil. ν_{max}/cm^{-1}: 2960 (m), 2927 (m), 1632 (s), 1439 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 – 6.97 (1H, m, C**6**-H, *A*+*B*), 4.06 (0.4H, p, *J* = 6.5 Hz, C**2**-H, *B*), 3.96 (0.6H, p, *J* = 6.5 Hz, C**2**-H, *A*), 3.43 (1H, p, *J* = 6.5 Hz, C**2**-H, *A*+*B*), 2.59 – 2.46 (0.6H, m, C**8**-H, *A*), 2.46 – 2.30 (1.4H m, C**8**-H, *A*, C**12**-H, *A*+*B*), 2.04 – 1.70 (1H, m, aliphatic C-H, *A*+*B*), 1.57 – 1.44 (6H, m, aliphatic C-H), 1.28 – 1.12 (7H, m, aliphatic C-H), 1.12 – 1.05 (5H, m, aliphatic C-H), 1.00 – 0.84 (6H, m, aliphatic C-H), 0.84 – 0.71 (6H, m, aliphatic C-H); HRMS: (ESI$^+$) calculated for $C_{21}H_{37}NO_2Na$ 358.2717. Found $[M+Na]^+$ 358.2710.

*Note: Due to complex rotamers, **137ad'** was characterised through comparison to **137ac'**.*

***N,N*-Diisopropyl-2-(4-methylpentan-2-yl)furan-3-carboxamide (135ah')**

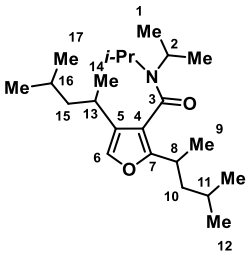


General Procedure K: The reaction was carried out with **(*R*)-L-16a** (R = Mesityl). Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (21.3 mg, 76%, 87:13 *e.r.*) as a yellow oil. ν_{max}/cm^{-1}: 2951 (m), 2931 (m), 1623 (s), 1438 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (1H, d, *J* = 2.0 Hz, C**6**-H), 6.22 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.25 – 3.29 (2H, m, C**2**-H), 3.20 – 3.05 (1H, m, C**8**-H), 1.73 – 1.57 (2H, m, C**10**-H_2), 1.57 – 0.98 (13H m, C**1**-H_3, C**11**-H), 1.23 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 0.86 (3H, d, *J* = 6.5 Hz, C**12**-H_3), 0.82 (3H, d, *J* = 6.5 Hz, C**12**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9 (C**3**), 159.3 (C**7**), 139.8 (C**6**), 117.4 (C**4**), 109.0 (C**5**), 45.0 (C**10**), 30.3 (C**8**), 26.1 (C**11**), 23.0 (C**12**), 22.6 (C**12**), 21.0 (C**1**), 19.8 (C**9**); HRMS: (ESI$^+$) calculated for $C_{17}H_{29}NO_2Na$ 302.2091. Found $[M+Na]^+$ 302.2094; $[\alpha]^{25}_D$ = - 24.6 (c = 0.20, $CHCl_3$);

SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:IPA 95:5, 2 mL/min, 140 bars, 60 °C). Retention times: 9.0 minutes (major), 9.8 minutes (minor), e.r. = 87:13.

*Note C**2** is not observed by ^{13}C NMR analysis*

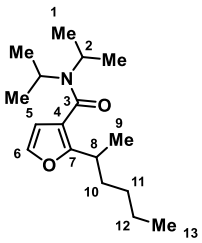
***N,N*-Diisopropyl-2,4-bis(4-methylpentan-2-yl)furan-3-carboxamide (137ah')**



General Procedure K: The reaction was carried out with **(*R*)-L-16a** (R = Mesityl). Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (9.00 mg, 24%, 0.7:0.3 mixture of rotamers *A:B*) as a colourless oil. a colourless oil. ν_{max}/cm^{-1}: 2958 (m), 2928 (m), 1633 (s), 1439 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (0.3H, s, C**6**-H, *B*), 7.01 (0.7H, d, *J* = 4.5 Hz, C**6**-H, *A*), 4.17 – 3.89 (1H, m, C**2**-H, *A*+*B*), 3.53 – 3.37 (1H, m, C**2**-H, *A*+*B*), 2.83 – 2.73 (0.3H, m, C**8**-H, *B*) 2.73 – 2.65 (0.7H, m, C**8**-H, *A*), 2.64 – 2.39 (1H, m, C**14**-H, *A*+*B*), 1.71 – 1.43 (10H, m, aliphatic C-H), 1.21 – 1.05 (14H, m, aliphatic C-H), 0.97 – 0.78 (12H, m, aliphatic C-H); HRMS: (ESI$^+$) calculated for $C_{23}H_{41}NO_2Na$ 386.3030. Found $[M+Na]^+$ 386.3040.

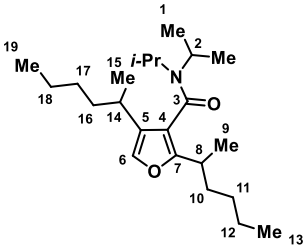
*Note: Due to complex rotamers, **137ah'** was characterised through comparison to **137ac'**.*

2-(Hexan-2-yl)-*N,N*-diisopropylfuran-3-carboxamide (135ac')



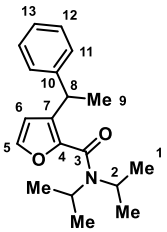
General Procedure K: The reaction was carried out with **(*R*)-L-16a** (R = Mesityl). Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (20.5 mg, 73%) as a colourless oil. ν_{max}/cm^{-1}: 2962 (m), 2929 (m), 1625 (s), 1438 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (1H, d, *J* = 2.0 Hz, C**6**-H), 6.22 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.17 – 3.88 (1H, m, C**2**-H), 3.61 – 3.25 (1H, m, C**2**-H), 3.05 – 2.95 (1H, m, C**8**-H), 1.75 – 1.59 (1H, m, C**10**-H), 1.58 – 1.47 (1H, m, C**10**-H), 1.46 – 1.05 (16H, m, C**1**-H_3, C**11**-H_2, C**12**-H_2), 1.24 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 0.84 (3H, t, *J* = 7.0 Hz, C**13**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0 (C**3**), 159.1 (C**7**), 139.8 (C**6**), 117.4 (C**4**), 109.0 (C**5**), 50.2 (C**2**), 46.1 (C**2**), 35.5 (C**10**), 32.5 (C**8**), 29.9 (C**11**), 22.8 (C**12**), 21.0 (C**1**), 19.4 (C**9**), 14.2 (C**13**); HRMS: (ESI$^+$) calculated for $C_{17}H_{29}NO_2Na$ 302.2091. Found $[M+Na]^+$ 302.2097; $[\alpha]^{25}_D$ = - 36.2 (c = 0.22, $CHCl_3$).

2,4-Di(hexan-2-yl)-*N*,*N*-diisopropylfuran-3-carboxamide (137ac')



General Procedure K: The reaction was carried out with **(*R*)-L-16a** (R = Mesityl). Purification of the residue by FCC (hexane/EtOAc 5-10%) afforded the title compound (2.5 mg, 9%) as a colourless oil. ν_{max}/cm^{-1}: 2961 (m), 2928 (m), 1632 (s), 1438 (s); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.00 (1H, s, C**6**-H), 4.10 – 3.93 (1H, m, C**2**-H), 3.54 – 3.35 (1H, m, C**2**-H), 2.79 – 2.63 (1H, m, C**8**-H), 2.62 – 2.42 (1H, m, C**14**-H), 1.72 – 1.58 (2H, m, C**hexane**-H), 1.55 – 1.46 (6H, m, C**hexane**-H), 1.37 – 1.07 (**22**H, m, C**hexane**-H, C**1**-H_3), 0.99 – 0.74 (6H, m, C**13**-H_3, C**9**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.1 (C**3**), 166.0 (C**3**), 166.0 (C**3**), 165.9 (C**3**), 156.5 (C**7**), 156.3 (C**7**), 155.4 (C**7**), 155.1 (C**7**), 136.0 (C**6**), 135.9 (C**6**), 135.7 (C**6**), 135.5 (C**6**), 130.5 (C**4**), 130.4 (C**4**), 130.3 (C**4**), 130.3 (C**4**), 118.2 (C**5**), 118.0 (C**5**), 117.9 (C**5**), 117.7 (C**5**), 50.6 (C**2**), 45.8 (C**2**), 37.8 (C**hexane**), 37.2 (C**hexane**), 36.7 (C**hexane**), 36.2 (C**hexane**), 35.9 (C**hexane**), 35.8 (C**hexane**), 35.0 (C**hexane**), 34.8 (C**hexane**), 33.0 (C**8**), 32.6 (C**8**), 33.0 (C**hexane**), 32.6 (C**hexane**), 30.2 (C**hexane**), 30.0 (C**hexane**), 29.9 (C**hexane**), 29.9 (C**hexane**), 29.8 (C**hexane**), 29.7 (C**14**), 29.6 (C**14**), 23.0 (C**1**), 22.9 (C**1**), 22.6 (C**1**), 22.6 (C**1**), 21.6 (C**1**), 21.4 (C**1**), 20.9 (C**hexane**), 20.7 (C**hexane**), 20.7 (C**hexane**), 20.5 (C**hexane**), 20.4 (C**hexane**), 20.3 (C**hexane**), 19.6 (C**hexane**), 19.5 (C**hexane**), 18.9 (C**hexane**), 18.7 (**C**hexane), 14.3 (C**9**/**13**), 14.2 (C**9**/**13**), 14.1 (C**9**/**13**); HRMS: (ESI$^+$) calculated for $C_{23}H_{41}NO_2Na$ 386.3030. Found $[M+Na]^+$ 386.2027.
Note: Due to complex rotamers and diasteriosisomers the ^{13}C NMR was tentatively assigned.

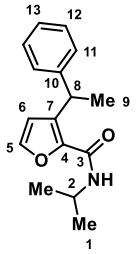
***N*,*N*-Diisopropyl-3-(1-phenylethyl)furan-2-carboxamide (140a')**



General Procedure L: The reaction was run at 100 °C for 24 h. Purification of the residue by FCC (hexane/Et_2O 10–20%) afforded the title compound (36.2 mg, 85%, 86.5:13.5 *e.r.*) as a colourless oil. ν_{max}/cm^{-1}: 2968 (m), 2982 (m), 1622 (s), 1439 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.25 (4H, m, C**11**-H, C**12**-H), 7.25 – 7.22 (1H, m, C**5**-H), 7.19 – 7.10 (1H, m, C**13**-H), 6.34 (1H, d, *J* = 1.5, Hz, C**6**-H), 4.46 (1H, q, *J* = 7.0 Hz, C**8**-H), 3.58 (1H, br. ap. s, C**2**-H), 1.58 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 1.49 – 0.85 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9 (C**3**), 146.1 (C**10**), 144.6 (C**4**), 140.9 (C**5**), 132.2 (C**7**), 128.4 (C**12**), 127.4 (C**11**), 126.1 (C**13**), 111.0 (C**6**), 49.8 (C**2**), 46.6 (C**2**), 34.9 (C**8**), 21.3 (C**9**), 20.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{25}NO_2Na$ 322.1777. Found $[M+Na]^+$ 322.1779; $[\alpha]^{25}_D$ = + 77.9 (c = 0.20, $CHCl_3$).

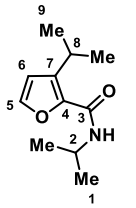
SFC Conditions: (DAICEL CHIRALPAK-IB column (25 cm), CO_2:MeOH 99:1, 2 mL/min, 140 bars, 60 °C). Retention times: 9.9 minutes (minor), 10.4 minutes (major), e.r. = 87:13.

***N*-Isopropyl-3-(1-phenylethyl)furan-2-carboxamide (141a')**



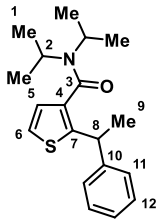
General Procedure L: The reaction was run at 120 °C for 48 h. Purification of the residue by FCC (hexane/EtOAc 5%) afforded the title compound (17.5 mg, 51%) as a colourless oil. ν_{max}/cm^{-1}: 3302 (br.), 2868 (m), 2927 (m), 1644 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.33 (2H, m, **11**-H), 7.32 – 7.21 (3H, m, C**5**-H, C**12**-H), 7.22 – 7.11 (1H, m, C**13**-H), 6.39 (1H, d, *J* = 2.0 Hz, C**6**-H), 6.13 (1H, br. d, *J* = 8.0 Hz, N-H), 5.14 (1H, q, *J* = 7.0 Hz, C**8**-H), 4.25 (1H, hept, *J* = 8.0, 6.5 Hz, C**2**-H), 1.57 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 1.27 – 1.20 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8 (C**3**), 145.5 (C**10**), 142.4 (C**5**), 141.4 (C**4**), 136.3 (C**7**), 128.5 (C**12**), 127.5 (C**11**), 126.3 (C**13**), 112.3 (C**6**), 40.9 (C**2**), 34.5 (C**8**), 23.1 (C**1**), 21.3 (C**9**); HRMS: (ESI$^+$) calculated for $C_{16}H_{20}NO_2$ 258.1489. Found $[M+H]^+$ 258.1497.

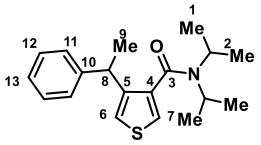
***N*,3-Diisopropylfuran-2-carboxamide (142)**



General Procedure L: The reaction was run at 120 °C for 48 h in the absence of styrene. Purification of the residue by FCC (hexane/EtOAc 0–15%) afforded the title compound (12.7 mg, 45%) as a yellow oil. ν_{max}/cm^{-1}: 3316 (m), 2957 (m), 2871 (m), 1644 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (1H. d, *J* = 2.0 Hz, C**5**-H), 6.43 (1H, d, *J* = 2.0 Hz, C**6**-H), 6.14 (1H, s, N-H), 4.24 – 4.20 (1H, m, C**2**-H), 3.85 – 3.77 (1H, m, C**8**-H), 1.23 (6H, d, *J* = 6.5 Hz, C**1**-H_3), 1.19 (6H, d, *J* = 7.0 Hz, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9 (C**3**), 142.3 (C**5**), 141.0 (C**4**), 138.6 (C**7**), 111.3 (C**6**), 40.9 (C**2**), 24.3 (C**8**), 23.3 (C**9**), 23.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{11}H_{18}NO_2$ 196.1332. Found $[M+H]^+$ 196.1332;

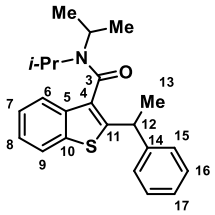
***N,N*-Diisopropyl-2-(1-phenylethyl)thiophene-3-carboxamide**





A flame-dried tube, fitted with a magnetic stirrer, was charged with **131** (0.143 mmol), $[Ir(cod)_2]BARF$ (5.0 mol%) and **(*rac*)-L-15a (**5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene (400 mol%) in anhydrous 1,4-dioxane (1.0 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 120 °C for 48 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 10–15%) afforded the title compound (30.9 mg, 68%, 0.7:0.3 mixture of regioisomers *A*:*B*) as a colourless oil. ν_{max}/cm^{-1}: 2967 (m), 2928 (m), 1625 (s), 1443 (s); ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.20 (4.3H, m, ArC<u>H</u>), 7.20 – 7.12 (2H, m, ArC<u>H</u>), 7.10 (1H, d, *J* = 5.0 Hz, C**6**-<u>H</u>, A, ArC<u>H</u>, *B*), 6.82 (0.7H, d, *J* = 5.0 Hz, C**5**-<u>H</u>, *A*), 4.70 (0.7H, q, *J* = 7.0 Hz, C**8**-<u>H</u>, *A*), 4.47 (0.3H q, *J* = 7.0 Hz, C**8**-<u>H</u>, *B*), 3.63 – 3.51 (1H, m, C**2**-<u>H</u>, *A*+*B*), 3.41 – 3.21 (1H, m, C**2**-<u>H</u>, *A*+*B*), 1.67 (2.1H, d, *J* = 7.0 Hz, C**9**-<u>H_3</u>, *A*), 1.57 (0.9H d, *J* = 7.0 Hz, C**9**-<u>H_3</u>, *B*), 1.54 – 0.98 (12H, m, C**1**-<u>H_3</u>, *A*+*B*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9 (C**3**, *A*), 166.6 (C**3**, *B*), 148.9 (C**7**, *A*), 146.2 (Ar<u>C</u>) 146.0 (Ar<u>C</u>), 145.7 (C**5**, *B*), 138.5 (Ar<u>C</u>), 135.1 (C**4**, A), 128.5 (C**11**/**12**, *A*), 128.4 (C**13**, *A*), 127.8 (C**11**/**12**, *B*), 127.4 (C**11**/**12**, *A*), 126.4 (C**11**/**12**, *B*), 126.1 (C**13**, *B*), 125.4 (C**5**, *A*), 122.3 (C**6**, *A*), 122.2 (C**6**, *B*), 120.9 (Ar<u>C</u>), 50.5 (C**2**, *A*+*B*), 45.8 (C**2**, *A*+*B*), 38.9 (C**8**, *B*), 38.6 (C**8**, *A*), 23.7 (C**9**, *A*), 22.9 (C**9**, *B*), 20.9 (C**1**, *A*+*B*), 20.6 (C**1**, *A*+*B*), 20.4 (C**1**, *A*+*B*), 20.1 (C**1**, *A*+*B*); HRMS: (ESI^+) calculated for $C_{19}H_{26}NOS$ 316.1730. Found $[M+H]^+$ 316.1727.

***N,N*-Diisopropyl-2-(1-phenylethyl)benzo[*b*]thiophene-3-carboxamide (146a')**



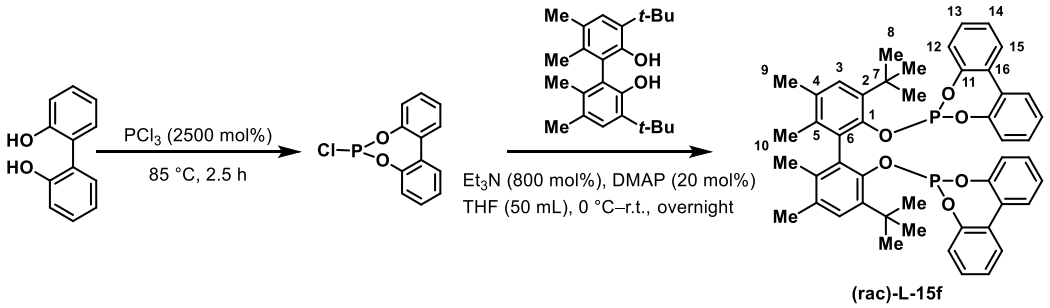
A flame-dried tube, fitted with a magnetic stirrer, was charged with **145** (0.143 mmol), $[Ir(cod)_2]BARF$ (5.0 mol%) and **(*rac*)-L-15a (**5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Styrene (400 mol%) in anhydrous 1,4-dioxane (1.0 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 120 °C for 48 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 10–15%) afforded the title compound (23.6 mg, 45%, 0.6:0.4 mixture of rotamers *A:B*) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.76 (0.6H, m, C**6**-<u>H</u>, *A*),

7.72 – 7.67 (0.4H, m, C**6**-H, *B*), 7.58 – 7.52 (1H, m, C**9**-H, *A*+*B*), 7.47 (0.8H, dd, *J* = 8.0, 1.5 Hz, C**15**-H, *B*), 7.40 – 7.33 (1.2H, m, C**15**-H, *A*), 7.34 – 7.24 (4H, m, C**7**-H, C**8**-H, C**16**-H, *A*+*B*), 7.24 – 7.17 (1H, m, C**17**-H, *A*+*B*), 4.69 (0.6H, q, *J* = 7.0 Hz, C**12**-H, *A*), 4.56 (0.4H, q, *J* = 7.0 Hz, C**12**-H, *B*), 3.87 (0.4H, hept, *J* = 6.5 Hz, C**2**-H, *B*), 3.66 – 3.55 (0.4H, m, C**2**-H, *B*), 3.55 – 3.47 (0.6H, m, C**2**-H, *A*), 3.47 – 3.38 (0.6H, m, C**2**-H, *A*), 1.78 (1.2H d, *J* = 7.0 Hz, C**13**-H_3, *B*), 1.73 (1.8H, d, *J* = 7.0 Hz, C**13**-H_3, *A*), 1.69 (1.4H, d, C**1**-H_3), 1.67 – 1.64 (2H, m, C**1**-H_3), 1.59 (2H, d, *J* = 6.5 Hz, C**1**-H_3), 1.18 (1.8H, d, *J* = 6.5 Hz, C**1**-H_3), 1.15 – 1.09 (1.2H, m, C**1**-H_3), 1.01 (1.8H, d, *J* = 6.5 Hz, C**1**-H_3), 0.46 (1.8H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (C**3**), 147.8 (C**11**), 147.5 (C**11**), 145.3 (C**14**), 143.8 (C**14**), 138.8 (C**5**), 138.2 (C**5**), 137.6 (C**10**), 137.3 (C**10**), 130.7 (C**4**), 129.9 (C**4**), 128.6 (C**16**), 128.5 (C**16**), 127.4 (C**15**), 127.3 (C**15**), 126.7 (C**17**), 124.4 (C**8**), 124.3 (C**8**), 124.3 (C**7**) 124.2 (C**7**), 122.3 (C**6**), 122.3 (C**6**), 122.0 (C**9**), 122.0 (C**9**), 50.9 (C**2**), 46.1 (C**2**), 46.0 (C**2**), 39.6 (C**12**), 39.2 (C**12**), 24.4 (C**13**), 23.8 (C**13**), 21.8 (C**1**), 21.4 (C**1**), 21.2 (C**1**), 21.1 (C**1**), 20.8 (C**1**), 20.7 (C**1**), 20.7 (C**1**), 20.6 (C**1**), 20.3 (C**1**). HRMS: (ESI^+) calculated for $C_{23}H_{27}NOSNa$ 388.1706. Found $[M+Na]^+$ 388.1708. Coalescence observed at 90 °C.

7.6 – Experimental Procedures and Data for the Studies in Chapter 4

7.6.1 – Ligand Synthesis

(*rac*)-L-15f



A flame dried resealable tube under an inert atmosphere was charged with biphenol (2.10 g, 11.3 mmol). PCl_3 (4.93 mL, 56.5 mmol) was added and the mixture was heated at reflux for 2 h. The mixture was cooled to ambient temperature and concentrated under high vacuum for 2 h (a second trap, cooled with liquid nitrogen, was placed between the reaction tube and the vacuum line). The tube was refilled four times with nitrogen during this 2 h period. The oily chlorophosphite was directly used in the next step without further purification. 3,3'-Di-tert-butyl-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (600 mg, 2.26 mmol) and DMAP (55.2 mg, 0.452 mmol) were added and the reaction tube was evacuated and refilled with nitrogen (three times) and then cooled to 0 °C. THF was added, followed by dropwise addition of Et_3N (2.52 mL, 18.7 mmol). The tube was sealed, and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was filtered through a pad of Celite® with Et_2O. The solution was concentrated *in* vacuo and purified by FCC (hexane/EtOAc 5–8%, SiO_2 deactivated with 10% of Et_3N). **(*rac*)-L-15f** was azeotropically dried with toluene (twice) then pentane (twice) to remove any traces of Et_3N to afford pure ligand (1.65 g, 93%) as a colourless solid. ν_{max}/cm^{-1}: 3064 (m), 2958 (m), 2914 (m), 1434 (s); ^{1}H NMR (400 MHz, C_6D_6): δ 7.40 (2H, s, C**3**-H), 7.23 – 7.12 (8H, m, ArCH), 7.05 (2H, td, *J* = 7.7, 1.7 Hz, ArCH), 6.98 (2H, td, *J* = 7.7, 1.8 Hz, ArCH), 6.92 (4H, tdd, *J* = 7.3, 5.8, 1.3 Hz, ArCH), 2.19 (6H, s, C**9**-H_3), 2.02 (6H, s, C**10**-H_3), 1.52 (18H, s, C**8**-H_3); ^{13}C NMR (101 MHz, C_6D6): δ 150.39 (t, *J* = 2.5 Hz, C**1**), 150.2 (ArC), 150.0 (ArC), 138.4 (C**2**), 136.6 (C**5**), 132.36 – 131.63 (m, C**11**), 130.0 (ArC), 129.9 (ArCH), 129.9 (ArCH), 129.0 (ArCH), 125.2 (ArCH), 125.1 (ArCH), 123.6 (ArCH), 122.9 (ArCH), 35.2 (C**7**), 30.9 (C**8**), 20.6 (C**9**), 17.7 (t, *J* = 3.6 Hz, C**10**); ^{31}P NMR (162 MHz, C_6D_6): δ 142.5; HRMS (MALDI) calculated for $C_{48}H_{48}O_6P_2Na$ 805.2818 Found $[M+Na]^+$ 805.2811; m.p. 152–154 °C (pentane).

7.6.2 – Substrate Synthesis

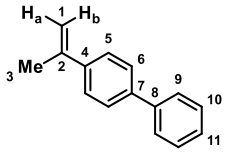
7.6.2.1 – Alkene Synthesis

147a', **147c'**, **147h'–147j' 147m', 147n', 147r'** and **147s'** *were purchased from commercial sources (Sigma)*

147e' *and* ***147q'*** *were synthesised by Miss Ellie Lester*

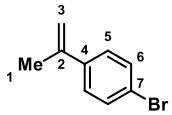
147o', ***147t'*** *and* ***147u'*** *were synthesised by Dr. Simon Grélaud*

4-(Prop-1-en-2-yl)-1,1'-biphenyl (147b')



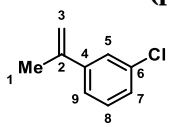
General Procedure M: Purification of the residue by FCC (hexane/EtOAc 5%) afforded the title compound (3.48 g, 88%) as a colourless solid. ν_{max}/cm^{-1}: 2974 (m), 2939 (m), 1627 (m), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.60 (2H, m, C**9**-H), 7.60 – 7.54 (4H, m, C**5**-H, C**6**-H), 7.49 – 7.42 (2H, m, C**10**-H), 7.39 – 7.31 (1H, m, C**11**-H), 5.44 (1H, dq, *J* = 1.5, 1.0 Hz, C**1**-(H_a)$_2$), 5.12 (1H, p, *J* = 1.5 Hz, C**1**-(H_b)$_2$), 2.20 (3H, dd, *J* = 1.5, 1.0 Hz, C**3**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.9 (C**2**), 140.9 (C**8**), 140.3 (C**7**), 140.3 (C**4**), 128.9 (C**10**), 127.4 (C**11**), 127.1 (C**9**), 127.1 (C**6**), 126.0 (C**5**), 112.6 (C**1**), 22.0 (C**3**); HRMS: (EI$^+$) calculated for $C_{15}H_{14}$ 194.1090. Found [M]$^+$ 194.1088; m.p. 118–120 °C (hexane/EtOAc).

1-Bromo-4-(prop-1-en-2-yl)benzene (147d')



General Procedure M: Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (1.79 g, 91%) as a colourless oil. ν_{max}/cm^{-1}: 2973 (m), 1623 (m), 1488 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.42 (2H, m, C**6**-H), 7.36 – 7.29 (2H, m, C**5**-H), 5.36 (1H, s, C**3**-H_2), 5.16 – 5.04 (1H, m, C**3**-H_2), 2.13 (3H, s, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.4 (C**2**), 140.3 (C**4**), 131.4 (C**6**), 127.3 (C**5**), 121.5 (C**7**), 113.2 (C**3**), 21.8 (C**1**); HRMS: (EI) calculated for $C_9H_9{}^{79}Br$ 195.9882. Found [M] 195.9882.

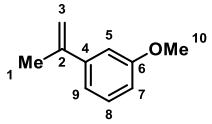
1-Chloro-3-(prop-1-en-2-yl)benzene (147f')



General Procedure M: Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (1.20 g, 79%) as a colourless oil. ν_{max}/cm^{-1}: 3088 (m), 2947 (m), 1593 (m), 1562 (s); ^{1}H NMR

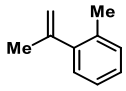
(400 MHz, $CDCl_3$): δ 7.44 – 7.40 (1H, m, C**5**-H), 7.35 – 7.29 (1H, m, C**9**-H), 7.24 – 7.22 (2H, m, C**7**-H, C**8**-H), 5.38 – 5.34 (1H, m, C**3**-H_2), 5.14 – 5.08 (1H, m, C**3**-H_2), 2.15 – 2.08 (3H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.3 (C**4**), 142.3 (C**2**), 134.4 (C**6**), 129.6 (C**8**), 127.5 (C**7**), 125.9 (C**5**), 123.8 (C**9**), 113.8 (C**3**), 21.8 (C**1**); HRMS: (EI) calculated for C_9H_9Cl 215.0387. Found [M] 215.0388.

1-Methoxy-3-(prop-1-en-2-yl)benzene (147g')



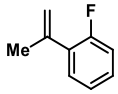
General Procedure M: Purification of the residue by FCC (hexane/EtOAc 5%) afforded the title compound (1.25 g, 85%) as a colourless oil. ν_{max}/cm^{-1}: 2943 (m), 2834 (m), 1576 (s), 1231 (s);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.22 (1H, m, C**8**-H), 7.07 (1H, ddd *J* = 7.5, 2.0, 1.0 Hz, C**7**-H), 7.02 – 6.99 (1H, m, C**5**-H), 6.83 (1H, ddd, *J* = 8.5, 2.0, 1.0 Hz, C**9**-H), 5.38- 5.36 (1H, m, C**3**-H_2), 5.10 – 5.08 (1H, m, C**3**-H_2), 3.83 (3H, s, C**10**-H_3), 2.16 – 2.14 (1H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7 (C**6**), 143.4 (C**2**), 143.0 (C**4**), 129.3 (C**8**), 118.3 (C**7**), 112.8 (C**3**), 112.8 (C**9**), 111.7 (C**5**), 55.4 (C**10**), 22.0 (C**1**); HRMS: (APCI) calculated for $C_{10}H_{12}O$ 149.0961. Found [M] 149.0959.

1-Methyl-2-(prop-1-en-2-yl)benzene (147k')



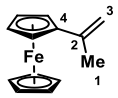
General Procedure M: Purification of the residue by FCC (hexane/EtOAc 5%) afforded the title compound (885 mg, 67%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.10 (4H, m), 5.23 – 5.15 (1H, m,), 4.88 – 4.81 (1H, m), 2.32 (3H, s), 2.09 – 2.01 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.0, 144.0, 134.6, 130.2, 128.0, 126.9, 125.7, 114.8, 24.5, 19.9. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[258]

1-Fluoro-2-(prop-1-en-2-yl)benzene (147l')



General Procedure M: Purification of the residue by FCC (hexane/EtOAc 5%) afforded the title compound (543 mg, 40%) as a colourless oil.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (1H, td, *J* = 7.5, 2.0 Hz), 7.26 – 7.20 (1H, m), 7.09 (1H, td, *J* = 7.5, 1.0 Hz), 7.10 – 6.98 (1H, m), 5.27 – 5.20 (2H, m), 2.15 (3H, dd, *J* = 2.5, 1.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1 (d, *J* = 248.1 Hz), 140.4, 130.4 (d, *J* = 13.6 Hz), 129.5 (d, *J* = 4.4 Hz), 128.8 (d, *J* = 8.4 Hz), 124.0 (d, *J* = 3.5 Hz), 116.7 (d, *J* = 3.9 Hz), 116.0 (d, *J* = 23.1 Hz), 23.2 (d, *J* = 3.4 Hz). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[259]

2-Ferrocenyl-2-propene (147p')



General Procedure M: Purification of the residue by FCC (hexane/EtOAc 0–5%) afforded the title compound (2.97 g, 75%) as an orange powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (1H, s C**3**-$\underline{H}_2$), 4.84 (1H, s, C**3**-$\underline{H}_2$), 4.47 – 4.34 (2H, m, ferrocenyl), 4.21 (2H, d, *J* = 3.5 Hz, ferrocenyl), 4.10 (5H, ap. s, ferrocenyl), 2.06 (3H, s, C**1**-$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.6 (C**3**), 108.4 (C**3**), 86.7 (C**4**), 69.4 (ferrocenyl), 68.7 (ferrocenyl), 66.0 (ferrocenyl), 21.7 (C**1**); HRMS: (nanospray) calculated for $C_{13}H_{14}Fe$ 226.0445. Found [M] 226.0440; m.p. 65–67 °C ($CDCl_3$).

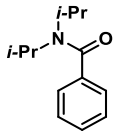
7.6.2.2 – Synthesis of Benzamide Substrates

90c*–*90g*, *90h*, *90m *and* ***90o*–*90t*, *90v*** *and* ***90w*** *were synthesised by Dr Giacomo Crisenza*

89b *was purchased from commercial sources (Sigma)*

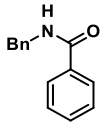
For the synthesis of ***98*** *see Section* ***7.4.1***

***N,N*-Diisopropylbenzamide (90h)**



General Procedure N: Purification of the residue by FCC (hexane/EtOAc 20–30%) afforded the title compound (1.20 g, 98%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (3H, m), 7.33 – 7.28 (2H, m), 4.07 – 3.31 (2H, m), 1.73 – 0.95 (12H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 139.1, 128.7, 128.6, 125.7, 51.0, 45.9, 20.9; m.p. 68–70 °C (hexane/EtOAc) (Lit.[260] 58–60 °C, *no recrystallisation solvent specified). The spectroscopic properties for this compound were consistent with the data available in the literature.*[260]

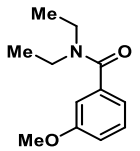
***N*-Benzylbenzamide (90i)**



To a flame-dried flask was added benzylamine (3.26 mL, 30.0 mmol) in dry THF (70 mL) under nitrogen. The solution was cooled to 0 °C, before the dropwise addition of benzoyl chloride (1.16 mL, 10.0 mmol). The reaction was warmed to ambient temperature and stirred overnight. The solution was concentrated *in vacuo* and the residue was dissolved in EtOAc (30 mL), washed with aq. HCl (2 M, 30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 30–40%) afforded the title compound (2.07 g, 98%) as a colourless solid. ^{1}H NMR

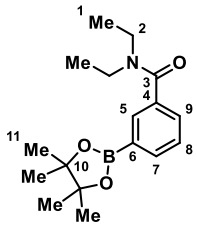
(400 MHz, $CDCl_3$): δ 7.84 – 7.75 (2H, m), 7.56 – 7.38 (1H, m), 7.48 – 7.38 (2H, m), 7.36 (4H, d, *J* = 4.5 Hz), 7.35 – 7.25 (1H, m), 6.44 (1H, br. s), 4.65 (2H, d, *J* = 5.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 138.3, 134.5, 131.7, 128.9, 128.7, 128.1, 127.8, 127.1, 44.3; m.p. 102–104 °C ($CDCl_3$) Lit. 102–105 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[261]

***N,N*-Diethyl-3-methoxybenzamide (90k)**



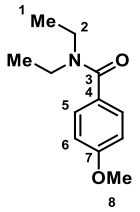
General Procedure O: Purification of the residue by FCC (hexane/EtOAc 40%) afforded the title compound (878 mg, 65%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (1H, ddd, *J* = 8.0, 7.5, 1.0 Hz), 6.95 – 6.89 (3H, m), 3.82 (3H, s), 3.54 (2H, br. s), 3.26 (2H, br. s), 1.25 (3H, br. s), 1.11 (3H, br. s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 159.7, 138.7, 129.7, 118.6, 115.2, 111.8, 55.5, 43.3, 39.3, 14.4, 13.0. *The spectroscopic properties for this compound were consistent with the data available in the literature*.[262]

***N,N*-Diethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (90l)**



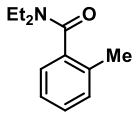
General Procedure O: Purification of the residue by FCC (1st column: hexane/EtOAc 60%; 2nd column: toluene/EtOAc 40%) afforded the title compound (461 mg, 46%) as colourless cubes. ν_{max}/cm^{-1}: 2976 (m), 2934 (m), 1626 (m), 1409 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.78 (2H, m, C**5**-H, C**7**-H), 7.46 – 7.41 (1H, m, C**9**-H), 7.40 – 7.35 (1H, m, C**8**-H), 3.53 (2H, br. s, C**2**-H_2), 3.23 (2H, br. s, C**2**-H_2), 1.33 (12H, s, C**11**-H_3), 1.23 (3H, br. s, C**1**-H_3), 1.08 (3H, br. s, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5 (C**3**), 136.9 (C**4**), 135.5 (C**7**), 132.7 (C**5**), 129.0 (C**8**), 127.8 (C**9**), 84.1 (C**10**), 43.5 (C**2**), 39.4 (C**2**), 25.0 (C**11**), 14.4 (C**1**), 13.1 (C**1**); HRMS: (ESI^+) calculated for $C_{17}H_{27}BNO_3$ 304.2082. Found $[M+H]^+$ 304.2078. m.p. 70–72 °C ($CDCl_3$).

***N,N*-Diethyl-4-methoxybenzamide (90n)**



General Procedure N: Purification of the residue by FCC (hexane/EtOAc 50%) afforded the title compound (1.31 g, 98%) as a colourless oil. ν_{max}/cm^{-1}: 3476 (m), 2971 (m), 1608 (m), 1424 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.31 (2H, m, C**5**-H), 6.95 – 6.85 (2H, m, C**6**-H), 3.82 (3H, s, C**8**-H_3), 3.52 – 3.30 (4H, m, C**2**-H_2), 1.24 – 1.11 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C**3**), 160.4 (C**7**), 129.7 (C**4**), 128.3 (C**5**), 113.8 (C**6**), 55.4 (C**8**), 43.4 (C**2**), 39.3 (C**2**), 13.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{12}H_{18}NO_2$ 208.1345. Found $[M+H]^+$ 208.1332.

***N,N*-Diethyl-2-methylbenzamide (90u)**



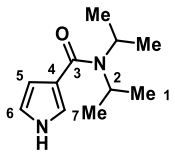
General Procedure N: Purification of the residue by FCC (hexane/EtOAc 50%) afforded the title compound (1.10 g, 89%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.25 (1H, m,), 7.24 – 7.20 (2H, m), 7.20 – 7.15 (1H, m), 3.90 – 3.37 (2H m), 3.15 (2H, q, *J* = 7.0 Hz), 2.31 (3H, s), 1.28 (3H, t, *J* = 7.0 Hz), 1.05 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 137.3, 134.0, 130.4, 128.6, 125.9, 125.6, 42.7, 38.8, 18.9, 14.1, 13.0. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[263-264]

7.6.2.3 – Synthesis of 5-Membered Heteroaromatic Substrates

*For the synthesis of substrates **126a**, **129**, **130**, **131**, **132**, **134a**, **139**, **145** see Section **7.5.1**.*

***134b** was synthesised by Miss Ellie Lester.*

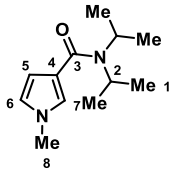
***N,N*-Diisopropyl-1*H*-pyrrole-3-carboxamide (151c)**



General Procedure H: Purification of the residue by FCC (hexane/EtOAc 80%) afforded the title compound (1.23 g, 71%) as colourless needles. ν_{max}/cm^{-1}: 3178 (m), 2957 (m), 2940 (m), 1582 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (1H, br. s, N-H), 7.02 – 6.79 (1H, m, C**6**-H), 6.69 – 6.48 (1H, m, C**7**-H), 6.32 – 6.08 (1H, m, C**5**-H), 4.74 – 3.09 (2H, m, C**2**-H), 1.35 (12H, s, C**1**-H_3); ^{13}C NMR (101 MHz,

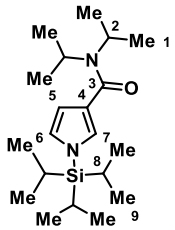
$CDCl_3$): δ 168.2 (C**3**), 120.8 (C**4**), 120.4 (C**6**), 117.9 (C**7**), 107.7 (C**5**), 47.6 (C**2**), 21.2 (C**1**); HRMS: (ESI^+) calculated for $C_{11}H_{19}N_2O$ 195.1492. Found $[M+H]^+$ 195.1489; m.p. 78–80 °C ($CDCl_3$).

***N,N*-Diisopropyl-1-methyl-1*H*-pyrrole-3-carboxamide (151a)**



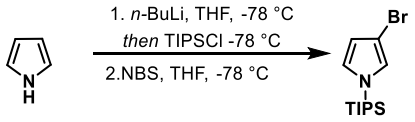
To a flame-dried flask was added NaH (125 mg, 3.12 mmol, 60% in oil) and dry THF (4.40 mL) under nitrogen. To the stirred solution was added **151b** (500 mg, 2.60 mmol) portion-wise and the resulting solution was stirred for 1 h. Methyl iodide (0.453 mL, 7.28 mmol) was added dropwise and the solution was stirred for 3 h, before being quenched with H_2O (10 mL) and extracted with Et_2O (3 ×10 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (CH_2Cl_2/EtOAc 20–30%) afforded the title compound (453 mg, 84%) as white needles. ν_{max}/cm^{-1}: 2954 (m), 2931 (m), 1603 (s), 1286 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 (1H, t, *J* = 2.0 Hz, C**7**-H), 6.50 (1H, t, *J* = 2.5 Hz, C**6**-H), 6.24 (1H, dd, *J* = 2.5, 2.0 Hz, C**5**-H), 4.24 – 3.73 (2H, m, C**2**-H), 3.63 (3H, s, C**8**-H_3), 1.34 (12H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8 (C**3**), 123.9 (C**7**), 121.4 (C**4**), 121.2 (C**6**), 108.4 (C**5**), 48.1 (C**2**), 36.2 (C**8**), 21.1 (C**1**); HRMS: (ESI^+) calculated for $C_{12}H_{21}N_2O$ 209.1648. Found $[M+H]^+$ 209.1649; m.p. 84–86 °C ($CDCl_3$).

***N,N*-Diisopropyl-1-(triisopropylsilyl)-1*H*-pyrrole-3-carboxamide (151b)**



To a stirred solution of **151b** (500 mg, 2.60 mmol) in dry THF (4 mL) under nitrogen, was added *n*-BuLi (1.32 mL, 3.12 mmol, 2.36 M in hexanes) dropwise at -78 °C. The solution was stirred for 30 minutes, before TIPSCl (0.612 mL, 2.86 mmol) was added dropwise. The mixture was warmed to ambient temperature and stirred for an additional 30 minutes, before the reaction was quenched with saturated aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (772 mg, 85%) as a colourless oil. ν_{max}/cm^{-1}: 2950 (m), 2868 (m), 1618 (s), 1243 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (1H, dd, *J* = 2.5, 1.5 Hz, C**5**-H), 6.66 (1H, t, *J* = 2.5 Hz, C**7**-H), 6.37 (1H, dd, *J* = 2.5, 1.5 Hz, C**6**-H), 4.39 – 3.67 (2H, m, C**2**-H), 1.49 – 1.22 (15H, m, C**1**-H_3, C**8**-H), 1.08 (18H, d, *J* = 7.5 Hz, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (C**3**), 126.6 (C**5**), 123.7 (C**7**), 123.4 (C**4**), 110.2 (C**6**), 48.2 (C**2**), 21.3 (C**1**), 17.9 (C**9**), 11.7 (C**8**); HRMS: (ESI^+) calculated for $C_{20}H_{39}N_2OSi$ 351.2826. Found $[M+H]^+$ 351.2829.

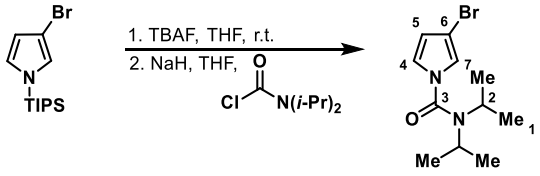
3-Bromo-1-(triisopropylsilyl)-1*H*-pyrrole



To a flame-dried flask was added pyrrole (1.57 mL, 22.6 mmol) in dry THF (36 mL) under nitrogen. *n*-BuLi (17.3 mL, 22.1 mmol, 1.6 M in hexanes) was added dropwise at -78 °C and the solution was stirred for 30 minutes, before TIPSCl (5.33 mL, 24.9 mmol) was added dropwise. The solution was stirred for 4 h before being warmed to ambient temperature. The reaction was quenched by the addition of NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to afford 1-(triisopropylsilyl)-1*H*-pyrrole (4.57 g, 90%) as a colourless oil. *The title compound was used in the next step without further purification.*

To a solution of 1-(triisopropylsilyl)-1*H*-pyrrole (4.50 g, 20.1 mmol) in dry THF (21 mL) was added NBS (3.94 mg, 22.2 mmol) at -78 °C. The solution was stirred for 1 h before being warmed to ambient temperature. The solution was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with saturated aq. $NaHCO_3$ (15 mL). The organic extract was dried over Na_2SO_4 and concentrated *in vacu*o. Purification of the residue by FCC (hexane/EtOAc 3%) afforded the title compound (6.08 mg, quantitative) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (1H, d, *J* = 1.5 Hz), 6.67 (1H, t, *J* = 2.5 Hz), 6.29 (1H, dd, *J* = 2.5, 1.5 Hz), 1.41 (3H, h, *J* = 7.5 Hz,), 1.09 (18H, d, *J* = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 124.8, 123.4, 113.2, 98.0, 17.9, 11.7. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[265]

3-Bromo-*N,N*-diisopropyl-1*H*-pyrrole-1-carboxamide

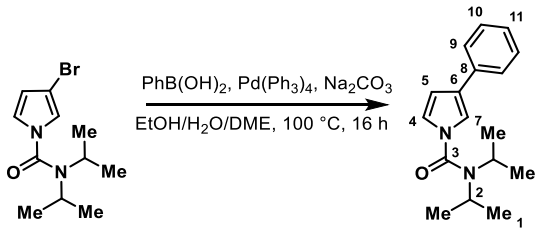


To a flame-dried flask was added 3-bromo-1-(triisopropylsilyl)-1H-pyrrole (1.00 g, 3.31 mmol) in THF (10 mL) under nitrogen. TBAF (1M in THF, 3.31 mL) was added dropwise and the resulting solution was stirred at ambient temperature for 30 minutes. The reaction mixture was diluted with Et_2O (20 mL) and washed with water (10 mL) and brine (10 mL). The organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. *The resulting residue was used without further purification.*

To a suspension of NaH (60% in oil, 159 mg, 3.97 mmol) in dry THF (3 mL) at 0 °C was added the above residue in dry THF (3.7 mL), dropwise over 10 minutes. The resulting solution was stirred at 0 °C for 2 h before diisopropyl carbomoyl chloride (596 mg, 3.64 mmol) in THF (3.0 mL) was added dropwise over 10 minutes. After stirring for 15 minutes the solution was warmed to ambient temperature

and stirred for a further 1 h. The reaction was quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (toluene/CH_2Cl_2 15%) afforded the title product (550 mg, 61%) as a colourless oil. ν_{max}/cm^{-1}: 2971 (m), 1685 (m), 1430 (s), 1321 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (1H, dd, *J* = 2.5, 1.5 Hz, C**7**-H), 6.90 (1H, dd, *J* = 3.0, 2.5 Hz, C**4**-H), 6.22 (1H, dd, *J* = 3.0, 1.5 Hz, C**5**-H), 3.81 (1H, p, *J* = 6.5 Hz, C**2**-H), 1.36 (12H, d, *J* = 6.5 Hz, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.5 (C**3**), 120.9 (C**4**), 119.5 (C**7**), 112.9 (C**5**), 98.7 (C**6**), 48.8 (C**2**), 21.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{11}H_{18}N_2O^{79}Br$ 273.0597. Found $[M+H]^+$ 273.0602.

***N*,*N*-Diisopropyl-3-phenyl-1*H*-pyrrole-1-carboxamide (126e)**

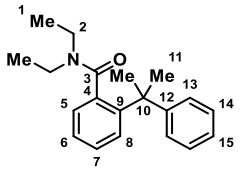


An oven-dried re-sealable tube, fitted with a magnetic stirrer bar, was charged with 3-bromo-*N*,*N*-diisopropyl-1*H*-pyrrole-1-carboxamide (100 mg, 0.366 mmol), phenylboronic acid (78.0 mg, 0.640 mmol), Na_2CO_3 (77.6 mg, 0.732 mmol) and $Pd(PPh_3)_4$ (21.1 mg, 0.018 mmol). The tube was fitted with a rubber septum and purged with nitrogen. EtOH/H_2O/DME (0.73:0.73:2.20 mL) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 100 °C for 16 h before being cooled to ambient temperature and quenched with water (5 mL). The mixture was extracted with Et_2O (3 × 5 mL) and the organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 10%) afforded the title compound (56 mg, 57%) as a colourless oil. ν_{max}/cm^{-1}: 2970 (m), 2981 (m), 1683 (s), 1431 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.48 (2H, m, C**9**-H), 7.35 (2H, dd, *J* = 8.5, 7.0 Hz, C**10**-H), 7.27 (1H, dd, *J* = 2.0, 2.0 Hz, C**4**-H), 7.24 – 7.16 (1H, m, C**11**-H), 7.00 (1H, dd, *J* = 3.0, 2.0 Hz, C**7**-H), 6.54 (1H, dd, *J* = 3.0, 2.0 Hz, C**5**-H), 3.88 (2H, hept, *J* = 6.5 Hz, C**2**-H), 1.39 (12H, d, *J* = 6.5 Hz, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4 (C**3**), 134.7 (C**8**), 128.7 (C**10**), 126.7 (C**6**), 126.7 (C**15**), 125.4 (C**11**), 121.0 (C**7**), 116.3 (C**4**), 108.5 (C**5**), 48.6 (C**2**), 21.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{22}N_2ONa$ 293.1624. Found $[M+Na]^+$ 293.1634.

7.6.3 – Hydroarylation Reactions

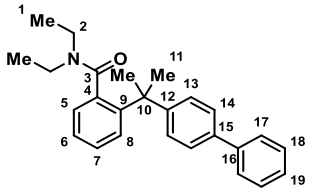
7.6.3.1 Alkene Hydroarylation with Benzamide Substrates

***N,N*-Diethyl-2-(2-phenylpropan-2-yl)benzamide (148ca')**



General Procedure P: The reaction was carried out with styrene derivative **147a'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 20%) afforded the title compound (28.5 mg, 67%) as an orange oil. ν_{max}/cm^{-1}: 2974 (m), 2939 (m), 1627 (m), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.41 (1H, m, C**8**-H), 7.34 – 7.27 (1H, m, C**7**-H), 7.26 – 7.15 (4H, m, C**13**-H, C**14**-H), 7.18 (1H, ddd, *J* = 7.5, 1.0, 1.0 Hz, C**6**-H), 7.16 – 7.10 (1H, m, C**15**-H), 7.03 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 3.10 – 2.97 (2H, m, C**2**-H$_2$), 2.86 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H$_2$), 2.36 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H$_2$), 1.83 (3H, s, C**11**-H$_3$), 1.69 (3H, s, C**11**-H$_3$), 1.02 (3H, t, *J* = 7.0 Hz, C**1**-H$_3$), 0.96 (3H, t, *J* = 7.0 Hz, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C**3**), 149.7 (C**12**), 146.6 (C**9**), 136.6 (C**4**), 128.5 (C**8**), 128.5 (C**7**), 128.0 (C**14**), 127.5 (C**5**), 127.2 (C**13**), 125.8 (C**6**), 125.7 (C**15**), 44.3 (C**10**), 44.0 (C**2**), 39.3 (C**2**), 33.0 (C**11**), 30.0 (C**11**), 13.6 (C**1**), 12.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{25}NONa$ 318.1828. Found $[M+Na]^+$ 318.1835.

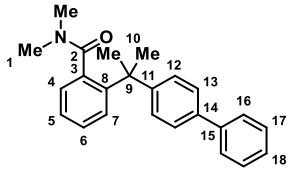
2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N,N*-diethylbenzamide (148cb')



General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (27.7 mg, 75%) as a yellow wax. ν_{max}/cm^{-1}: 2970 (m), 2930 (m), 1628 (s), 1487 (s), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (2H, dd, *J* = 8.0, 1.5 Hz, C**17**-H), 7.52 (1H, d, *J* = 8.5 Hz, C**8**-H), 7.49 (2H, d, *J* = 8.5 Hz, C**18**-H), 7.43 (2H, dd, *J* = 8.5, 7.0 Hz, C**14**-H), 7.36 – 7.30 (4H, m, C**7**-H, C**13**-H, C**19**-H), 7.21 (1H, ddd, *J* = 7.5, 7.5, 1.5 Hz, C**6**-H), 7.05 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 3.17 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H$_2$), 3.06 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H$_2$), 2.88 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H$_2$), 2.37 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H$_2$), 1.89 (3H, s, C**11**-H$_3$), 1.73 (3H, s, C**11**-H$_3$), 1.01 – 0.98 (3H, m, C**1**-H$_3$), 0.97 – 0.94 (3H, m, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C**3**), 148.8 (C**12**), 146.7 (C**9**), 141.1 (C**16**), 138.5 (C**15**), 136.6 (C**4**), 128.9 (C**14**), 128.6 (C**7**), 128.2 (C**8**), 127.8 (C**13**), 127.6 (C**5**), 127.2 (C**19**), 127.0 (C**17**), 126.6 (C**18**), 125.9 (C**6**), 44.2 (C**2**), 44.1 (C**10**), 39.3 (C**2**), 33.1 (C**11**),

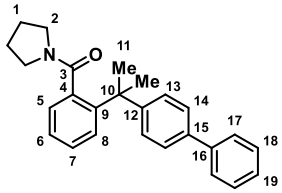
30.0 (C**11**), 13.7 (C**1**), 13.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{26}H_{30}NO$ 372.2322. Found $[M+H]^+$ 372.2315.

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-dimethylbenzamide (148eb')



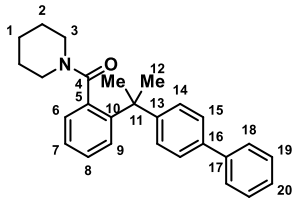
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 10–30%) afforded the title compound (16.4 mg, 48%) as a colourless wax. ν_{max}/cm^{-1}: 2961 (m), 2925 (m), 1633 (s), 1487 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, dd, *J* = 7.5, 1.0 Hz, C**7**-H), 7.61 – 7.54 (2H, m, C**16**-H), 7.52 – 7.48 (2H, m, C**13**-H), 7.47 – 7.39 (2H, m, C**17**-H), 7.41 – 7.29 (4H, m, C**6**-H, C**12**-H, C**18**-H), 7.20 (1H, ddd, *J* = 7.5, 1.5, 1.5 Hz, C**5**-H), 6.98 (1H, dd, *J* = 7.5, 1.5 Hz, C**4**-H), 2.57 (3H, s, C**1**-H$_3$), 2.27 (3H, s, C**1**-H$_3$), 1.91 (3H, s, C**10**-H$_3$), 1.74 (3H, s, C**10**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4 (C**2**), 148.2 (C**11**), 147.0 (C**8**), 141.1 (C**15**), 138.5 (C**14**), 136.3 (C**3**), 129.0 (C**17**), 128.7 (C**6**), 128.1 (C**12**), 128.0 (C**4**), 127.4 (C**7**), 127.3 (C**18**), 127.0 (C**16**), 126.4 (C**13**), 126.0 (C**5**), 43.7 (C**9**), 39.4 (C**1**), 34.2 (C**1**), 33.1 (C**10**), 29.8 (C**10**); HRMS: (ESI$^+$) calculated for $C_{24}H_{25}NO$ 344.2009. Found $[M+H]^+$ 344.2011.

(2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)phenyl)(pyrrolidin-1-yl)methanone (148fb')



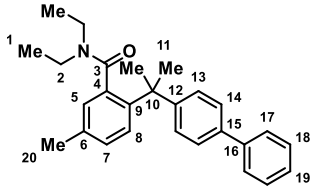
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–40%) afforded the title compound (18.9 mg, 51%) as a colourless wax. ν_{max}/cm^{-1}: 2969 (m), 2871 (m), 1621 (s), 1417 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* = 7.5 Hz, C**8**-H), 7.58 – 7.51 (2H, m, C**17**-H), 7.47 (2H, d, *J* = 8.0 Hz, C**14**-H), 7.45 – 7.41 (2H, m, C**18**-H), 7.42 – 7.28 (4H, m, C**7**-H, C**13**-H, C**19**-H), 7.27 – 7.16 (1H, m, C**6**-H), 7.06 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 3.37 – 3.29 (1H, m, C**2**-H$_2$), 2.97 – 2.87 (1H, m, C**2**-H$_2$), 2.86 – 2.75 (1H, m, C**2**-H$_2$), 2.52 – 2.40 (1H, m, C**2**-H$_2$), 1.96 (3H, s, C**11**-H$_3$), 1.73 (3H, s, C**11**-H$_3$), 1.62 – 1.38 (3H, m, C**1**-H$_2$), 1.29 – 1.15 (1H, m, C**1**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9 (C**3**), 148.2 (C**12**), 146.9 (C**9**), 141.1 (C**16**), 138.5 (C**15**), 137.5 (C**4**), 129.0 (C**18**), 128.8 (C**7**), 128.2 (C**5**), 128.0 (C**13**), 127.3 (C**19**), 127.1 (C**8**), 127.0 (**17**), 126.4 (C**14**), 126.2 (C**6**), 48.2 (C**2**), 45.0 (C**2**), 43.6 (C**10**), 33.4 (C**11**), 29.9 (C**11**), 25.4 (C**1**), 24.2 (C**1**); HRMS: (ESI$^+$) calculated for $C_{26}H_{27}NO$ 370.2165. Found $[M+H]^+$ 370.2168.

(2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)phenyl)(piperidin-1-yl)methanone (148gb')



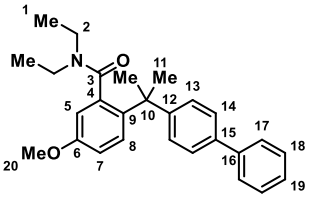
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (12.0 mg, 31%) as an orange oil. ν_{max}/cm^{-1}: 2930 (m), 2852 (m), 1627 (s), 1430 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.55 (2H, m, C**18**-H), 7.55 – 7.51 (1H, m, C**9**-H), 7.51 – 7.47 (2H, m, C**15**-H), 7.47 – 7.39 (2H, m, C**19**-H), 7.39 – 7.30 (4H, m, C**8**-H, C**14**-H, C**20**-H), 7.23 – 7.16 (1H, m, C**7**-H), 7.03 (1H, dd, *J* = 7.5, 1.5 Hz, C**6**-H), 4.18 – 4.02 (1H, m, C**3**-H_2), 3.08 – 2.90 (1H, m, C**3**-H_2), 2.43 – 2.27 (1H, m, C**3**-H_2), 2.28 – 2.13 (1H, m, C**3**-H_2), 1.88 (3H, s, C**12**-H_3), 1.74 (3H, s, C**12**-H_3), 1.71 – 1.60 (1H, m, C**2**-H_2), 1.54 – 1.35 (2H, m, C**2**-H_2), 1.35 – 1.25 (3H, m, C**1**-H_2, C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1 (C**4**), 148.6 (C**13**), 146.8 (C**10**), 141.2 (C**17**), 138.5 (C**16**), 136.3 (C**5**), 128.9 (C**19**), 128.6 (C**8**), 128.0 (C**9**), 128.0 (C**14**), 127.5 (C**6**), 127.2 (C**20**), 127.1 (C**18**), 126.6 (C**15**), 126.0 (C**7**), 48.5 (C**3**), 43.9 (C**11**), 41.9 (C**3**), 33.0 (C**12**), 30.0 (C**12**), 25.8 (C**1**), 25.5 (C**2**), 24.7 (C**2**); HRMS: (ESI$^+$) calculated for $C_{27}H_{29}NO$ 384.2322. Found $[M+H]^+$ 384.2316.

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diethyl-5-methylbenzamide (148db')



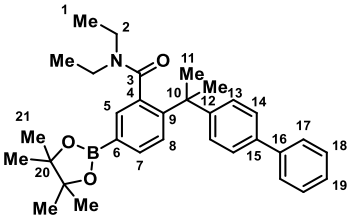
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (23.9 mg, 62%) as an orange oil. ν_{max}/cm^{-1}: 2968 (m), 2929 (m), 1628 (s), 1486 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.53 (2H, m, C**17**-H), 7.48 (2H, d, *J* = 8.0 Hz, C**14**-H), 7.46 – 7.41 (2H, m, C**18**-H), 7.38 (1H, d, *J* = 8.0 Hz, C**8**-H), 7.36 – 7.31 (3H, m, C**13**-H, C**19**-H), 7.13 (1H, dd, *J* = 8.0, 2.0 Hz, C**7**-H), 6.91 – 6.84 (1H, m, C**5**-H), 3.26 – 3.03 (2H, m, C**2**-H_2), 2.91 (1H, dq, *J* = 14.5, 7.5 Hz, C**2**-H_2), 2.39 (1H, dq, *J* = 14.5, 7.5 Hz, C**2**-H_2), 2.31 (3H, s, C**20**-H_3), 1.86 (3H, s, C**11**-H_3), 1.71 (3H, s, C**11**-H_3), 1.09 – 0.92 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8 (C**3**), 149.1 (C**12**), 143.7 (C**9**), 141.1 (C**16**), 138.4 (C**15**), 136.4 (C**4**), 135.4 (C**6**), 129.3 (C**7**), 128.9 (C**18**), 128.3 (C**8**), 128.2 (C**5**), 127.7 (C**13**), 127.2 (C1**9**), 127.0 (C**17**), 126.6 (C**14**), 44.1 (C**2**), 43.7 (C**10**), 39.3 (C**2**), 33.0 (C**11**), 30.0 (C**11**), 20.8 (C**20**), 13.7 (C**1**), 12.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{27}H_{31}NO$ 386.2478. Found $[M+Na]^+$ 386.2475.

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diethyl-5-methoxybenzamide (148kb')



General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–30%) afforded the title compound (21.0 mg, 52%) as a colourless oil. ν_{max}/cm^{-1}: 2966 (m), 2930 (m), 1630 (s), 1466 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.54 (2H, m, C**17**-H), 7.53 – 7.46 (2H, m, C**14**-H), 7.45 – 7.38 (3H, m, C**8**-H, C**18**-H), 7.36 – 7.30 (3H, m, C**13**-H, C**19**-H), 6.86 (1H, dd, *J* = 9.0, 3.0 Hz, C**7**-H), 6.58 (1H, d, *J* = 3.0 Hz, C**5**-H), 3.79 (3H, s, C**20**-H_3), 3.23 – 3.04 (2H, m, C**2**-H_2), 2.93 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 2.39 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 1.85 (3H, s, C**11**-H_3), 1.70 (3H, s, C**11**-H_3), 1.03 – 0.94 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C**3**), 157.3 (C**6**), 149.2 (C**12**), 141.1 (C**16**), 138.8 (C**9**), 138.4 (C**15**), 137.5 (C**4**), 129.7 (C**8**), 128.9 (C**18**), 127.7 (C**13**), 127.2 (C**19**), 127.0 (C**17**), 126.6 (C**14**), 114.1 (C**7**), 112.9 (C**5**), 55.4 (C**20**), 44.1 (C**2**), 43.4 (C**10**), 39.3 (C**2**), 33.2 (C**11**), 30.1 (C**11**), 13.8 (C**1**), 12.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{27}H_{31}NO_2$ 402.2428. Found $[M+H]^+$ 402.2424.

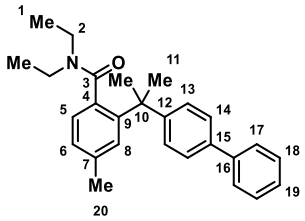
2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (148lb')



General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–30%) afforded the title compound (9.10 mg, 18%) as a yellow oil. ν_{max}/cm^{-1}: 2974 (m), 2929 (m), 1629 (s), 1359 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (1H, dd, *J* = 8.0, 1.5 Hz, C**7**-H), 7.58 – 7.53 (2H, m, C**17**-H), 7.58 – 7.40 (6H, m, C**5**-H, C**8**-H, C**14**-H, C**18**-H), 7.37 – 7.27 (3H, m, C**13**-H, C**19**-H), 3.18 – 3.05 (2H, m, C**2**-H_2), 2.87 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H_2), 2.38 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H_2), 1.87 (3H, s, C**11**-H_3), 1.72 (3H, s, C**11**-H_3), 1.32 (12H, s, C**21**-H_3), 1.01 – 0.91 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C**3**), 149.8 (C**9**), 148.7 (C**12**), 141.1 (C**6**), 138.5 (C**15**), 136.0 (C**4**), 135.0 (C**7**), 134.3 (C**5**), 128.9 (ArCH), 127.8 (C**13**), 127.7 (C**8**), 127.2 (C**19**), 127.1 (C**17**), 126.7 (ArCH), 84.0 (C**20**), 44.4 (C**10**), 44.2 (C**2**), 39.3 (C**2**), 33.0 (C**11**), 29.9 (C**11**), 25.0 (C**21**), 13.6 (C**1**), 13.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{32}H_{40}NO_3B$ 498.3174. Found $[M+H]^+$ 498.3163.

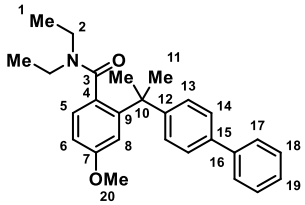
*Note: C**6** was not observed by ^{13}C NMR.*

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diethyl-4-methylbenzamide (148mb')



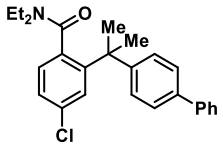
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (28.1 mg, 73%) as a yellow oil. ν_{max}/cm^{-1}: 2968 (m), 2934 (m), 1626 (s), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.53 (2H, m, C**17**-H), 7.50 – 7.46 (2H, m, C**14**-H), 7.43 (2H, dd, *J* = 7.5, 1.5 Hz, C**18**-H), 7.36 – 7.30 (4H, m, C**8**-H, C**13**-H, C**19**-H), 7.02 (1H, dd, *J* = 7.5, 1.5 Hz, C**6**-H), 6.94 (1H, d, *J* = 7.5 Hz, C**5**-H), 3.20 – 2.97 (2H, m, C**2**-H_2), 2.88 (1H, dq, *J* = 14.5, 7.5 Hz, C**2**-H_2), 2.37 (3H, s, C**20**-H_3), 2.35 – 2.27 (1H, m, C**2**-H_3), 1.88 (3H, s, C**11**-H_3), 1.72 (3H, s, C**11**-H_3), 1.01 – 0.91 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8 (C**3**), 148.9 (C**12**), 146.6 (C**9**), 141.2 (C**16**), 138.4 (C**15**), 138.2 (C**7**), 133.8 (C**4**), 128.9 (C**18**), 128.8 (C**8**), 127.8 (C**13**), 127.6 (C**5**), 127.2 (C**19**), 127.0 (C**17**), 126.6 (C**14**), 126.5 (C**6**), 44.2 (C**2**), 43.9 (C**10**), 39.3 (C**2**), 33.2 (C**11**), 30.0 (C**11**), 21.7 (C**20**), 13.7 (C**1**), 13.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{27}H_{31}NO$ 386.2478. Found $[M+H]^+$ 386.2474.

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diethyl-4-methoxybenzamide (148nb')



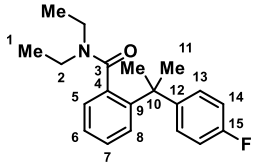
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–30%) afforded the title compound (26.2 mg, 65%) as an orange oil. ν_{max}/cm^{-1}: 2968 (m), 2938 (m), 1619 (s), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.53 (2H, m, C**17**-H), 7.50 – 7.40 (4H, m, C**14**-H, C**18**-H), 7.36 – 7.29 (3H, m, C**13**-H, C**19**-H), 7.10 (1H, d, *J* = 2.5 Hz, C**8**-H), 6.99 (1H, d, *J* = 8.5 Hz, C**5**-H), 6.73 (1H, dd, *J* = 8.5, 2.5 Hz, C**6**-H), 3.82 (3H, s, C**20**-H_3), 3.12 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H_2), 3.02 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H_2), 2.87 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H_2), 2.31 (1H, dq, *J* = 14.0, 7.0 Hz, C**2**-H_2), 1.90 (3H, s, C**11**-H_3), 1.71 (3H, s, C**11**-H_3), 0.94 (6H, t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5 (C**3**), 159.6 (C**7**), 148.9 (C**9**), 148.4 (C**12**), 141.1 (C**16**), 138.5 (C**15**), 129.4 (C**4**), 128.9 (C**5**), 128.9 C**18**), 127.7 (C**13**), 127.2 (C1**9**), 127.0 (C**14**), 126.6 (C**17**), 114.9 (C**8**), 109.8 (C**6**), 55.4 (C**20**), 44.2 (C**2**), 44.1 (C**10**), 39.3 (C**2**), 33.3 (C**11**), 29.8 (C**11**), 13.8 (C**1**), 13.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{27}H_{31}NO_2$ 402.2428. Found $[M+H]^+$ 402.2423.

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-4-chloro-*N*,*N*-diethylbenzamide (148ob')



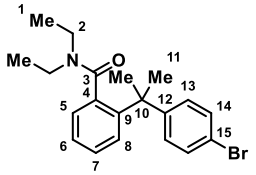
General Procedure P: The reaction was carried out with styrene derivative **147b'** (400 mol%) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 – 2.97 (2H, m), 2.88 (1H, dq, *J* = 14.5, 7.0 Hz), 2.69 (1H, dq, *J* = 14.5, 7.0 Hz), 1.79 (3H, s), 1.60 (3H, s), 0.85 (3H, t, *J* = 7.0 Hz), 0.82 (3H, t, *J* = 7.0 Hz).

***N*,*N*-Diethyl-2-(2-(4-fluorophenyl)propan-2-yl)benzamide (148cc')**



General Procedure P: The reaction was carried out with styrene derivative **147c'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (23.1 mg, 74%) as a yellow oil. ν_{max}/cm^{-1}: 2970 (m), 2934 (m), 1627 (s), 1507 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (1H, dd, *J* = 8.0, 1.0 Hz, C**8**-H), 7.30 (1H, ddd, *J* = 8.0, 1.5, 1.0 Hz, C**7**-H), 7.24 – 7.16 (3H, m, C**6**-H, C**13**-H), 7.03 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 6.98 – 6.88 (2H, m, C**14**-H), 3.25 – 3.09 (2H, m, C**2**-H_2), 2.87 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 2.44 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 1.81 (3H, s, C**11**-H_3), 1.67 (3H, s, C**11**-H_3), 1.03 (3H, t, *J* = 7.0 Hz, C**1**-H_3), 0.99 (3H, t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C**3**), 161.0 (d, *J* = 244.0 Hz, C**15**), 146.5 (C**9**), 145.6 (d, *J* = 3.0 Hz, C**12**), 136.4 (C**4**), 128.77 (d, *J* = 7.5 Hz, C**13**), 128.7 (C**7**), 128.3 (C**8**), 127.6 (C**5**), 126.0 (C**6**), 114.56 (d, *J* = 20.9 Hz, C**14**), 44.1 (C**2**), 43.9 (C**10**), 39.2 (C**2**), 33.0 (C**11**), 30.3 (C**11**), 13.7 (C**1**), 12.9 (C**1**); ^{19}F NMR (377 MHz, $CDCl_3$) δ -118.07 (ddd, *J* = 8.5, 5.5 Hz); HRMS: (ESI^{+}) calculated for $C_{20}H_{24}NOF$ 314.1915. Found $[M+H]^{+}$ 314.1912.

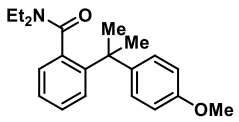
2-(2-(4-Bromophenyl)propan-2-yl)-*N*,*N*-diethylbenzamide (148cd')



General Procedure P: The reaction was carried out with styrene derivative **147d'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–30%) afforded the title compound (9.50 mg, 25%) as a yellow oil. ν_{max}/cm^{-1}: 2968 (m), 2928 (m), 1628 (s), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, dd, *J* = 8.0, 1.0 Hz, C**8**-H), 7.39 – 7.34 (2H, m, C**14**-H), 7.31 (1H, ddd, *J* = 8.0, 1.5, 1.0 Hz, C**7**-H), 7.20 (1H, ddd, *J* = 8.0, 1.5, 1.0 Hz, C**6**-H), 7.17 – 7.09 (2H, m, C**13**-H), 7.04 (1H,

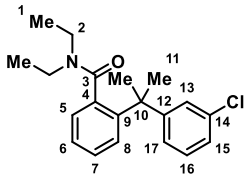
dd, *J* = 8.0, 1.5 Hz, C**5**-H), 3.22 – 3.07 (2H, m, C**2**-H_2), 2.87 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 2.44 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 1.80 (3H, s, C**11**-H_3), 1.66 (3H, s, C**11**-H_3), 1.05 – 0.97 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5 (C**3**), 148.9 (C**12**), 146.2 (C**9**), 136.4 (C**4**), 131.0 (C**14**), 129.2 (C**13**), 128.7 (C**7**), 128.3 (C**8**), 127.7 (C**5**), 126.1 (C**6**), 119.6 (C**15**), 44.1 (C**10**), 44.1 (C**2**), 39.2 (C**2**), 32.8 (C**11**), 30.1 (C**11**), 13.7 (C**1**), 12.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{24}NO^{79}Br$ 374.1114. Found $[M+H]^+$ 374.1105.

***N*,*N*-Diethyl-2-(2-(4-methoxyphenyl)propan-2-yl)benzamide (148ce')**



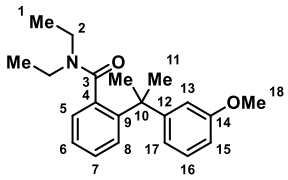
General Procedure P: The reaction was carried out with styrene derivative **147e'** (400 mol%) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 – 3.09 (2H, m), 1.79 (3H, s), 1.65 (3H, s), 1.05 – 0.99 (3H, m), 0.96 (3H, t, *J* = 7.1 Hz).

2-(2-(3-Chlorophenyl)propan-2-yl)-*N*,*N*-diethylbenzamide (148cf')



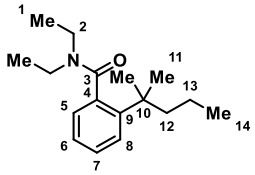
General Procedure P: The reaction was carried out with styrene derivative **147f'** (400 mol%), Ir(cod)$_2$]BARF (7.5 mol%) and **(*rac*)-L-15f (**7.5 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–30%) afforded the title compound (21.5 mg, 65%) as a yellow oil. ν_{max}/cm^{-1}: 2959 (m), 2931 (m), 1629 (s), 1423 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, dd, *J* = 8.0, 1.0 Hz, C**8**-H), 7.32 (1H, ddd, *J* = 8.0, 1.5, 1.0 Hz, C**7**-H), 7.22 (1H, dd, *J* = 7.5, 1.0 Hz, C**6**-H), 7.20 – 7.15 (3H, m, C**13**-H, C**16**-H, C**17**-H), 7.13 (1H, ddd, *J* = 7.5, 4.0, 2.0 Hz, C**15**-H), 7.05 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 3.23 – 3.05 (2H, m, C**2**-H_2), 2.86 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 2.41 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 1.82 (3H, s, C**11**-H_3), 1.66 (3H, s, C**11**-H_3), 1.06 – 0.95 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4 (C**3**), 151.9 (C**12**), 145.9 (C**9**), 136.5 (C**4**), 133.8 (C**14**), 129.3 (C**16**), 128.8 (C**7**), 128.1 (C**8**), 127.7 (C**5**), 127.6 (Ar**C**H), 126.1 (C**6**), 126.0 (C**15**), 125.6 (Ar**C**H), 44.4 (C**10**), 43.9 (C**2**), 39.4 (C**2**), 33.0 (C**11**), 29.9 (C**11**), 13.8 (C**1**), 13.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{24}NOCl$ 330.1619. Found $[M+H]^+$ 330.1612.

***N,N*-Diethyl-2-(2-(3-methoxyphenyl)propan-2-yl)benzamide (148cg')**



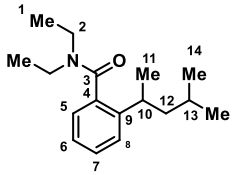
General Procedure P: The reaction was carried out with styrene derivative **147g'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–30%) afforded the title compound (22.9 mg, 70%) as an orange oil. ν_{max}/cm^{-1}: 2967 (m), 2933 (m), 1627 (s), 1424 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (1H, dd, *J* = 8.0, 1.5 Hz, C**8**-H), 7.31 – 7.25 (1H, m, C**7**-H), 7.21 – 7.13 (2H, m, C**6**-H, C**16**-H), 7.03 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 6.86 – 6.77 (2H, m, C**13**-H, C**17**-H), 6.69 (1H, dd, *J* = 8.0, 3.5 Hz, C**15**-H), 3.76 (3H, s, C**18**-H_3), 3.28 – 3.10 (2H, m, C**2**-H_2), 2.91 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 2.44 (1H, dq, *J* = 14.5, 7.0 Hz, C**2**-H_2), 1.80 (3H, s, C**11**-H_3), 1.68 (3H, s, C**11**-H_3), 1.03 (3H, t, *J* = 7.0 Hz, C**1**-H_3), 0.98 (3H, t, *J* = 7.0 Hz, C**1**-H_3);^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C**3**), 159.3 (C**14**), 151.6 (C**12**), 146.4 (C**9**), 136.5 (C**4**), 128.9 (C**16**), 128.6 (C**8**), 128.5 (C**7**), 127.5 (C**5**), 125.8 (C**6**), 120.0 (ArCH), 113.7 (ArCH), 110.5 (C**15**), 55.2 (C**18**), 44.4 (C**10**), 43.7 (C**2**), 39.1 (C**2**), 32.9 (C**11**), 29.9 (C**11**), 13.6 (C**1**), 12.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{21}H_{27}NO_2$ 326.2115. Found $[M+H]^+$ 326.2112.

***N,N*-Diethyl-2-(2-methylpentan-2-yl)benzamide (148ch')**



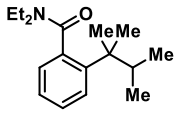
General Procedure P: The reaction was carried out with styrene derivative **147h'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (6.00 mg, 23%) as a yellow oil. ν_{max}/cm^{-1}: 2957 (m), 2871 (m), 1633 (s), 1422 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (1H, dd, *J* = 8.0, 1.0 Hz, C**8**-H), 7.28 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz, C**7**-H), 7.17 (1H, ddd, *J* = 7.5, 1.0, 1.0 Hz, C**6**-H), 7.04 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 3.77 (1H, dq, *J* = 13.5, 7.0 Hz, C**2**-H_2), 3.34 (1H, dq, *J* = 13.5, 7.0 Hz, C**2**-H_2), 3.19 (1H, dq, *J* = 13.5, 7.0 Hz, C**2**-H_2), 3.04 (1H, dq, *J* = 13.5, 7.0 Hz, C**2**-H_2), 1.81 (1H, ddd, *J* = 13.5, 11.5, 5.0 Hz, C**12**-H_2), 1.60 – 1.50 (1H, m, C**12**-H_2), 1.35 (3H, s, C**11**-H_3), 1.32 (3H, s, C**11**-H_3), 1.24 (3H, t, *J* = 7.0 Hz, C**1**-H_3), 1.19 – 1.10 (2H, m, C**13**-H_2), 1.08 (3H, t, *J* = 7.0 Hz, C**1**-H_3), 0.83 (3H, t, *J* = 7.0 Hz, C**14**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1 (C**3**), 145.4 (C**9**), 136.3 (C**4**), 128.5 (C**8**), 128.3 (C**7**), 127.5 (C**5**), 125.6 (C**6**), 47.2 (C**12**), 43.4 (C**2**), 39.8 (C**10**), 38.5 (C**2**), 29.4 (C**11**), 29.1 (Cf**11**), 18.3 (C**13**), 14.9 (C**14**), 13.4 (C**1**), 12.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{27}NO$ 262.2165. Found $[M+H]^+$ 262.2160.

***N,N*-Diethyl-2-(4-methylpentan-2-yl)benzamide (148ch'')**



General Procedure P: The reaction was carried out with styrene derivative **147h'** (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (9.40 mg, 36%) as a colourless solid. ν_{max}/cm^{-1}: 2956 (m), 2868 (m), 1633 (s), 1425 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.30 (2H, m, C**7**-H, C**8**-H), 7.23 – 7.17 (1H, m, C**6**-H), 7.14 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 3.99 – 3.82 (1H, m, C**2**-H$_2$), 3.35 – 3.26 (2H, m, C**2**-H$_2$), 3.25 – 3.02 (1H, m, C**2**-H$_2$), 2.93 – 2.82 (1H, m, C**10**-H), 1.62 – 1.53 (1H, m, C**13**-H), 1.49 (2H, dq, *J* = 10.0, 7.0, 6.0 Hz, C**12**-H$_2$), 1.31 – 1.26 (3H, m, C**1**-H$_3$), 1.22 – 1.16 (3H, m, C**11**-H$_3$), 1.13 – 1.02 (3H, m, C**1**-H$_3$), 0.93 – 0.83 (6H, m, C**14**-H$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.0 (C**3**), 170.8 (C**3**), 144.9 (C**9**), 144.3 (C**9**), 136.7 (C**4**), 136.5 (C**4**), 129.0 (C**8**), 128.9 (C**8**), 126.5 (C**7**), 126.3 (C**7**), 125.9 (C**6**), 125.7 (C**6**), 125.6 (C**5**), 125.4 (C**5**), 48.1 (C**12**), 46.9 (C**12**), 43.0 (C**2**), 43.0 (C**2**), 38.7 (C**2**), 38.6 (C**2**), 33.9 (C**10**), 33.5 (C**10**), 25.9 (C**13**), 25.8 (C**13**), 23.3 (C**14**), 23.3 (C**14**), 23.0 (C**14**), 22.6 (C**11**), 22.4 (C**14**), 21.6 (C**11**), 14.1 (C**1**), 14.0 (C**1**), 13.0 (C**1**), 12.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{27}NO$ 262.2165. Found $[M+H]^+$ 262.2163.

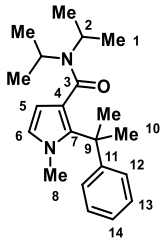
2-(2,3-Dimethylbutan-2-yl)-*N,N*-diethylbenzamide (148cn')



General Procedure P: The reaction was carried out with styrene derivative **147n'** (400 mol%) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 – 3.02 (1H, m), 2.95 (1H, dq, *J* = 14.0, 7.0 Hz), 2.29 – 2.19 (2H, m), 1.05 – 0.93 (6H, m), 0.74 (3H, d, *J* = 7.0 Hz), 0.65 (3H, d, *J* = 7.0 Hz).

7.6.3.2 Alkene Hydroarylation with Pyrrole Substrates

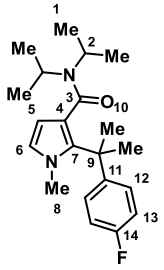
***N,N*-Diisopropyl-1-methyl-2-(2-phenylpropan-2-yl)-1*H*-pyrrole-3-carboxamide (151aa')**



General Procedure Q: The reaction was carried out with styrene derivative **147a'** (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/EtOAc 30–50%) afforded the title compound (28.3 mg, 87%) as an orange oil. ν_{max}/cm^{-1}: 2954 (m), 2929 (m), 1620 (s), 1440 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (2H, dd, *J* = 8.0, 1.0 Hz, C**12**-H), 7.23 (2H, dd, *J* = 8.0, 1.0 Hz, C**13**-H), 7.15 – 7.06 (1H, m, C**14**-H), 6.41 (1H, d, *J* = 2.5 Hz, C**6**-H), 6.30 (1H, d, *J* = 2.5 Hz, C**5**-H), 3.99 – 3.10 (2H, m, C**2**-H), 3.55 (3H, s, C**8**-H_3), 1.70 (6H, s, C**10**-H_3), 1.48 – 0.80 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2 (C**3**), 150.8 (C**11**), 132.8 (C**7**), 127.9 (C**13**), 126.7 (C**12**), 125.3 (C**14**), 119.9 (C**4**), 119.7 (C**5**), 119.6 (C**6**), 39.1 (C**9**), 36.1 (C**8**), 31.2 (C**10**), 20.7 (C**1**); HRMS: (ESI$^+$) calculated for $C_{21}H_{30}N_2ONa$ 349.2250. Found $[M+H]^+$ 349.2267.

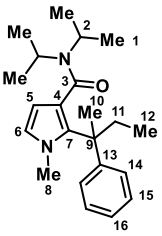
*Note: C**2** was not observed by ^{13}C NMR analysis.*

2-(2-(4-Fluorophenyl)propan-2-yl)-*N*,*N*-diisopropyl-1-methyl-1*H*-pyrrole-3-carboxamide (151ac')



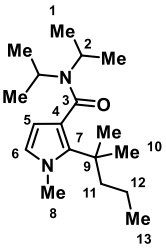
General Procedure Q: The reaction was carried out with styrene derivative **147c'** (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/EtOAc 20–40%) afforded the title compound (25.5 mg, 74%) as a colourless oil. ν_{max}/cm^{-1}: 2855 (m), 2932 (m), 1619 (s), 1506 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (2H, m, C**12**-H), 6.94 – 6.83 (2H, m, C**13**-H), 6.41 (1H, d, *J* = 2.5 Hz, C**6**-H), 6.31 (1H, d, *J* = 2.5 Hz, C**5**-H), 3.91 – 2.88 (2H, m, C**2**-H), 3.55 (3H, s, C**8**-H_3), 1.68 (6H, s, C**10**-H_3), 1.32 – 0.92 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0 (C**3**), 160.9 (d, *J* = 243.0 Hz, C**14**), 146.6 (d, *J* = 3.0 Hz, C**11**), 132.7 (C**7**), 128.2 (d, *J* = 7.5 Hz, C**12**), 119.8 (C**4**), 119.7 (C**6**), 119.6 (C**5**), 114.36 (d, *J* = 21.0 Hz, C**13**), 49.2 (C**2**), 45.9 (C**2**), 38.7 (C**9**), 36.2 (C**8**), 31.4 (C**10**), 20.7 (C**1**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -119.29; HRMS: (ESI$^+$) calculated for $C_{21}H_{29}FNO$ 345.2337. Found $[M+H]^+$ 345.2326.

***N,N*-Diisopropyl-1-methyl-2-(2-phenylbutan-2-yl)-1*H*-pyrrole-3-carboxamide (151aj')**



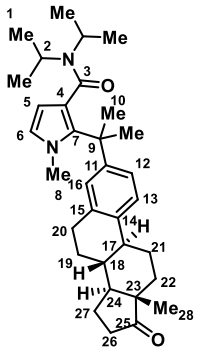
General Procedure Q: The reaction was carried out with styrene derivative **147j'** (400 mol%) and was run for 16 h. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (25.0 mg, 73%) as an orange oil. ν_{max}/cm^{-1}: 2954 (m), 2927 (m), 1619 (s), 1440 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (2H, dd, *J* = 8.0, 1.5 Hz, C**14**-H), 7.25 – 7.19 (2H, m, C**15**-H), 7.15 – 7.07 (1H, m, C**16**-H), 6.41 (1H, d, *J* = 2.5 Hz, C**6**-H), 6.29 (1H, d, *J* = 2.5 Hz, C**5**-H), 4.01 – 3.58 (1H, m, C**2**-H), 3.55 (3H, s, C**8**-H_3), 3.40 – 2.96 (1H, m, C**2**-H), 2.35 – 2.20 (1H, m, C**11**-H_2), 2.02 (1H, dq, *J* = 14.5, 7.5 Hz, C**11**-H_2), 1.65 (3H, s, C**10**-H_3), 1.40 – 0.82 (12H, m, C**1**-H_3), 0.71 (1H, t, *J* = 7.5 Hz, C**12**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (C**3**), 149.4 (C**13**), 132.3 (C**7**), 127.8 (C**15**), 127.4 (C**14**), 125.2 (C**16**), 120.3 (C**5**), 112.0 (C**4**), 119.6 (C**6**), 42.7 (C**9**), 36.2 (C**8**), 34.3 (C**11**), 26.6 (C**10**), 20.7 (C**1**), 9.2 (C**12**); HRMS: (ESI$^+$) calculated for $C_{22}H_{33}N_2O$ 341.2587. Found $[M+H]^+$ 341.2582.
*Note: C**2** was not observed by ^{13}C NMR analysis.*

***N,N*-Diisopropyl-1-methyl-2-(2-methylpentan-2-yl)-1*H*-pyrrole-3-carboxamide (151ah')**



General Procedure Q: The reaction was carried out with alkene derivative **147h'** (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/EtOAc 20–30%) afforded the title compound (24.3 mg, 83%) as a yellow oil. ν_{max}/cm^{-1}: 2957 (m), 2929 (m), 1623 (s), 1439 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (1H, d, *J* = 2.5 Hz, C**5**/**6**-H), 6.29 (1H, d, *J* = 2.5 Hz, C**5**/**6**-H), 4.16 – 3.26 (2H, m, C**2**-H), 3.54 (3H, s, C**8**-H_3), 1.64 – 1.52 (2H, m, C**11**-H_2), 1.39 – 1.07 (14H, m, C**1**-H_3, C**12**-H_2), 1.23 (6H, s, C**10**-H_3), 0.86 (3H, t, *J* = 7.5 Hz, C**13**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3 (C**3**), 131.8 (C**7**), 119.7 (C**4**), 119.1 (C**6**/**5**), 118.9 (C**6**/**5**), 45.9 (C**11**), 36.1 (C**8**), 34.8 (C**9**), 29.2 (C**10**), 20.8 (C**1**), 18.3 (C**12**), 15.0 (C**13**); HRMS: (ESI$^+$) calculated for $C_{18}H_{32}N_2O$ 293.2587. Found $[M+H]^+$ 293.2576.
*Note: C**2** was not observed by ^{13}C NMR analysis.*

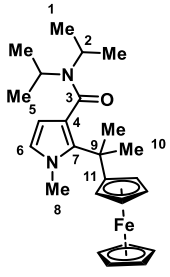
***N*,*N*-Diisopropyl-1-methyl-2-(2-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)propan-2-yl)-1*H*-pyrrole-3-carboxamide (151ao')**



General Procedure Q: The reaction was carried out with styrene derivative **147o'** (150 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 20–40%) afforded the title compound (26.6 mg, 53%) as beige plates. ν_{max}/cm^{-1}: 2962 (m), 2928 (m), 2859(m), 1737 (s), 1611 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.08 (2H, m, C**12**-H, C**13**-H), 7.07 (1H, s, C**16**-H), 6.37 (1H, d, *J* = 2.5 Hz, C**5**/**6**-H), 6.31 (1H, d, *J* = 2.5 Hz, C**5**/**6**-H), 3.96 – 3.66 (1H, m, C**2**-H), 3.53 (3H, s, C**8**-H_3), 3.37 – 3.14 (1H, m, C**2**-H), 2.84 (2H, dd, *J* = 9.0, 4.0 Hz, C**19**-H_2), 2.47 (1H, dd, *J* = 18.5, 9.0 Hz, C**27**-H_2), 2.42 – 2.32 (1H, m, C**18**-H), 2.30 – 2.17 (1H, m, CH), 2.17 – 2.08 (1H, m, CH), 2.08 – 1.85 (3H, m, CH), 1.67 (6H, d, *J* = 4.5 Hz, C**10**-H_3), 1.64 – 1.12 (15H, m, CH, C**1**-H_3), 0.87 (3H, s, C**28**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 221.2 (C**25**), 168.2 (C**3**), 148.1 (C**11**), 136.3 (C**14**), 135.4 (C**15**), 133.1 (C**7**), 127.1 (C**16**), 124.8 (C**12**/**13**), 124.7 (C**12**/**13**), 119.9 (C**4**), 119.6 (C**5**/**6**), 119.6 (C**5**/**6**), 50.7 (CH), 48.1 (C**9**), 44.5 (CH), 38.5 (CH), 38.4 (CH), 36.3 (C**8**), 36.0 (C**27**), 31.8 (CH), 31.2 (C**10**), 29.8 (C**19**), 26.8 (CH), 25.8 (C**18**), 21.7 (C**1**), 20.7 (C**23**), 14.0 (C**28**); m.p. 268–270 °C ($CDCl_3$). *A mass could not be observed by ESI or MALDI.*

*Note: C**2** was not observed by ^{13}C NMR analysis.*

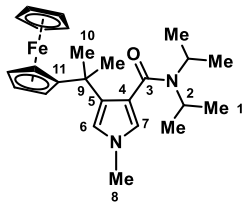
(151ap' C2)



General Procedure Q: The reaction was carried out with styrene derivative **147p'** (400 mol%) and was run for 24 h. Purification of the residue by FCC (hexane/EtOAc 20–30%) afforded the title compound (14.3 mg, 33%) as an orange oil. ν_{max}/cm^{-1}: 2956 (m), 2927 (m), 1602 (s), 1440 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (1H, d, *J* = 2.0 Hz, C**6**-H), 5.96 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.64 – 4.22 (1H, m, C**2**-H), 4.19 (5H, ap. s, ferrocene), 4.12 – 4.07 (4H, m, ferrocene), 4.00 – 3.67 (1H, m, C**2**-H), 3.31

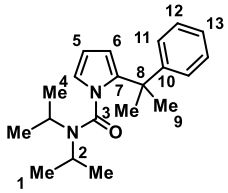
(3H, s, C**8**-H$_3$), 1.71 (6H, s, C**10**-H$_3$), 1.41 – 1.19 (12H, m, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2 (C**3**), 140.8 (C**7**), 125.5 (C**6**), 118.2 (C**4**), 106.6 (C**5**), 68.7 (ferrocene), 67.6 (C**11**), 66.9 (ferrocene), 49.1 (C**2**), 36.7 (C**8**), 34.4 (C**9**), 30.0 (C**10**), 21.3 (C**1**); HRMS: (ESI$^+$) calculated for $C_{25}H_{35}N_2OFe$ 435.2094. Found $[M+H]^+$ 435.2097.

(151ap' C4)



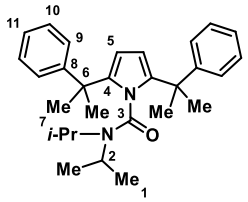
General Procedure Q: The reaction was carried out with styrene derivative **147p'** (400 mol%) and was run for 24 h. Purification of the residue by FCC (hexane/EtOAc 20–30%) afforded the title compound (11.0 mg, 25%, rotamers *A:B*) as an orange oil. ν_{max}/cm^{-1}: 2965 (m), 2928 (m), 1622 (s), 1440 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (0.15H, d, *J* = 3.0 Hz, *B*, C**6**/**7**-H), 6.31 (0.85H, d, *J* = 3.0 Hz, *A*, C**6**/**7**-H), 5.91 (0.15H, d, *J* = 3.0 Hz, *B*, C**6**/**7**-H), 5.73 (0.85H, d, *J* = 3.0 Hz, *A*, C**6**/**7**-H), 4.23 – 4.07 (11H, m, *A*+*B*, ferrocene, C**2**-H), 3.55 (0.45H, s, *B*, C**8**-H$_3$), 3.40 (2.55H, s, *A*, C**8**-H$_3$), 2.04 (0.9H, s, *B*, C**10**-H$_3$), 1.71 (5.1H s, *A*, C**10**-H$_3$), 1.66 – 0.75 (12H, m, *A*+*B*, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1 (C**3**), 133.7 (C**5**), 119.6 (pyrrole), 119.2 (pyrrole), 119.1 (C**4**), 68.6 (ferrocene), 67.0 (C**11**), 66.7 (ferrocene), 46.6 (C**2**), 36.0 (C**9**), 34.4 (C**8**), 29.8 (C**10**), 20.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{25}H_{35}N_2OFe$ 435.2094. Found $[M+H]^+$ 435.2095.

***N*,*N*-Diisopropyl-2-(2-phenylpropan-2-yl)-1*H*-pyrrole-1-carboxamide (152aa')**



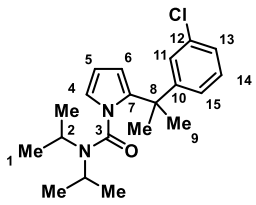
General Procedure Q: The reaction was carried out with styrene derivative **147a'** (400 mol%) and was run for 48 h. Purification of the residue by FCC (toluene/Et_2O 1–2%) afforded the title compound (31. 3 mg, 72%) as a yellow oil. ν_{max}/cm^{-1}: 2969 (m), 2933 (m), 1685 (s), 1423 (s), 1322 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.28 (2H, m, C**11**-H), 7.27 – 7.21 (2H, m, C**12**-H), 7.17 – 7.10 (1H, m, C**13**-H), 6.57 (1H, dd, *J* = 3.0, 1.5 Hz, C**4**-H), 6.20 (1H, dd, *J* = 3.0, 1.5 Hz, C**5**-H), 6.14 – 6.07 (1H, m, C**6**-H), 3.30 (2H, h, *J* = 6.5 Hz, C**2**-H), 1.77 (6H, s, C**9**-H$_3$), 1.12 (6H, d, *J* = 6.5 Hz, C**1**-H$_3$), 1.04 – 0.93 (6H, m, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8 (C**3**), 148.8 (C**10**), 142.2 (C**7**), 128.2 (C**12**), 126.7 (C**11**), 125.7 (C**13**), 120.1 (C**4**), 108.1 (C**5**), 107.4 (C**6**), 48.3 (C**2**), 40.0 (C**8**), 31.2 (C**9**), 20.7 (C**1**), 20.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{29}N_2O$ 313.2274. Found $[M+H]^+$ 313.2283. m.p. 63–65 °C ($CDCl_3$).

***N*,*N*-Diisopropyl-2,5-bis(2-phenylpropan-2-yl)-1*H*-pyrrole-1-carboxamide (153aa')**



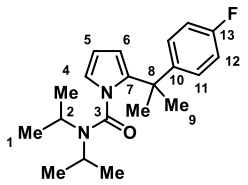
General Procedure Q: The reaction was carried out with styrene derivative **147a'** (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/Et_2O 3%) afforded the title compound (3.50 mg, 8%) as an orange oil. ν_{max}/cm^{-1}: 2966 (m), 2928 (m), 1686 (s), 1430 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.34 (2H, m, C**9**-H), 7.31 – 7.21 (6H, m, C**9**-H, C**10**-H), 7.20 – 7.09 (2H, m, C**11**-H), 6.24 (1H, d, *J* = 2.0 Hz, C**5**-H), 6.03 (1H, d, *J* = 2.0 Hz, C**5**-H), 3.34 – 3.20 (2H, m, C**2**-H), 1.72 (6H, s, C**7**-H_3), 1.62 (6H, s, C**7**-H_3), 1.13 – 0.92 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.2 (C**3**), 150.9 (C**8**), 148.9 (C**8**), 141.8 (C**4**), 132.7 (C**4**), 128.2 (C**10**), 127.9 (C**10**), 126.7 (C**9**), 126.5 (C**9**), 125.6 (C**11**), 125.6 (C**11**), 116.9 (C**5**), 107.6 (C**5**), 40.1 (C**7**), 38.4 (C**7**), 31.2 (C**2**), 31.0 (C**8**), 20.7 (C**1**), 20.2 (C**1**); HRMS: (ESI$^+$) calculated for $C_{29}H_{38}N_2O$ 431.3057. Found $[M+H]^+$ 431.3056.

2-(2-(3-Chlorophenyl)propan-2-yl)-*N*,*N*-diisopropyl-1*H*-pyrrole-1-carboxamide (152af')



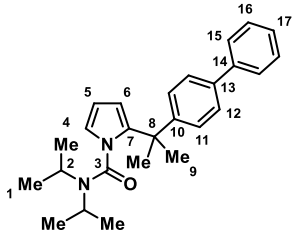
General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/EtOAc 0–2.5%) afforded the title compound (10.6 mg, 31%) as a colourless oil. ν_{max}/cm^{-1}: 2971 (m), 2931 (m), 1688 (s), 1324 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.23 (1H, m, C**11**-H), 7.20 – 7.17 (2H, m, C**14**-H, C**15**-H), 7.15 – 7.10 (1H, m, C**13**-H), 6.57 (1H, dd, *J* = 3.5, 2.0 Hz, C**4**-H), 6.21 (1H, dd, *J* = 3.5, 2.0 Hz, C**6**-H), 6.12 – 6.09 (1H, m, C**5**-H), 3.33 (1H, hept, *J* = 6.5 Hz, C**2**-H), 1.75 (6H, s, C**9**-H_3), 1.14 (6H, d, *J* = 6.5 Hz, C**1**-H_3), 1.05 – 0.95 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6 (C**3**), 151.0 (C**10**), 141.4 (C**7**), 134.0 (C**12**), 129.4 (C**15**), 127.2 (C**11**), 126.0 (C**13**), 125.0 (C**14**), 120.4 (C**4**), 108.3 (C**6**), 107.6 (C**5**), 48.5 (C**2**), 48.2 (C**2**), 40.1 (C**8**), 31.1 (C**9**), 20.8 (C**1**), 20.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{27}N_2OCl$ 347.1885. Found $[M+H]^+$ 471.1886.

2-(2-(4-Fluorophenyl)propan-2-yl)-*N*,*N*-diisopropyl-1*H*-pyrrole-1-carboxamide (152ac')



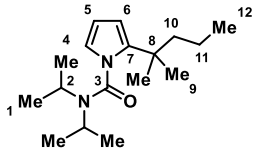
General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 0–5%) afforded the title compound (17.5 mg, 53%) as a colourless oil. ν_{max}/cm^{-1}: 2970 (m), 2933 (m), 1685 (s), 1508 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.06 (2H, m, C**11**-H), 6.94 – 6.75 (2H, m, C**12**-H), 6.49 (1H, dd, *J* = 3.5, 2.0 Hz, C**4**-H), 6.11 (1H, dd, *J* = 3.5, 2.0 Hz, C**6**-H), 6.05 – 5.98 (1H, m, C**5**-H), 3.27 (2H, hept, *J* = 6.5 Hz, C**2**-H), 1.67 (6H, s, C**9**-H_3), 1.08 (6H, d, *J* = 6.5 Hz, C**1**-H_3), 1.04 – 0.90 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.09 (d, *J* = 243.5 Hz, C**13**), 152.8 (C**3**), 144.7 (d, *J* = 3.0 Hz, C**10**), 141.8 (C**7**), 128.2 (d, *J* = 8.0 Hz, C**11**), 120.2 (C**4**), 114.7 (d, *J* = 20.9 Hz, C**12**), 108.2 (C**6**), 107.5 (C**5**), 48.5 (C**2**), 39.7 (C**8**), 31.3 (C**9**), 20.7 (C**1**), 20.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{27}N_2OF$ 331.2180 Found $[M+H]^+$ 331. 2169.

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diisopropyl-1*H*-pyrrole-1-carboxamide (152ab')



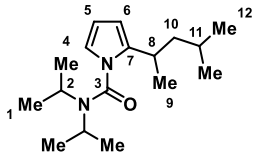
General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was run for 48 h. Purification of the residue by FCC (toluene/Et_2O 0–2%) afforded the title compound (13.2 mg, 34%) as a yellow oil. ν_{max}/cm^{-1}: 2968 (m), 2927 (m), 1687 (s), 1325 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.51 (2H, m, C**15**-H), 7.49 – 7.45 (2H, m, C**12**-H), 7.44 – 7.39 (2H, m, C**16**-H), 7.39 – 7.35 (2H, m, C**11**-H), 7.34 – 7.26 (1H, m, C**17**-H), 6.58 (1H, dd, *J* = 3.5, 2.0 Hz, C**4**-H), 6.24 (1H, dd, *J* = 3.5, 2.0 Hz, C**6**-H), 6.17 – 6.08 (1H, m, C**5**-H), 3.38 – 3.23 (2H, m, C**2**-H), 1.81 (6H, s, C**9**-H_3), 1.20 – 1.06 (6H, m, C**1**-H_3), 1.03 – 0.84 (6H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8 (C**3**), 147.9 (C**10**), 142.2 (C**7**), 141.3 (C**14**), 138.5 (C**13**), 128.8 (C**16**), 127.2 (C**11**), 127.1 (C**17**), 127.1 (C**15**), 127.0 (C**12**), 120.3 (C**4**), 108.1 (C**6**), 107.5 (C**5**), 48.4 (C**2**), 39.9 (C**8**), 31.1 (C**9**), 20.8 (C**1**), 20.1 (C**1**); HRMS: (ESI$^+$) calculated for $C_{26}H_{32}N_2O$ 389.2587. Found $[M+H]^+$ 389.2575.

***N,N*-Diisopropyl-2-(2-methylpentan-2-yl)-1*H*-pyrrole-1-carboxamide (152ah')**



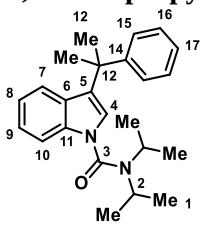
General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/EtOAc 0–4%) afforded the title compound (14.8 mg, 53%) as a colourless oil. ν_{max}/cm^{-1}: 2960 (m), 2934 (m), 1687 (s), 1324 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (1H, dd, *J* = 3.0, 2.0 Hz, C**4**-H), 6.09 – 6.04 (1H, m, C**5**-H), 5.95 (1H, dd, *J* = 3.0, 2.0 Hz, C**6**-H), 3.51 (2H, hept, *J* = 6.5 Hz, C**2**-H), 1.76 – 1.61 (2H, m, C**10**-H_2), 1.40 – 1.25 (12H, m, C**1**-H_3), 1.30 (6H, s, C**9**-H_3), 1.24 – 1.12 (2H, m, C**11**-H_2), 0.87 (3H, t, *J* = 7.0 Hz, C**12**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2 (C**3**), 141.5 (C**7**), 119.4 (C**4**), 107.6 (C**5**), 107.2 (C**6**), 48.6 (C**2**), 46.9 (C**2**), 45.0 (C**10**), 36.0 (C**8**), 28.6 (C**9**), 20.6 (C**1**), 20.3 (C**1**), 18.3 (C**11**), 14.9 (C**12**); HRMS: (ESI$^+$) calculated for $C_{17}H_{30}N_2O$ 279.2431. Found $[M+H]^+$ 279.2425.

***N,N*-Diisopropyl-2-(4-methylpentan-2-yl)-1*H*-pyrrole-1-carboxamide (152ah'')**



General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was run for 48 h. Purification of the residue by FCC (hexane/EtOAc 0–4%) afforded the title compound (5.5 mg, 19%) as a colourless oil. ν_{max}/cm^{-1}: 2960 (m), 2928 (m), 1685 (s), 1327 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (1H, dd, *J* = 3.0, 1.5 Hz, C**4**-H), 6.11 – 6.06 (1H, m, C**5**-H), 5.97 – 5.90 (1H, m, C**6**-H), 3.78 – 3.45 (2H, m, C**2**-H), 3.13 – 3.01 (1H, m, C**8**-H), 1.74 – 1.58 (1H, m, C**11**-H), 1.49 (1H, ddd, *J* = 14.0, 8.0, 6.5 Hz, C**10**-H_2), 1.40 – 1.29 (13H, m, C**1**-H_3, C**10**-H_2), 1.19 (3H, d, *J* = 7.0 Hz, C**9**-H_3), 0.89 (3H, d, *J* = 4.0 Hz, C**12**-H_3), 0.87 (3H, d, *J* = 4.0 Hz, C**12**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.0 (C**3**), 140.7 (C**7**), 117.7 (C**4**), 108.5 (C**5**), 105.1 (C**6**), 48.6 (C**2**), 47.2 (C**10**), 28.7 (C**8**), 25.7 (C**11**), 23.6 (C**12**), 22.2 (C**12**), 20.9 (C**9**), 20.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{30}N_2O$ 279.2431. Found $[M+H]^+$ 279.2427.

***N,N*-Diisopropyl-3-(2-phenylpropan-2-yl)-1*H*-indole-1-carboxamide (155a')**

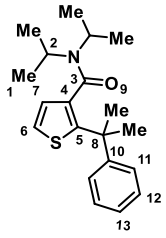


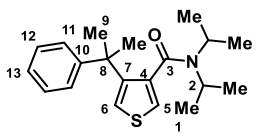
General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was run for 48 h. Purification of the residue by FCC (toluene/Et_2O 0–5%) afforded the title compound (36.3 mg,

99%) as a yellow oil. ν_{max}/cm^{-1}: 2958 (m), 2933 (m), 1674 (s), 1428 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* = 8.0 Hz, C**10**-H), 7.28 – 7.22 (2H, m, C**15**-H), 7.20 – 7.12 (2H, m, C**16**-H), 7.11 – 7.03 (2H, m, C9-H, C**17**-H), 7.00 (1H, s, C**4**-H), 6.90 (1H, d, *J* = 8.0 Hz, C**7**-H), 6.83 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**8**-H), 3.75 (2H, hept, *J* = 6.5 Hz, C**2**-H), 1.67 (6H, s, C**12**-H_3), 1.33 (12H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.2 (C**3**), 149.1 (C**14**), 137.2 (C**11**), 128.2 (C**15**), 128.1 (C**5**), 127.6 (C**6**), 126.5 (C**16**), 125.9 (C**17**), 123.0 (C**9**), 122.0 (C**4**), 121.5 (C**7**), 120.7 (C**8**), 113.0 (C**10**), 48.7 (C**2**), 39.0 (C**12**), 30.4 (C**13**), 21.5 (C**1**); HRMS: (ESI$^+$) calculated for $C_{24}H_{30}N_2O$ 363.2431. Found $[M+H]^+$ 363.2422.

7.6.3.3 Alkene Hydroarylation with Thiophene Substrates

(**156a'/157a'**)



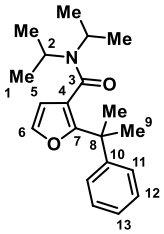


General Procedure Q: The reaction was carried out with styrene derivative (400 mol%) and was ran for 48 h. Purification of the residue by FCC (hexane/EtOAc 0–5%) afforded the title compound (28.1 mg, 85%, 0.6:0.4, *A:B*) as a yellow oil. ν_{max}/cm^{-1}: 2968 (m), 2930 (m), 1626 (s), 1441 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.36 (1.2H, m, C**11**-H, *A*), 7.31 – 7.22 (2.8H, m, C**11**-H, *B*, C**12**-H, A+*B*), 7.21 – 7.11 (1H, m, C**13**-H, *A*+*B*), 7.07 (0.4H, d, *J* = 3.0 Hz, C**5**-H, *B*), 7.06 (0.6H, d, *J* = 5.0 Hz, C**6**-H, *A*), 7.01 (0.4H, d, *J* = 3.0 Hz, C**6**-H, *B*), 6.75 (0.6H, d, *J* = 5.0 Hz, C**7**-H, *A*), 3.70 (0.6H, hept, *J* = 6.5 Hz, C**2**-H, *A*), 3.62 – 3.50 (0.4H, m, C**2**-H, *B*), 3.39 – 3.19 (1H, m, C**2**-H, *A*+*B*), 2.08 – 1.66 (6H, m, C**9**-H_3, *A*+*B*), 1.49 – 1.18 (6H, m, C**1**-H_3, *A*+*B*), 1.11 – 0.53 (6H, m, C**1**-H_3, *A*+*B*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7 (C**3**, *A*), 167.4 (C**3**, *B*), 152.3 (C**5**, *A*), 149.6 (C**7**, *B*) , 138.7 (C**4**, *B*), 134.3 (C**4**, *A*), 128.3 (C**12**, *B*), 128.2 (C**12**, *A*), 126.7 (C**11**, *B*), 126.6 (C**11**, *A*), 126.6 (C**7**, *A*), 126.2 (C**13**, *A*), 125.9 (C**13**, *B*), 123.4 (C**5**, *B*), 122.4 (C**6**, *A*), 121.9 (C**6**, *B*), 50.5 (C**2**, *A*+*B*), 45.8 (C**2**, *A*+*B*), 42.7 (C**8**, *A*), 42.0 (C**8**, *B*), 32.8 (C**9**, *A*), 30.9 (C**9**, *A*), 29.8 (C**9**, *B*), 29.5 (C**9**, B), 21.2 (C**1**, *A*+*B*), 20.4 (C**1**, *A*+*B*); HRMS: (ESI$^+$) calculated for $C_{20}H_{27}NOSNa$ 352.1706. Found $[M+Na]^+$ 352.1699.

7.6.3.4 Alkene Hydroarylation with Furan Substrates

*Hydroarylation products **159ag'**, **159aq'**, **159ae'**, **159ah'**, **159as'** and **159ba'** were synthesised by Miss Ellie Lester.*

_N,N_-Diisopropyl-2-(2-phenylpropan-2-yl)furan-3-carboxamide (159aa')



General Procedure Q: The reaction was carried out with styrene derivative (150 mol%) and was ran for 24 h. Purification of the residue by FCC (toluene/Et_2O 5–10%) afforded the title compound (40.2 mg, 94%) as a yellow oil. ν_{max}/cm^{-1}: 2969 (m), 2932 (m), 1623 (s), 1435 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.21 (4H, m, C**11**-H, C**12**-H), 7.21 – 7.19 (1H, m, C**6**-H), 7.16 – 7.11 (1H, m, C**13**-H) 6.19 (1H, d, *J* = 1.9 Hz, C**5**-H), 3.98 (1H, hept, *J* = 7.0 Hz, C**2**-H), 3.38 (1H, hept, *J* = 7.0 Hz, C**2**-H), 1.71 (6H, s, C**9**-H), 1.43 (6H, d, *J* = 7.0 Hz, C**1**-H_3), 1.06 (6H, d, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2 (C**3**), 157.5 (C**7**), 148.0 (C**10**), 140.2 (C**6**), 128.3 (C**12**), 126.2 (C**13**), 126.1 (C**11**), 117.9 (C**4**), 109.6 (C**5**), 50.9 (C**2**), 45.8 (C**2**), 41.6 (C**8**), 28.4 (C**9**), 20.7 (C**1**), 20.32 (C**1**); HRMS: (ESI^+) calculated for $C_{20}H_{27}NO_2$ 314.2115. Found $[M+H]^+$ 314.2124.

*The structure of compound **159aa'** was confirmed by single crystal X-ray diffraction of crystals obtained from $CHCl_3$ (Figure **8**).*

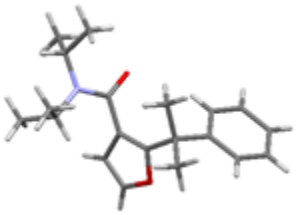
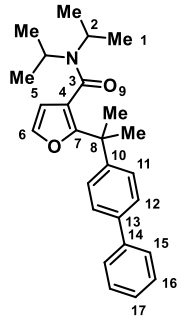


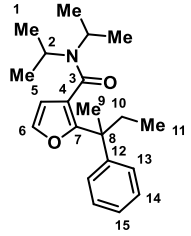
Figure 8

2-(2-([1,1'-Biphenyl]-4-yl)propan-2-yl)-*N*,*N*-diisopropylfuran-3-carboxamide (159ab')



General Procedure Q: The reaction was carried out with styrene derivative (150 mol%) and was ran for 24 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (33.7 mg, 86%) as a colourless oil. ν_{max}/cm^{-1}: 2969 (m), 2927 (m), 1626 (s), 1438 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.54 (2H, m, C**11**-H), 7.53 – 7.50 (2H, m, C**12**-H), 7.44 – 7.39 (2H, m, C**16**-H), 7.39 – 7.36 (2H, m, C**15**-H), 7.35 – 7.30 (1H, m, C**17**-H), 7.26 (1H, d, *J* = 2.0 Hz, C**6**-H), 6.24 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.01 (1H, hept, *J* = 6.5 Hz, C**2**-H), 3.39 (1H, hept, *J* = 6.5 Hz, C**2**-H), 1.76 (6H, s, C**9**-H_3), 1.44 (6H, d, *J* = 6.5 Hz, C**1**-H_3), 1.09 (6H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2 (C**3**), 157.6 (C**7**), 147.1 (C**10**), 141.1 (C**14**), 140.2 (C**6**), 139.1 (C**13**), 128.8 (C**16**), 127.2 (C**11**), 127.2 (C**17**) 127.1 (C**12**), 126.6 (C**15**), 118.0 (C**4**), 109.7 (C**5**), 50.9 (C**2**), 45.8 (C**2**), 41.5 (C**8**), 28.5 (C**9**), 20.7 (C**1**), 20.4 (C**1**); HRMS: (ESI$^+$) calculated for $C_{26}H_{31}NO_2$ 390.2428. Found $[M+H]^+$ 390.2417.

***N*,*N*-Diisopropyl-2-(2-phenylbutan-2-yl)furan-3-carboxamide (159aj')**

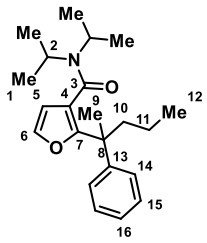


General Procedure Q: The reaction was carried out with styrene derivative (150 mol%), **(*R*)-L-16f** and was ran for 24 h. Purification of the residue by FCC (hexane/EtOAc 0–20%) afforded the title compound (23.8mg, 73%, 90:10 *e.r.*) as a colourless oil. ν_{max}/cm^{-1}: 2968 (m), 2937 (m), 1629 (s), 1438 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.24 (4H, m, C**13**-H, C**14**-H), 7.23 (1H, d, *J* = 2.0 Hz, C**6**-H), 7.18 – 7.11 (1H, m, C**15**-H), 6.20 (1H, d, *J* = 2.0 Hz, C**5**-H), 3.99 (1H, hept, *J* = 6.5 Hz, C**2**-H), 3.38 (1H, hept, *J* = 6.5 Hz, C**2**-H), 2.38 – 2.21 (1H, m, C**10**-H_2), 2.15 – 2.01 (1H, m, C**10**-H_2), 1.63 (3H, s, C**9**-H_3), 1.49 – 1.38 (6H, m, C**1**-H_3), 1.09 (3H, d, *J* = 6.5 Hz, C**1**-H_3), 1.03 (3H, d, *J* = 6.5 Hz, C**1**-H_3), 0.76 (3H, t, *J* = 7.5 Hz, C**11**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3 (C**3**), 156.8 (C**7**), 147.5 (C**12**), 140.2 (C**6**), 128.3 (C**14**), 126.6 (C**13**), 126.1 (C**15**), 119.2 (C**4**), 109.6 (C**5**), 50.8 (C**2**), 45.8 (C**8**),

45.6 (C**2**), 32.8 (C**10**), 24.2 (C**9**), 20.8 (C**1**), 20.7 (C**1**), 20.4 (C**1**), 20.3 (C**1**), 9.2 (C**11**); HRMS: (ESI^+) calculated for $C_{21}H_{29}NO_2$ 328.2271. Found $[M+H]^+$ 328.2262; $[\alpha]^{25}_D$ = - 24.2 (c = 0.20, $CHCl_3$).

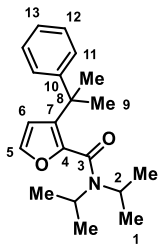
Chiral SFC Conditions: (DAICEL CHIRALPAK-IE column (25 cm), CO_2:MeOH 97:3 to 94:6 over 30 minutes, 2 mL/min, 140 bars, 60 °C). Retention times: 19.0 minutes (major), 20.4 minutes (minor), *e.r.* = 90:10.

***N,N*-Diisopropyl-2-(2-phenylpentan-2-yl)furan-3-carboxamide (159ar')**



General Procedure Q: The reaction was carried out with styrene derivative (150 mol%) and was ran for 24 h. Purification of the residue by FCC (hexane/EtOAc 0–10%) afforded the title compound (25.5 mg, 75%) as an orange oil. ν_{max}/cm^{-1}: 2961 (m), 2872 (m), 1630 (s), 1437 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.24 (4H, m, C**14**-H, C**15**-H), 7.23 (1H, d, *J* = 2.0 Hz, C**6**-H), 7.19 – 7.11 (1H, m, C**16**-H), 6.20 (1H, d, *J* = 2.0 Hz, C**5**-H), 4.01 (1H, hept, *J* = 6.5 Hz, C**2**-H), 3.39 (1H, hept, *J* = 6.5 Hz, C**2**-H), 2.26 – 1.92 (2H, m, C**10**-H_2), 1.66 (3H, s, C**9**-H_3), 1.49 – 1.42 (6H, m, C**1**-H_3), 1.29 – 1.13 (2H, m, C**11**-H_2), 1.12 – 1.02 (6H, m, C**1**-H_3), 0.88 (3H, t, *J* = 7.0 Hz, C**12**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4 (C**3**), 157.0 (C**7**), 147.5 (C**13**), 140.3 (C**6**), 128.3 (C**15**), 126.6 (C**14**), 126.1 (C**16**), 118.9 (C**4**), 109.6 (C**5**), 50.9 (C**2**), 45.8 (C**2**), 45.3 (C**8**), 42.6 (C**10**), 24.7 (C**9**), 20.8 (C**1**), 20.7 (C**1**), 20.4 (C**1**), 20.3 (C**1**), 17.9 (C**11**), 14.8 (C**12**); HRMS: (ESI^+) calculated for $C_{22}H_{31}NO_2Na$ 364.2247. Found $[M+Na]^+$ 364.2249.

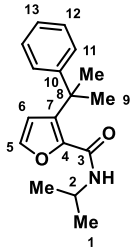
***N,N*-Diisopropyl-3-(2-phenylpropan-2-yl)furan-2-carboxamide (160a)**



General Procedure Q: The reaction was carried out with styrene derivative (150 mol%) and was ran for 24 h. Purification of the residue by FCC (hexane/EtOAc 0–5%) afforded the title compound (19.1 mg, 43%) as a colourless oil. ν_{max}/cm^{-1}: 2968 (m), 2929 (m), 1634 (s), 1438 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.29 (2H, m, C**11**-H), 7.28 – 7.23 (2H, m, C**12**-H), 7.21 (1H, d, *J* = 2.0 Hz, C**5**-H), 7.19 – 7.10 (1H, m, C**13**-H), 6.19 (1H, d, *J* = 2.0 Hz, C**6**-H), 3.58 – 3.48 (1H, m, C**2**-H), 3.43 – 3.29 (1H, m, C**2**-H), 1.68 (6H, s, C**9**-H_3), 1.37 (6H, d, *J* = 6.5 Hz, C**1**-H_3), 1.09 (6H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8 (C**3**), 149.6 (C**10**), 144.6 (C**4**), 140.2 (C**5**), 133.2 (C**7**), 128.1

(C**12**), 126.5 (C**11**), 125.8 (C**13**), 111.7 (C**6**), 50.8 (C**2**), 46.0 (C**2**), 38.2 (C**8**), 30.3 (C**9**), 20.8 (C**1**), 20.2 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{27}NO_2Na$ 336.1934. Found $[M+Na]^+$ 336.1942.

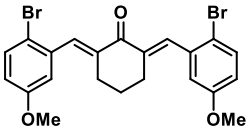
***N*-Isopropyl-3-(2-phenylpropan-2-yl)furan-2-carboxamide (161a')**



General Procedure Q: The reaction was carried out with styrene derivative (150 mol%) and was ran for 24 h. Purification of the residue by FCC (hexane/EtOAc 0–10%) afforded the title compound (8.4 mg, 19%) as a colourless oil. ν_{max}/cm^{-1}: 3316 (m), 2972 (m), 2925 (m), 1660 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (1H, d, *J* = 2.0 Hz, C**5**-H), 7.32 – 7.26 (4H, m, C**11**-H, C**12**-H), 7.22 – 7.13 (1H, m, C**13**-H), 6.45 (1H, d, *J* = 2.0 Hz, C**6**-H), 5.76 (1H, br. s, N-H), 4.03 (1H, hept, *J* = 6.5 Hz, C**2**-H), 1.75 (6H, s, C**9**-H_3), 1.03 (6H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0 (C**3**), 149.9 (C**10**), 142.8 (C**4**), 141.4 (C**5**), 138.6 (C**7**), 128.3 (C**12**), 126.2 (C**11**), 126.0 (C**13**), 113.4 (C**6**), 40.9 (C**2**), 38.7 (C**8**), 30.3 (C**9**), 22.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{22}NO_2$ 272.1645. Found $[M+H]^+$ 272.1645.

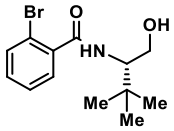
7.6.4 – Synthesis of Alternative SPINOL Ligands

2,6-Bis((*E*)-2-bromo-5-methoxybenzylidene)cyclohexan-1-one (171)



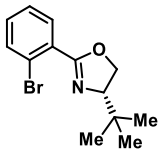
The title compound was synthesised following a literature procedure.[167] To a stirred solution of NaOH (186 mg, 4.64 mmol) dissolved on EtOH (2.20 mL) and water (2.20 mL) was added a solution of cyclohexanone (120 µL, 1.16 mmol) and 2-bromo-5-methoxy benzaldehyde (500 mg, 2.33 mmol) in EtOH (6.0 mL) dropwise. The solution was stirred overnight. The resulting solution was filtered and the solid was washed with H_2O and dried under vacuum to afford the title compound (366 mg, 64%) as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (2H, s), 7.51 (2H, d, *J* = 9.0 Hz), 6.84 (2H, d, *J* = 3.0 Hz), 6.76 (2H, dd, *J* = 9.0, 3.0 Hz), 3.80 (6H, s), 2.76 (4H, t, *J* = 5.0 Hz), 1.87 – 1.70 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.7, 158.5, 137.7, 137.2, 136.5, 133.6, 116.5, 115.6, 115.3, 55.7, 28.4, 23.2; m.p. 113–116 °C ($CDCl_3$). (Lit. 165–166 °C, *no recrystallisation solvent specified). The spectroscopic properties for this compound were consistent with the data available in the literature.*[167]

(*S*)-2-Bromo-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide



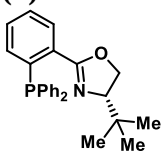
The title compound was synthesised following a literature procedure.[266] To a round-bottomed flask was added Na_2CO_3 (2.39 g, 22.5 mmol) dissolved in H_2O (19 mL). A solution of (*S*)-*t*-leucinol (0.960 mL, 7.50 mmol) in CH_2Cl_2 (25 mL) was added, followed by dropwise addition of 2-bromobenzoyl chloride (1.73 mL, 8.63 mmol). The biphasic mixture was stirred vigorously for 2 h, before the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/acetone 25%) afforded the title compound (2.06 g, 91%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.54 (2H, m), 7.41 – 7.33 (1H, m), 7.28 (1H, dd, *J* = 7.5, 1.5 Hz), 6.12 (1H, br. s), 4.06 (1H, ddd, *J* = 9.5, 7.5, 3.5 Hz), 4.01 – 3.89 (1H, m), 3.74 – 3.62 (1H, m), 2.25 – 2.13 (1H, m), 1.03 (9H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 138.1, 133.5, 131.5, 129.9, 127.8, 119.2, 63.3, 60.5, 33.9, 27.3; m.p. 116–118 °C ($CDCl_3$) (Lit.[267] 110–112 °C, hexane/acetone); $[\alpha]^{25}_D$ = + 2.1 (c = 0.13, $CHCl_3$). T*he spectroscopic properties for this compound were consistent with the data available in the literature*.[266]

(*S*)-2-(2-Bromophenyl)-4-(tert-butyl)-4,5-dihydrooxazole



The title compound was synthesised following a literature procedure.[266] To a round-bottom flask fitted with a condenser was added *(S)*-2-Bromo-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide (2.00 g, 6.66 mmol), *p*-toluenesulfonyl chloride (1.65 g, 8.66 mmol), CH_2Cl_2 (50 mL) and NEt_3 (4.64 mL, 33.3 mmol). The solution was heated at reflux overnight. H_2O (7 mL) was added and the solution was heated to 75 °C for a further 2 h. The reaction mixture was cooled to ambient temperature, the organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (1.85 g, 99%) as a colourless oil. ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.64 (2H, m), 7.33 (1H, m), 7.27 (1H, m), 4.38 (1H, dd, *J* = 10.5, 8.5 Hz), 4.31 – 4.19 (1H, m), 4.11 (1H, dd, *J* = 10.5, 8.5 Hz), 1.00 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9, 133.8, 131.6, 131.4, 130.4, 127.2, 122.0, 76.8, 69.1, 34.2, 26.1. *The spectroscopic properties for this compound were consistent with the data available in the literature*.[266]

(*S*)-*t*-Bu-PHOX



The title compound was synthesised following a literature procedure.[266] To an oven dried Schlenk tube was added CuI (156 mg, 0.818 mmol), $HPPh_2$ (2.14 mL, 12.3 mmol), DMEDA (0.625 mL, 5.72 mmol) and toluene (28 mL) under nitrogen. The reaction mixture was stirred at ambient temperature for 30 minutes before Cs_2CO_3 (7.99 g, 24.5 mmol) and (*S*)-2-(2-Bromophenyl)-4-(tert-butyl)-4,5-dihydrooxazole (1.84 g, 6.54 mmol) in toluene (28 mL) was added dropwise. The tube was sealed and heated at 110 °C for 5 h. The solution was cooled to ambient temperature, filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by FCC (toluene/Et2O 1%) afforded the title compound (1.51 g, 60%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 – 7.89 (1H, m), 7.41 – 7.20 (12H, m), 6.92 – 6.82 (1H, m), 4.13 – 4.05 (2H, m), 4.04 – 3.99 (1H, m), 3.90 – 3.84 (1H, m), 0.73 (9H, s); ^{31}P NMR (162 MHz, $CDCl_3$): δ -5.34. m.p. 113–116 °C ($CDCl_3$). (Lit. 114–116 °C, *no recrystallisation solvent specified)*; $[\alpha]^{25}_D$ = - 60.0 (c = 0.30, $CHCl_3$). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[268-269]

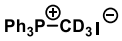
[Ircod(*S*)-*t*-Bu-PHOX]BARF

The title compound was synthesised following a literature procedure.[270] To a flame dried resealable Schlenk tube was added $[Ir(cod)Cl]_2$ (80.0 mg, 0.119 mmol), (*S*)-*t*-Bu-PHOX (92.2 mg, 0.238 mmol) and dry CH_2Cl_2 (2.50 mL) under nitrogen. The solution was heated at reflux and stirred for 1 h. The mixture was cooled to ambient temperature and NaBARF (339 mg, 0.372 mmol) and H_2O (2.50 mL) were added and the tube was vigorously stirred for 10 minutes. The mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by recrystallisation (EtOH/H_2O) afforded the title compound (270 mg, 74%) as a bright orange powder. ν_{max}/cm^{-1}: 2970 (m), 1354 (s), 1277 (s), 1124 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 – 8.14 (1H, m), 7.74 – 7.68 (8H, m), 7.66 – 7.53 (3H, m), 7.53 – 7.50 (6H, m), 7.50 – 7.40 (5H, m), 7.36 – 7.29 (1H, m), 7.17 – 7.05 (2H, m), 5.00 – 4.89 (2H, m), 4.57 (1H, dd, *J* = 10.0, 3.0 Hz), 4.35 – 4.25 (1H, m), 3.94 (1H, dd, *J* = 9.0, 3.0 Hz), 3.54 – 3.44 (1H, m), 3.12 – 2.98 (1H, m), 2.66 – 2.30 (4H, m), 2.09 – 1.88 (2H, m), 1.69 – 1.59 (1H, m), 1.51 – 1.34 (1H, m), 0.62 (9H, s); Characteristic ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.8 (1:1:1:1 pattern, $^1J_{B\text{-}C}$ = 50.0 Hz), 134.9, 123.6 (q, $^1J_{F\text{-}C}$ = 272.5 Hz), *Note: ^{13}C NMR analysis was complex to assign but characteristic BARF signals have been identified by comparison to similar complexes;*[116] ^{31}P NMR (162 MHz, $CDCl_3$): δ 17.34; HRMS: (Nanospray$^+$) calculated for $C_{33}H_{38}NOP$ 688.2320. Found $[M]^+$ 688.2341, *Note: mass was observed in the absence of BARF*; m.p. 180–182 °C (CH_2Cl_2).

7.6.5 – Mechanistic Studies

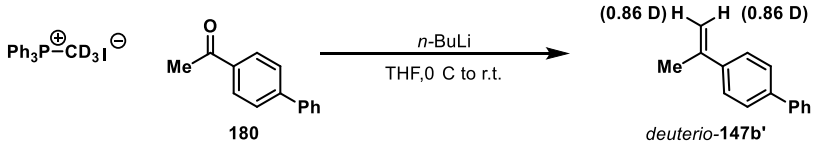
7.6.5.1 – Deuterium Labelling Experiments

Methyl-d_3-triphenylphosphonium iodide



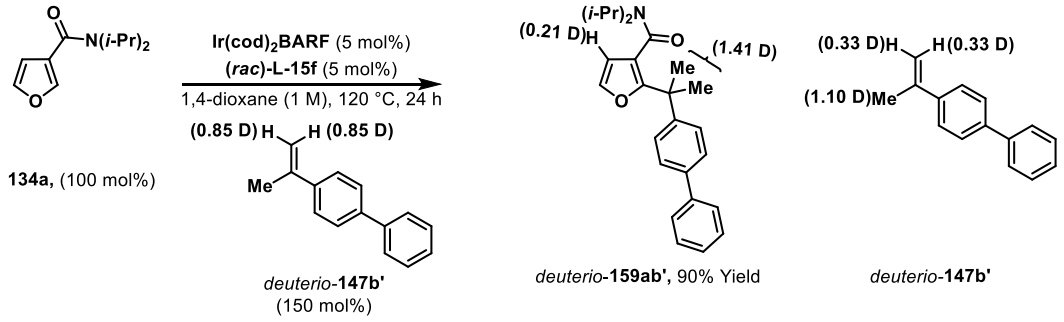
The title compound was prepared following a literature procedure.[271] To a suspension of PPh_3 (5.00 g, 19.1 mmol) in THF (33 mL) was added CD_3I (1.40 mL, 22.9 mmol). The mixture was heated to reflux for 1 h, before being cooled to ambient temperature. The resulting white solid was filtered and washed with benzene (2 × 20 mL) and dried under reduced pressure to afford the title compound (7.50 g, 97%) as a white solid. The material was used in the next step without further purification.

4-(Prop-1-en-2-yl-1,1-d2)-1,1'-biphenyl *(deuterio*-**147b'**)



To a suspension of methyl-d_3-triphenylphosphonium iodide (2.75 g, 9.21 mmol) in THF (25 mL), under nitrogen, was added *n*-BuLi (5.76 mL, 9.21 mmol, 1.6 M in hexanes) dropwise at 0 ˚C. The resulting solution was stirred for 1 h, before 4-acetylbiphenyl (1.51 g, 7.67 mmol) in THF (25 mL) was added dropwise. The reaction was slowly warmed to ambient temperature and stirred for 4 h. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 5%) provided *deuterio*-**147b'** (600 mg, 40% yield, 86% deuteration) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 – 7.53 (6H, m), 7.50 – 7.40 (2H, m), 7.38 – 7.32 (1H, m), 5.45 – 5.42 (0.14H, m), 5.15 – 5.10 (0.14H, m), 2.20 (3H, s); ^{2}H NMR (61 MHz, $CHCl_3$): δ 5.48 (0.86D, s), 5.16 (0.86D, s); m.p. 120–122 °C ($CDCl_3$).

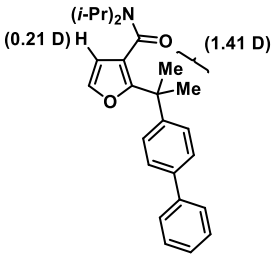
Deuterium Labelling Experiment of 134a



A flame-dried re-sealable tube, fitted with a magnetic stirrer, was charged with substrate **134a** (19.5mg, 0.1 mmol), [Ir(cod)$_2$]BARF (5.0 mol%) and **(*rac*)-L-15f (**5.0 mol%). The tube was fitted with a rubber septum and purged with nitrogen. *Deuterio*-**147b'** derivative (29.4 mg, 0.15 mmol) in anhydrous 1,4-dioxane (0.1 mL) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 120 °C for 24 h before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC (hexane/EtOAc 10–20%) afforded the *deuterio*-products.

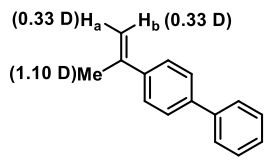
The data for the deuterated products is presented below:

*deuterio-**159ab'***



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.53 (2H, m), 7.53 – 7.49 (2H, m), 7.44 – 7.39 (2H, m), 7.39 – 7.36 (2H, m), 7.34 – 7.29 (1H, m), 7.26 (1H, d, *J* = 2.0 Hz), 6.23 (0.79H, d, *J* = 2.0 Hz), 4.01 (1H, hept, *J* = 6.5 Hz), 3.38 (1H, hept, *J* = 6.5 Hz), 1.82 – 1.68 (4.59H, m), 1.44 (6H, d, *J* = 6.5 Hz), 1.08 (6H, d, *J* = 6.5 Hz); ^{2}H NMR (77 MHz, $CHCl_3$): δ 6.28 (0.21D, s), 1.74 (1.41D, s). *Deuterium incorporation was calculated by integration of both ^{1}H NMR and ^{2}H NMR signals.*

*deuterio-**147b'***



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.53 (6H, m), 7.49 – 7.41 (2H, m), 7.40 – 7.31 (1H, m), 5.48 – 5.41 (0.67H, m, H_b), 5.15 – 5.06 (0.67H, m, H_a), 2.25 – 2.16 (1.9H, m); ^{2}H NMR (77 MHz, $CHCl_3$): δ 5.49 (0.33D, s), 5.16 (0.33D, s), 2.19 (1.10D, d, *J* = 2.5 Hz).

7.6.5.2 – ^{13}C-KIE Determination Experiments (Singleton Method)

Procedure for large scale reactions:

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with furan substrate **134a** (391 mg, 2.00 mmol), **147b'** (389 mg, 2.00 mmol), [Ir(cod)$_2$]BARF (0.10 mmol, 5 mol%) and **(*rac*)-L-15f** (0.10 mmol, 5 mol%). The tube was fitted with a rubber septum and purged with nitrogen. Anhydrous 1,4-dioxane (2.0 mL) was added *via* syringe and the tube was sealed with a Young's tap. The reaction vessel was placed into a pre-heated heating block at 120 ^{o}C and stirred for 6 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude mixture was transferred into a 20 mL volumetric flask, which was previously charged with a known amount of internal standard (1,3,5-trimethoxybenzene, ~85 mg), and the flask was filled with $CDCl_3$, pre-treated over anhydrous K_2CO_3. Six aliquots of 0.4 mL each were taken from the solution and transferred into six NMR tubes, which were subsequently diluted with additional 0.3 mL of pre-treated $CDCl_3$ each. A ^{1}H NMR spectrum was recorded for each sample employing a 500 MHz instrument, using the following parameters: 16 scans, $\pi/2$ pulse, 6.5 s acquisition time and 40 s relaxation delay. The conversion of the alkene starting material (**F**) was determined by integration of the C**1**-$\underline{H}_b$ signal of **159ab'** against the aromatic C-$\underline{H}$ signal of the internal standard. The remaining crude material was purified by FCC to recover unreacted **147b'**.

Quantitative ^{13}C NMR analysis: All NMR samples were prepared employing ~100 mg of recovered **147b'** in 0.7 mL of pre-treated $CDCl_3$. The ^{13}C NMR spectra were recorded at 126 MHz using inverse gated decoupling and employing a 500 MHz instrument equipped with a CryoProbe^{TM}. The spectra were recorded according to the following parameters: 1024 scans, $\pi/6$ pulse, 15 s relaxation delay. A total of five spectra were recorded for each sample. The resulting five FIDs were processed at the same time applying the same phase correction, a fifteenth order polynomial fit baseline correction and 256K zero filling. Integrations were numerically determined using a constant region for each peak corresponding to eight times of the peak widths at half height ($\pm$ 8$w_{1/2}$). The peak belonging to C**8** of **147b'** was chosen as the internal standard and was set with an integration of 1000.

Formulas applied for the determination of ^{13}C KIEs: The formulas employed in the calculations for the determination of the KIE were reported by Saunders[171] and Singleton[177] and are summarized as follows:

F = conversion of starting material.

R/R_0 = proportion of the minor isotopic component in recovered material compared to the original starting material.

$\Delta(R/R_0)$ = $R/R_0((\Delta R/R)^2 + (\Delta R_0/R_0)^2)^{1/2}$

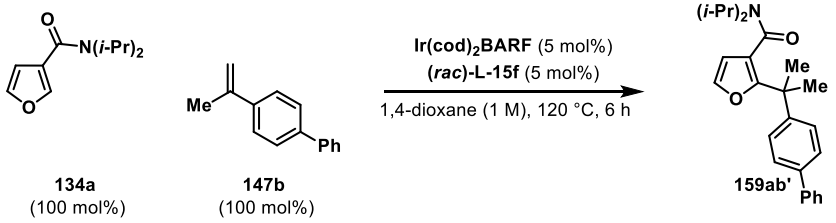
$$\mathbf{KIE} = \frac{\ln(1-F)}{\ln[(1-F)R/R_0]}$$

$$\mathbf{\Delta KIE_F} = \frac{\partial KIE}{\partial F}\,\Delta F = \frac{-ln(R/R_0)}{(1-F)ln^2[(1-F)R/R_0]}\,\Delta F$$

$$\mathbf{\Delta KIE_R} = \frac{\partial KIE}{\partial (R/R_0)}\,\Delta(R/R_0) = \frac{-ln(1-F)}{(R/R_0)ln^2[(1-F)R/R_0]}\,\Delta R/R_0$$

$$\mathbf{\Delta KIE} = KIE*((\Delta KIE_R/KIE)^2 + (\Delta KIE_F/KIE)^2)^{1/2}$$

^{13}C KIE determination for the hydroarylation of 147b' with 134a:



134a (100 mol%) **147b** (100 mol%) **159ab'**

^{1}H NMR analysis provided a conversion of 59.7 ± 0.2% for the first experiment and of 64.0 ± 0.4% for the second experiment. Purification of the crude mixture by FCC (hexane/EtOAc 0–5%) afforded 128 mg (38% recovered) for the first sample and 122 mg (36% recovered) for the second sample.

Tables are reported on the next pages.

First experiment:

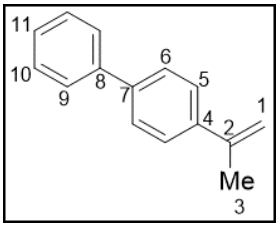
Conversion (F)						
fid1	**fid2**	**fid3**	**fid4**	**fid5**	**F**	**ΔF**
59.7	60.0	59.4	59.7	59.7	**59.7**	**0.2**

^{13}C-NMR integration of alkene starting material (R_0)							
ppm peaks	**fid1**	**fid2**	**fid3**	**fid4**	**fid5**	**R_0**	**ΔR_0**
142.8 (C2)	1037.3	1037.5	1040.8	1040.4	1040.7	**1039.3**	**1.8**
140.2 (C7/4)	2052.9	2054.5	2056.9	2058.0	2057.4	**2055.9**	**2.2**
112.6 (C1)	900.7	899.0	899.0	901.4	899.8	**900.0**	**1.1**
21.9 (C3)	955.7	956.5	957.3	957.7	957.9	**957.0**	**0.9**
140.8 (C8)	1000.0	1000.0	1000.0	1000.0	1000.0	**1000.0**	**0.0**

^{13}C-NMR integration of alkene from 59.7 ± 0.2 % conversion reaction (R)							
ppm peaks	**fid1**	**fid2**	**fid3**	**fid4**	**fid5**	**R**	**ΔR**
142.8 (C2)	1052.1	1051.8	1052.3	1051.5	1051.4	**1051.8**	**0.4**
140.2 (C7/4)	2058.1	2057.8	2057.3	2058.8	2056.7	**2057.7**	**0.8**
112.6 (C1)	927.1	927.6	928.3	927.3	928.7	**927.8**	**0.7**
21.9 (C3)	938.2	938.7	938.0	938.6	937.4	**938.2**	**0.5**
140.8 (C8)	1000.0	1000.0	1000.0	1000.0	1000.0	**1000.0**	**0.0**

Determination of ^{13}C KIEs						
ppm peaks	**R/R_0**	**$\Delta(R/R_0)$**	**ΔKIE_F**	**ΔKIE_R**	**KIE**	**ΔKIE**
142.8 (C2)	1.012008	0.001771	-0.000078	0.001977	1.013308	0.001978
140.2 (C7/4)	1.000876	0.001119	-0.000006	0.001233	1.000964	0.001233
112.6 (C1)	1.030912	0.001428	-0.000208	0.001632	1.034659	0.001645
21.9 (C3)	0.980314	0.001082	0.000121	0.001163	0.978591	0.001169
140.8 (C8)	1	0	0	0	1	0

Output	
C	**KIE**
C2	**1.013 ± 0.002**
C7/4	**1.001 ± 0.001**
C1	**1.035 ± 0.002**
C3	**0.979 ± 0.001**



Second experiment:

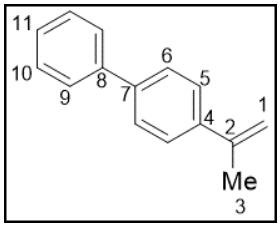
Conversion (F)						
fid1	**fid2**	**fid3**	**fid4**	**fid5**	**F**	**ΔF**
64.4	63.6	64.1	64.1	63.6	**64.0**	**0.4**

^{13}C-NMR integration of alkene SM (R_0)							
ppm peaks	**fid1**	**fid2**	**fid3**	**fid4**	**fid5**	**R_0**	**ΔR_0**
142.8 (C2)	1037.3	1037.5	1040.8	1040.4	1040.7	**1039.3**	**1.8**
140.2 (C7/4)	2052.9	2054.5	2056.9	2058.0	2057.4	**2055.9**	**2.2**
112.6 (C1)	900.7	899.0	899.0	901.4	899.8	**900.0**	**1.1**
21.9 (C3)	955.7	956.5	957.3	957.7	957.9	**957.0**	**0.9**
140.8 (C8)	1000.0	1000.0	1000.0	1000.0	1000.0	**1000.0**	**0.0**

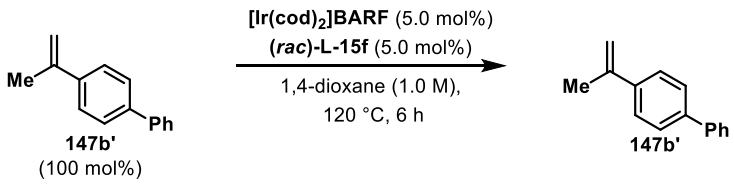
^{13}C-NMR integration of alkene from 64.0 ± 0.4 % conversion reaction (R)							
ppm peaks	**fid1**	**fid2**	**fid3**	**fid4**	**fid5**	**R**	**ΔR**
142.8 (C2)	1053.1	1052.1	1052.3	1054.3	1054.1	**1053.2**	**1.0**
140.2 (C7/C4)	2060.6	2062.7	2064.9	2068.0	2066.7	**2064.6**	**3.0**
112.6 (C1)	929.9	931.3	930.3	931.1	931.7	**930.9**	**0.7**
21.9 (C3)	940.3	941.2	939.0	940.4	940.8	**940.3**	**0.8**
140.8 (C8)	1000.0	1000.0	1000.0	1000.0	1000.0	**1000.0**	**0.0**

Determination of ^{13}C KIEs						
ppm peaks	**R/R_0**	**$\Delta(R/R_0)$**	**ΔKIE_F**	**ΔKIE_R**	**KIE**	**ΔKIE**
142.8 (C2)	1.013316	0.001986	-0.000127	0.001971	1.013132	0.001975
140.2 (C7/4)	1.004202	0.001794	-0.000040	0.001765	1.004126	0.001766
112.6 (C1)	1.034312	0.001469	-0.000337	0.001489	1.034187	0.001526
21.9 (C3)	0.982571	0.001276	0.000159	0.001230	0.983063	0.001240
140.8 (C8)	1	0	0	0	1	0

Output	
C	**KIE**
C2	**1.013 ± 0.002**
C7/4	**1.004 ± 0.002**
C1	**1.034 ± 0.002**
C3	**0.983 ± 0.001**



^{13}C KIE determination for 147b' under Ir(I)-catalysis



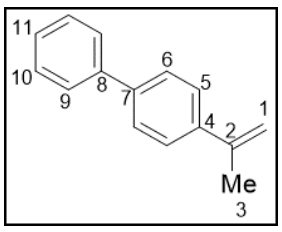
The reaction was carried out on a 1.00 mmol scale, in the absence of furan **134a**. Purification of the crude mixture by FCC (hexane/EtOAc 0–1%) afforded 193 mg (97% recovered).

^{13}C-NMR integration of alkene SM (R_0)								
ppm peaks	**fid1**	**fid2**	**fid3**	**fid4**	**fid5**	**fid6**	**R_0**	**ΔR_0**
142.8 (C2)	1038.3	1042.3	1046.1	1047.6	1041.8	1039.7	**1042.6**	**3.6**
140.2 (C7/4)	2058.6	2061.6	2067.7	2070.1	2062.7	2061.2	**2063.7**	**4.4**
112.6 (C1)	892.3	896.8	902.4	907.6	905.5	905.0	**901.6**	**5.9**
21.9 (C3)	957.5	959.0	961.1	961.4	959.6	959.4	**959.7**	**1.4**
140.8 (C8)	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0	**1000.0**	**0.0**

^{13}C-NMR integration of recovered alkene								
ppm peaks	**fid1**	**fid2**	**fid3**	**fid4**	**fid5**	**fid6**	**R**	**ΔR**
142.8 (C2)	1040.6	1043.6	1043.0	1041.5	1043.5	1042.7	**1042.5**	**1.2**
140.2 (C7/4)	2057.0	2057.9	2059.0	2057.6	2060.7	2060.9	**2058.9**	**1.6**
112.6 (C1)	918.2	920.3	920.5	919.5	918.9	919.7	**919.5**	**0.9**
21.9 (C3)	942.3	942.8	944.4	945.3	946.2	946.9	**944.7**	**1.8**
140.8 (C8)	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0	**1000.0**	**0.0**

ppm peaks	**R/R_0**	**$\Delta(R/R_0)$**
142.8 (C2)	0.999856	0.003639
140.2 (C7/4)	0.997674	0.002249
112.6 (C1)	1.019872	0.006721
21.9 (C3)	0.984352	0.002415
140.8 (C8)	1	0

Output	
C	**KIE**
C2	**1.000 ± 0.004**
C7/4	**0.998 ± 0.002**
C1	**1.020 ± 0.007**
C3	**0.984 ± 0.002**

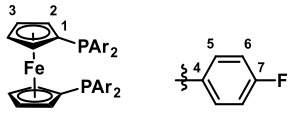


7.7 – Experimental Procedures and Data for the Studies in Chapter 5

7.7.1 – Ligand Synthesis

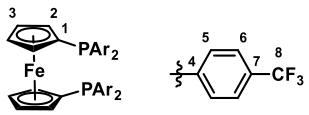
*For the synthesis of 1,1'-Bis(dichlorophosphino)ferrocene **193** see Section **7.4.5***

L-20a



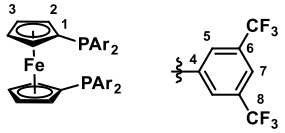
General Procedure R: The reaction was carried out with 1-bromo-4-fluorobenzene (1.17 mL, 10.6 mmol) to afford the title compound (157 mg, 14%) as an orange powder. ν_{max}/cm^{-1}: 3075 (m), 1587 (s), 1493 (m), 1224 (s), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.23 (8H, m, C**6**-H), 7.09 – 6.99 (8H, m, C**5**-H), 4.35 (4H, app. t, *J* = 2.0 Hz, C**3**-H), 3.97 (4H, app. q, *J* = 2.0 Hz, C**2**-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.4 (d, $^{1}J_{C\text{-}F}$ = 249.0 Hz, C**7**), 135.3 (dd, $^{2}J_{C\text{-}F}$ = 21.0, $^{3}J_{C\text{-}P}$ = 8.0 Hz, C**6**), 134.2 (dd, $^{1}J_{C\text{-}P}$ = 10.0, $^{4}J_{C\text{-}F}$ = 3.5 Hz, C**4**), 115.5 (dd, $^{3}J_{C\text{-}F}$ = 21.0, $^{2}J_{C\text{-}P}$ = 8.0 Hz, C**5**), 76.8 (C**1**), 73.7 (d, $^{2}J_{C\text{-}P}$ = 15.0 Hz, C**2**), 72.7 (dd, $^{3}J_{C\text{-}P}$ = 3.5, $^{4}J_{C\text{-}P}$ = 1.5 Hz, C**3**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -112.3 (tq, *J* = 9.5, 5.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ -19.3; HRMS: (MALDI) calculated for $C_{34}H_{24}F_4FeP_2$ 626.0634. Found [M] 626.0628; m.p. 140–141 °C (cyclohexane).

L-20b



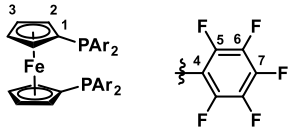
General Procedure R: The reaction was carried out with 4-bromobenzotrifluoride (1.48 mL, 10.6 mmol) to afford the title compound (179 mg, 12%) as an orange powder. ν_{max}/cm^{-1}: 2926 (m), 1606 (s), 1319 (s), 1121 (s), 1059 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (8H, d, *J* = 7.5 Hz, C**6**-H), 7.38 (8H, app. t, *J* = 7.5 Hz, C**5**-H), 4.33 (4H, app. t, *J* = 2.0 Hz, C**3**-H), 3.99 (4H, app. q, *J* = 2.0 Hz, C**2**-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.0 (d, $^{1}J_{C\text{-}P}$ = 13.0 Hz, C**4**), 133.8 (d, $^{2}J_{C\text{-}P}$ = 20.0 Hz, C**5**), 131.1 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz, C**7**), 125.2 (dd, $^{3}J_{C\text{-}F}$ = 7.0, $^{4}J_{C\text{-}F}$ = 3.5 Hz, C**6**), 125.1 (q, $^{1}J_{C\text{-}F}$ = 273 Hz, C**8**), 75.0 (d, $^{1}J_{C\text{-}P}$ = 7.5 Hz, C**1**), 74.0 (d, $^{2}J_{C\text{-}P}$ = 15.0 Hz, C**2**), 73.0 – 72.9 (m, C**3**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -62.7, ^{31}P NMR (162 MHz, $CDCl_3$): δ -16.6; HRMS: (MALDI) calculated for $C_{38}H_{24}F_{12}FeP_2$ 826.0506. Found [M] 826.0499; m.p. 151–153 °C (cyclohexane).

L-20c



General Procedure R: The reaction was carried out with (1,3)-bis(trifluoromethyl)-5-bromobenzene (1.42 mL, 8.22 mmol) to afford the title compound (632 mg, 42%) as an orange powder. ν_{max}/cm^{-1}: 2923 (m), 2858 (m), 1352 (s), 1273 (s), 1095 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (4H, s, C**7**-H), 7.69 (8H, app. d, *J* = 6.5 Hz, C**5**-H), 4.44 (4H, app. t, *J* = 2.0 Hz, C**3**-H), 4.00 (4H, app. q, *J* = 2.0 Hz, C**2**-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.3 (d, $^{1}J_{C\text{-}P}$ = 17.5 Hz, C**4**), 132.9 (dd, $^{2}J_{C\text{-}P}$ = 21.0, $^{3}J_{C\text{-}F}$ = 3.5 Hz, C**5**), 132.1 (qd, $^{2}J_{C\text{-}F}$ = 33.5, $^{3}J_{C\text{-}P}$ = 6.5 Hz, C**6**), 123.4 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz, C**7**), 122.9 (q, $^{1}J_{C\text{-}F}$ = 278.0 Hz, C**8**) 73.8 (d, $^{1}J_{C\text{-}P}$ = 7.0 Hz, C**1**), 73.6 (d, $^{2}J_{C\text{-}P}$ = 15.5 Hz, C**2**), 73.3 – 73.2 (m, C**3**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -62.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ -14.9; HRMS: (MALDI) calculated for $C_{42}H_{20}F_{24}FeP_2$ 1098.0002. Found [M] 1098.0014; m.p. 145–147 °C (cyclohexane).

L-20d



General Procedure R: The reaction was carried out with bromopentafluorobenzene (1.32 mL, 10.6 mmol) to afford the title compound (40.8 mg, 3%) as an orange powder. ν_{max}/cm^{-1}: 2929 (m), 1638 (m), 1514 (s), 1469 (s), 1086 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.42 (4H, app. t, *J* = 2.0 Hz, C**3**-H), 4.29 (4H, app. q, *J* = 2.0 Hz, C**2**-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5 (d, $^{1}J_{C\text{-}F}$ = 242.0 Hz, C**6**), 142.7 (d, $^{1}J_{C\text{-}F}$ = 257.5 Hz, C**7**), 137.8 (d, $^{1}J_{C\text{-}F}$ = 256.0 Hz, C**5**), 109.0 (dt, $^{1}J_{C\text{-}P}$ = 34.5, $^{2}J_{C\text{-}F}$ = 20.5 Hz, C**4**), 74.8 (d, $^{2}J_{C\text{-}P}$ = 20.5 Hz, C**2**), 73.2 (C**3**), 68.9 (C**1**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -129.2 (–) -129.5 (8F, m, F_{meta}), -149.0 – -149.2 (4F, m, F_{para}), -159.5 (–) -159.8 (8F, m, F_{ortho}); ^{31}P NMR (162 MHz, $CDCl_3$): δ -58.4; HRMS: (MALDI) calculated for $C_{34}H_8F_{20}FeP_2$ 913.9126. Found [M] 913.9120; m.p. 194–196 °C (cyclohexane).

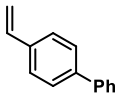
7.7.2 – Substrate Synthesis

7.7.2.1 – Alkene Synthesis

91a', **91c'**, **91e' 91g'**, **91i'**, , **91n**–**91p'**, **91r'**, **91s'**, **91t'**, **91v'**–**91x'**, **91ab'**–**91ad'**, **197** *were purchased from commercial sources (Sigma or Alfa).*

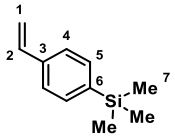
91z and **91aa'** *were synthesised by Dr. Giacomo Crisenza*.

4-Vinyl-1,1'-biphenyl (91k')



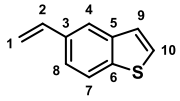
To a suspension of methyltriphenylphosphonium iodide (4.72 mg, 13.2 mmol) and biphenyl-4-carboxaldehyde (2.00 g, 11.0 mmol) in THF (50 mL) at 0 °C, was added NaH (1.93 g, 48.3 mmol, 60% in oil) portion-wise. The solution was warmed to ambient temperature and stirred for 5 h. The mixture was diluted with CH_2Cl_2 (90 mL), washed with water (50 mL) and brine (3 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by recrystallisation (*i*PrOH) afforded the title compound (1.80 g, 91%) as colourless plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.55 (4H, m), 7.50 (2H, d, *J* = 8.0 Hz), 7.45 (2H, ddd, *J* = 7.5, 6.5, 1.5 Hz), 7.39 – 7.30 (1H, m), 6.77 (1H, dd, *J* = 17.5, 11.0 Hz), 5.81 (1H, dd, *J* = 17.5, 1.0 Hz), 5.29 (1H, dd, *J* = 11.0, 1.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 140.7, 136.7, 136.5, 128.9, 127.5, 127.4, 127.1, 126.8, 114.0; m.p. 118–120 °C (*i*PrOH) (Lit.[272] 118–119 °C, *no recrystallisation solvent specified*). *The spectroscopic proprieties of this compound were consistent with the data available in the literature.*[272]

Trimethyl(4-vinylphenyl)silane (91q')



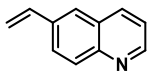
The title compound was prepared following a literature procedure.[273] To an oven-dried Schlenk tube was added magnesium turnings (265 mg, 10.9 mmol), THF (11 mL), chlorotrimethylsilane (0.693 mL, 5.46 mmol) and 4-bromostyrene (0.714 mL, 5.46 mmol) under nitrogen. The Schlenk tube was placed in a commercial ultrasonic cleaning bath (Ultrawave Ltd. SFE 510/1, 220–240 KHz, 275 W) and sonicated for 3 h. The mixture was washed with aq. saturated NaCl solution (10 mL) and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/Et_2O 0–5%) afforded the title compound (673 mg, 70%) as a colourless oil. ν_{max}/cm^{-1}: 3063 (m), 2956 (m), 1629 (m), 824 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (2H, d, *J* = 8.0 Hz, C**4**-H), 7.42 (2H, d, *J* = 8.0 Hz, C**5**-H), 6.74 (1H, dd, *J* = 17.5, 11.0 Hz, C**2**-H), 5.80 (1H, dd, *J* = 17.5, 1.0 Hz, C**1**-H), 5.27 (1H, dd, *J* = 11.0, 1.0 Hz, C**1**-H), 0.29 (9H, s, C**7**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.3 (C**6**), 138.1 (C**3**), 137.0 (C**2**), 133.7 (C**4**), 125.7 (C**5**), 114.2 (C**1**), -0.9 (C**7**). *A mass could not be observed by ESI or MALDI.*

5-Vinylbenzo[*b*]thiophene (91u')



General Procedure S: Purification of the residue by FCC (hexane) afforded the title compound (350 mg, 90%) as a colourless solid. ν_{max}/cm^{-1}: 2959 (m), 2921 (m), 1627 (s), 1426 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (1H, dd, *J* = 8.5, 1.0 Hz, C**8**-H), 7.81 (1H, d, *J* = 1.0 Hz, C**4**-H), 7.46 (1H, dd, *J* = 8.5, 1.0 Hz, C**7**-H), 7.44 (1H, d, *J* = 5.5 Hz, C**9**-H), 7.32 (1H, dd, *J* = 5.5, 1.0 Hz, C**10**-H), 6.84 (1H, dd, *J* = 17.5, 11.0 Hz, C**2**-H), 5.81 (1H, dd, *J* = 17.5, 1.0 Hz, C**1**-H_2), 5.28 (1H, dd, *J* = 11.0, 1.0 Hz, C**1**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.1 (C**5**), 139.3 (C**6**), 137.1 (C**2**), 134.1 (C**3**), 127.0 (C**9**), 124.1 (C**10**), 122.6 (ArCH), 122.4 (C**7**), 121.8 (ArCH), 113.6 (C**1**); m.p. 34–36 °C ($CDCl_3$); *A mass could not be observed by ESI or MALDI.*

6-Vinylquinoline (91y')



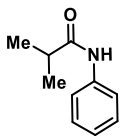
General Procedure S: Purification of the residue by FCC (CH_2Cl_2/EtOAc 10%) afforded the title compound (325 mg, 87%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (1H, dd, *J* = 4.5, 1.5 Hz), 8.12 (1H, dd, *J* = 8.5, 2.0 Hz), 8.06 (1H, d, *J* = 8.5 Hz), 7.87 (1H, dd, *J* = 8.5, 2.0 Hz), 7.72 (1H, d, *J* = 2.0 Hz), 7.38 (1H, dd, *J* = 8.5, 4.5 Hz), 6.89 (1H, dd, *J* = 17.5, 11.0 Hz), 5.91 (1H, d, *J* = 17.5 Hz), 5.40 (1H, d, *J* = 11.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4, 148.3, 136.3, 136.2, 135.9, 129.8, 128.5, 127.1, 125.9, 121.6, 115.6. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[274]

7.7.2.2 – Synthesis of Acetanilide Substrates

60a, **60c**, **60e**, **60k**, **60y**, **60aa** and **60ah** *were purchased from commercial sources (Sigma or Alfa).*

60b, **60f**, **60g**, **60j**, **60m**, **60r**, **60s**, **60v**, **60z**, **60af**, **60ag**, **89a, 89b** and **90c** *were synthesised by Dr. Giacomo Crisenza.*

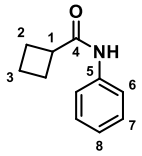
***N*-Phenylisobutyramide (60l)**



The title compound was synthesised following a modified literature procedure.[275] To a solution of aniline (1.10 mL, 12.0 mmol), CH_2Cl_2 (20 mL), and triethylamine (1.60 mL, 12.0 mmol), was added dropwise isobutryl chloride (1.05 mL, 10.0 mmol). The resulting solution was stirred at ambient temperature overnight. The resulting mixture was washed with aq. HCl (1 M, 3 × 50 mL), aq. KOH (2 M, 3 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC

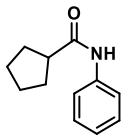
(hexane/EtOAc 40%) afforded the title compound (1.63 g, quantitative) as a colourless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, s), 7.52 (1H, s), 7.34 – 7.27 (2H, m), 7.14 – 7.04 (1H, m), 2.51 (1H, hept, *J* = 7.0 Hz), 1.26 (3H, s), 1.24 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4, 138.2, 129.1, 124.3, 119.9, 36.8, 19.8; m.p. 102–104 °C (hexane/EtOAc) (Lit.[276] 98–99 °C, *recrystallisation solvent not specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[276]

***N*-Phenylcyclobutanecarboxamide (60n)**



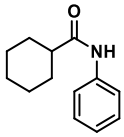
To an oven-dried flask was added EDCI (1.07 g, 5.57 mmol) and DMAP (6.18 mg, 0.051 mmol) under nitrogen. CH_2Cl_2 (27 mL), aniline (0.461 mL, 5.07 mmol) and cyclobutene carboxylic acid (0.509 mL, 5.32 mmol) were added. The resulting solution was stirred at ambient temperature until full consumption of aniline was observed by TLC. The reaction mixture was washed with aq. saturated $NaHCO_3$ solution (20 mL), before being dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 60%) afforded the title compound (602 mg, 68%) as colourless needles. ν_{max}/cm^{-1}: 3249 (m), 2943 (m), 1655 (s), 1443 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* = 8.0 Hz, C**6**-H), 7.31 (2H, t, *J* = 8.0 Hz, C**7**-H), 7.13 – 7.04 (2H, m, C**8**-H, N-H), 3.16 (1H, p, *J* = 8.5 Hz, C**1**-H), 2.48 – 2.32 (2H, m, C**2**-H_2), 2.29 – 2.18 (2H, m, C**2**-H_2), 2.08 – 1.82 (2H, m, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.1 (C**4**), 138.2 (C**5**), 129.1 (C**7**), 124.1 (C**8**), 119.8 (C**6**), 41.0 (C**1**), 25.4 (C**2**), 18.2 (C**3**); HRMS: (ESI$^+$) calculated for $C_{11}H_{13}NONa$ 198.0889. Found $[M+Na]^+$ 198.0892; m.p. 103–106 °C ($CDCl_3$).

***N*-Phenylcyclopentanecarboxamide (60o)**



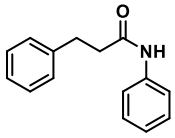
General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (842 mg, 89% yield) as a colourless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* = 8.0 Hz), 7.30 (3H, t, *J* = 8.0 Hz), 7.08 (1H, t, *J* = 8.0 Hz,), 2.68 (1H, p, *J* = 8.0 Hz), 2.00 – 1.84 (4H, m), 1.84 – 1.71 (2H, m), 1.68 – 1.53 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 138.3, 129.1, 124.1, 119.8, 47.0, 30.7, 26.2; m.p. 159–161 °C (hexane/EtOAc) (Lit.[277] 162–163 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[277]

***N*-Phenylcyclohexanecarboxamide (60p)**



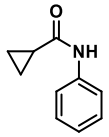
General Procedure T: Purification if the residue by recrystallisation (hexane/EtOAc) afforded the title compound (936 mg, 85% yield) as white needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (2H, d, *J* = 7.5 Hz), 7.36 – 7.25 (2H, m), 7.21 (1H, br. s), 7.09 (1H, t, *J* = 7.5 Hz), 2.30 – 2.16 (1H, m), 2.01 – 1.91 (2H, m), 1.89 – 1.78 (2H, m), 1.77 – 1.67 (1H, m), 1.64 – 1.46 (2H, m), 1.41 – 1.15 (3H, m); ^{13}C NMR (101 MHz,$CDCl_3$): δ 174.5, 138.2, 129.1, 129.1, 124.2, 119.9, 46.7, 29.8, 25.8, 25.8; m.p. 144–146 °C (hexane/EtOAc) (Lit.[277] 145–146 °C *no recrystallisation solvent specified*) *The spectroscopic properties for this compound were consistent with the data available in the literature.*[277]

***N*,3-Diphenylpropanamide (60q)**



To a solution of K_2CO_3 (207 mg, 1.50 mmol), aniline (0.091 mL, 1.00 mmol), *N*-dimethylimidazole (8.0 µL, 0.1 mmol), TMEDA (11 µL, 0.100 mmol) and CH_3CN (1 mL) at 0 °C, was added hydrocinnamoyl chloride (0.222 mL, 1.50 mmol) dropwise. The solution was stirred for 1 h, before warmed to ambient temperature. The reaction was quenched by the addition of H_2O (3 mL) and extracted with EtOAc (3 × 5 mL). The organic extracts were combined, washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (175 mg, 78%) as colourless plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (2H, d, *J* = 8.0 Hz), 7.30 – 7.21 (4H, m), 7.20 – 7.14 (3H, m), 7.03 (1H, t, *J* = 7.5 Hz), 6.95 (1H, br. s), 3.00 (2H, t, *J* = 7.5 Hz), 2.60 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 140.8, 137.9, 129.1, 128.8, 128.5, 126.5, 124.4, 120.04, 39.6, 31.7; m.p. 96–98 °C (hexane/EtOAc) (Lit. 92–93 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*

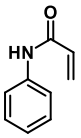
***N*-Phenylcyclopropanecarboxamide (60t)**



The title compound was prepared following a literature procedure.[278] Aniline (0.290 mL, 3.22 mmol) and K_2CO_3 (534 mg) were suspended in dry MeCN (26 mL). Cyclopropane carboxylic acid chloride (0.290 mL, 3.22 mmol) was added dropwise at ambient temperature over 5 minutes. The resulting solution was stirred for 2.5 hours. The solvent was removed *in vacuo*, before the residue was taken up in CH_2Cl_2 (13 mL). The organic extract was washed with water (2 × 13 mL), dried over Na_2SO_4 and

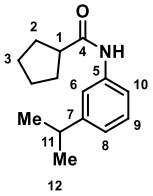
concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (258 mg, 50% yield) as colourless needles. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (3H, d, *J* = 8.0 Hz,), 7.30 (2H, t, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 8.0 Hz), 1.55 – 1.45 (1H, m), 1.22 – 1.01 (2H, m), 0.91 – 0.76 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 138.3, 129.1, 124.2, 119.8, 15.9, 8.1; m.p. 109–110 °C (Lit.[279] 110 °C, $CHCl_3$/hexane). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[279]

***N*-Phenylacrylamide (60u)**



The title compound was prepared following a literature procedure.[280] To a solution of K_2CO_3 (1.00 g, 10.0 mmol) and acryloyl chloride (0.809 mL, 10.0 mmol) in H_2O (2.5 mL) and acetone (10 mL) at 0 °C was added aniline (0.456 mL, 5.00 mL) dropwise over 5 minutes. The solution was stirred at 0 °C for 2 hours before the resulting white precipitate was filtered off. The solution was concentrated *in vacuo*, suspended in water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by FCC (hexane/ EtOAc 40%) to afford the title compound (304 mg, 41% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.54 (2H, m), 7.42 (1H, br. s), 7.37 – 7.29 (2H, m), 7.13 (1H, t, *J* = 7.5 Hz), 6.43 (1H, dd, *J* = 17.0, 1.5 Hz,), 6.26 (1H, dd, *J* = 17.0, 10.0 Hz), 5.76 (1H, dd, *J* = 10.0, 1.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7, 137.9, 131.4, 129.2, 127.9, 124.7, 120.2; m.p. 101–103 °C (hexane/EtOAc) (Lit.[281] 103–104 °C, *no recrystallisation solvent specified*) *The spectroscopic properties for this compound were consistent with the data available in the literature.*[282]

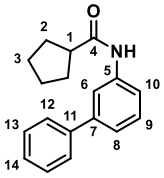
***N*-(3-Isopropylphenyl)cyclopentanecarboxamide (60w)**



General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (1.16 g, quantitative) as colourless needles. ν_{max}/cm^{-1}: 3295 (m), 2958 (m), 2858 (m), 1656 (s), 1510 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.42 (1H, m, C**8**-H), 7.41 (1H, s, N-H), 7.36 – 7.29 (1H, m, C**10**-H), 7.28 – 7.17 (1H, m, C**9**-H), 6.95 (1H, d, *J* = 7.5 Hz, C**6**-H), 2.86 (1H, hept, *J* = 6.5 Hz, C**11**-H), 2.67 (1H, p, *J* = 8.0 Hz, C**1**-H), 1.98 – 1.49 (8H, m, C**2**-H_2, C**3**-H_2), 1.23 (6H, d, *J* = 6.5 Hz, C**12**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8 (C**4**), 150.0 (C**7**), 138.3 (C**5**), 128.9 (C**9**), 122.3 (C**6**), 118.0 (C**8**), 117.3 (C**10**), 47.0 (C**1**), 34.3 (C**11**), 30.7 (cyclopentyl), 26.2 (cyclopentyl), 24.0 (C**12**);

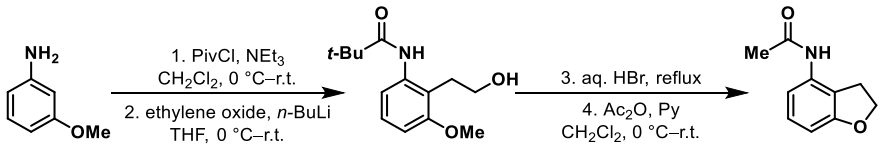
HRMS: (ESI$^+$) calculated for $C_{15}H_{21}NONa$ 254.1515. Found $[M+Na]^+$ 254.1514; m.p. 52–54 °C (hexane/EtOAc).

***N*-([1,1'-Biphenyl]-3-yl)cyclopentanecarboxamide (60x)**



General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (1.14 g, 88%) as a colourless powder. ν_{max}/cm^{-1}: 3296 (m), 2951 (m), 1658 (s), 1550 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (1H, s, C**6**-H), 7.61 – 7.56 (2H, m, C**12**-H), 7.48 (1H, dd, *J* = 8.0, 2.0 Hz, ArCH), 7.45 – 7.39 (2H, m, C**13**-H), 7.38 – 7.31 (2H, m, C**9**-H, ArCH), 7.27 (1H, s, N-H), 2.71 (1H, p, *J* = 8.0 Hz, C**1**-H), 2.02 – 1.87 (4H, m, cyclopentyl), 1.86 – 1.71 (2H, m, cyclopentyl), 1.69 – 1.58 (2H, m, cyclopentyl); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8 (C**4**), 142.3 (C**7**), 140.8 (C**11**), 138.7 (C**5**), 129.5 (ArCH), 128.9 (C**13**), 127.6 (ArCH), 127.3 (C**12**), 123.0 (ArCH), 118.6 (ArCH), 47.1 (C**1**), 30.7 (cyclopentyl), 26.2 (cyclopentyl); HRMS: (ESI$^+$) calculated for $C_{18}H_{20}NO$ 266.1539. Found $[M+H]^+$ 266.1541; m.p. 110–112 °C (hexane/EtOAc).

Preparation of 2,3-Dihydro-4-benzofuranacetanilide (60d)



The title compound was prepared following a literature procedure.[116]

Step 1: To a solution of *m*-anisidine (5.00 mL, 44.5 mmol) and triethylamine (7.40 mL, 53.4 mmol) in CH_2Cl_2 (114 mL) at 0 °C was added pivaloyl chloride (6.58 mL, 53.4 mmol) dropwise over 15 minutes. The resulting suspension was stirred at ambient temperature for 3 hours, before being quenched with aq. HCl (1 M, 70 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, washed with brine (70 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (9.46 g, quantitative) as a beige solid. ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.39 (1H, t, *J* = 2.5 Hz), 7.31 (1H, br. s,), 7.20 (1H, t, *J* = 8.0 Hz), 6.93 (1H, dd, *J* = 8.0, 2.5 Hz), 6.66 (1H, dd, *J* = 8.0, 2.5 Hz), 3.81 (3H, s), 1.32 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 160.3, 139.5, 129.7, 111.9, 110.5, 105.4, 55.5, 39.8, 27.8; m.p. 114–116 °C ($CHCl_3$) (Lit.[283] 106–108 °C, hexane/EtOAc*). The spectroscopic properties for this compound were consistent with the data available in the literature.*[283]

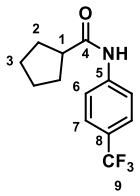
Step 2: Methyl 4-acetamido-3-(1-phenylvinyl)benzoate (9.60 g, 46.3 mmol) was dissolved in THF (175 mL) and cooled to 0 °C. *n*-BuLi (1.6 M in hexanes, 72 mL) was added dropwise over 1 h with vigorous stirring and the resulting solution was stirred for 2 hours. Ethylene oxide (2.5 M in THF, 28 mL) was

added dropwise over 1 h, before the solution was warmed to ambient temperature and stirred overnight. The reaction was quenched by the addition of water (25 mL) before being concentrated *in vacuo*. The residue was re-suspended in water (50 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, washed with saturated aq. Na_2CO_3 (35 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC (hexane/EtOAc 30%) to afford the title compound (9.56 g, 82%) as a colourless solid. ^{1}H NMR (400 MHz, CDCl3): δ 8.86 (1H, br. s), 7.43 (1H, dd, *J* = 8.0, 1.0 Hz), 7.18 (1H, t, *J* = 8.0 Hz), 6.67 (1H, dd, *J* = 8.0, 1.0 Hz), 3.94 – 3.85 (2H, m), 3.80 (3H, s,), 2.92 – 2.80 (2H, m), 2.22 (1H, t, *J* = 4.0 Hz), 1.30 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 157.7, 138.3, 127.2, 120.6, 117.0, 106.9, 77.5, 77.2, 76.8, 63.9, 55.7, 39.7, 27.8, 27.3; HRMS: (ESI^+) calculated for $C_{17}H_{17}NO_2Na$ 290.1151. Found $[M+Na]^+$ 290.1146; m.p. 117–119 °C ($CDCl_3$) (Lit.[284] 118–119.5 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[284]

Step 3: *N*-(2-(2-Hydroxyethyl)-3-methoxyphenyl)pivalamide (9.56 g, 38.0 mmol) was suspended in aq. HBr (48%, 103 mL) and the solution was heated to 100 °C overnight. The reaction mixture was cooled to ambient temperature and the pH of the solution was adjusted to 9 by the slow addition of NaOH pellets. The mixture was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, washed with aq. NaOH (2M, 100 mL) and water (60 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude title product (5.10 g, 99%) as a brown oil. The crude material was employed in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (1H, t, *J* = 8.0 Hz), 6.28 (1H, d, *J* = 8.0 Hz), 6.22 (1H, dd, *J* = 8.0, 1.0 Hz), 4.59 (2H, t, *J* = 8.5 Hz), 3.77 – 3.41 (2H, m,), 3.02 (2H, t, *J* = 8.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2, 143.4, 129.1, 111.3, 107.7, 100.3, 71.1, 27.3. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[116]

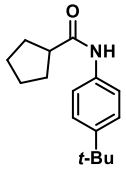
Step 4: 2,3-Dihydrobenzofuran-4-amine (5.10 g, 37.7 mmol) was dissolved in CH_2Cl_2 (54 mL) and pyridine (1.80 mL) and cooled to 0 °C. Acetic anhydride (3.92 mL, 41.5 mmol) was added dropwise over 10 minutes. The solution was warmed to ambient temperature and stirred for 2 hours. The reaction was quenched by the addition of water (75 mL) and extracted with CH_2Cl_2 (3 × 180 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$ (3 × 75 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (4.27 g, 64%) as white plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (1H, d, *J* = 8.0 Hz), 7.10 (1H, t, *J* = 8.0 Hz), 6.94 (1H, br. s), 6.62 (1H, d, *J* = 8.0 Hz), 4.60 (2H, t, *J* = 8.5 Hz), 3.14 (2H, t, *J* = 8.5 Hz), 2.18 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 160.9, 134.4, 128.9, 118.9, 114.2, 106.5, 71.2, 28.4, 24.4; m.p. 125–126 °C (hexane/EtOAc) (Lit.[116] 126–127 °C, hexane/EtOAc). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[116]

***N*-(4-(Trifluoromethyl)phenyl)cyclopentanecarboxamide (60ab)**



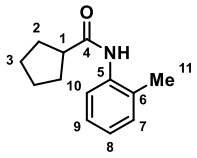
General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (878 mg, 68%) as a colourless powder. ν_{max}/cm^{-1}: 3300 (m), 2970 (m), 1668 (s), 1527 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (2H, d, *J* = 8.5 Hz, C**6**-H), 7.55 (2H, d, *J* = 8.5 Hz, C**7**-H), 7.42 (1H, s, N-H), 2.70 (1H, p, *J* = 8.0 Hz, C**1**-H), 2.00 – 1.84 (4H, m, cyclopentyl), 1.84 – 1.73 (2H, m, cyclopentyl), 1.69 – 1.54 (2H, m, Cyclopentyl); ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.1 (C**4**), 141.3 (C**5**), 126.4 (q, *J* = 4.0 Hz, C**7**), 125.9 (q, *J* = 32.0 Hz, C**8**), 124.2 (q, *J* = 271.0 Hz, C**9**), 119.4 (C**6**), 47.0 (C**1**), 30.7 (cyclopentyl), 26.2 (cyclopentyl); HRMS: (ESI$^+$) calculated for $C_{13}H_{15}NOF_3$ 258.1103. Found $[M+H]^+$ 258.1098; m.p. 170–172 °C (hexane/EtOAc).

***N*-(4-(*tert*-Butyl)phenyl)cyclopentanecarboxamide (60ac)**



General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (885 mg, 72%) as colourless crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 7.13 (1H, s), 2.66 (1H, p, *J* = 8.0 Hz), 1.99 – 1.49 (8H, m), 1.30 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7, 147.1, 135.7, 125.9, 119.7, 46.9, 34.5, 31.5, 30.7, 26.1; m.p. 151–153 °C (hexane/EtOAc). (Lit. m.p., *not stated*). *The spectroscopic properties for this compound were consistent with the data available in the literature.* [285]

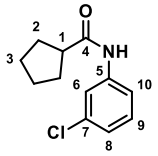
***N*-(*o*-Tolyl)cyclopenanecarboxamide (60ad)**



General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (742 mg, 74%) as a colourless powder. ν_{max}/cm^{-1}: 3270 (m), 2956 (m), 2864 (m), 1650 (s), 1532 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.80 (1H, m, C**10**-H), 7.21 – 7.13 (2H, m, C**7**-H, C**9**-H), 7.09 – 7.00 (1H, m, C**8**-H), 6.98 (1H, s,nH), 2.72 (1H, p, *J* = 8.0 Hz, C**1**-H), 2.24 (3H, s, C**11**-H_3), 1.99 – 1.54 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6 (C**4**), 136.0 (C**5**), 130.5 (C**7**), 128.8 (C**6**), 126.9 (C**9**), 125.0 (C**8**), 123.1 (C**10**), 46.9 (C**1**), 30.7 (cyclopentyl), 26.1 (cyclopentyl), 17.9

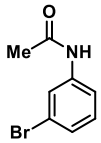
(C**11**); HRMS: (ESI$^+$) calculated for $C_{13}H_{18}NO$ 204.1383. Found $[M+H]^+$ 204.1381; m.p. 130–132 °C (hexane/EtOAc).

***N*-(3-Chlorophenyl)cyclopentanecarboxamide (60ae)**



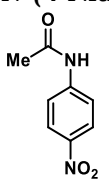
General Procedure T: Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (972 mg, 87%) as a colourless powder. ν_{max}/cm^{-1}: 3288 (m), 2959 (m), 2869 (m), 1661 (s), 1593 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, s, C**6**-H), 7.42 – 7.30 (2H, m, C**10**-H, N-H), 7.26 – 7.16 (1H, m, C**9**-H), 7.05 (1H, dd, *J* = 8.0, 1.0 Hz, C**8**-H), 2.67 (1H, p, *J* = 8.0 Hz, C**1**-H), 2.01 – 1.84 (4H, m, cyclopentyl), 1.83 – 1.68 (2H, m, cyclopentyl), 1.68 – 1.48 (2H, m, cyclopentyl); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9 (C**4**), 139.4 (C**5**), 134.7 (C**7**), 130.0 (C**9**), 124.2 (C**8**), 120.0 (C**6**), 117.8 (C**10**), 47.0 (C**1**), 30.7 (cyclopentyl), 26.1 (cyclopentyl); HRMS: (ESI$^+$) calculated for $C_{12}H_{14}NO^{35}ClNa$ 246.0656. Found $[M+Na]^+$ 246.0665; m.p. 109–111 °C (hexane/EtOAc).

***N*-(3-Bromophenyl)acetamide (60i)**



The title compound was prepared following a literature procedure.[286] To a solution of 3-bromoaniline (0.633 mL, 5.81 mmol) and acetic anhydride (1.10 mL, 11.6 mmol) at 0 °C was added sulfuric acid (0.1 mL). The solution was stirred for 1 h, before ice (~5.00 g) was added. The resulting white precipitate was collected by filtration, dissolved in EtOAc (10 mL), washed with water (10 mL) and concentrated *in vacuo*. Purification of the residue by recrystallisation (hexane/EtOAc) afforded the title compound (1.10 g, 89%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.74 (1H, m), 7.66 (1H, br. s), 7.40 (1H, d, *J* = 8.0 Hz), 7.22 (1H, d, *J* = 8.0 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 2.17 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 139.3, 130.4, 127.4, 123.0, 122.7, 118.5, 24.7; m.p. 85–87 °C (hexane/EtOAc) (Lit.[287] 85–86 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistenet with the data available in the literature.*[288]

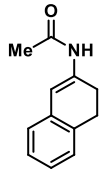
***N*-(4-Nitrophenyl)acetamide (60ai)**



To pyridine (1.10 mL) and acetyl chloride (0.240 mL, 4.34 mmol) in dry CH_2Cl_2 (5.5 mL) was added 4-nitroaniline (500 mg, 3.62 mmol) and pyridine (1.10 mL) dropwise at 0 °C over 10 minutes. The solution was stirred at ambient temperature overnight. The resulting slurry was concentrated *in vacuo*

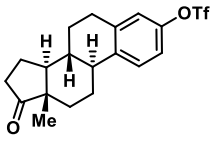
before being taken up in CH_2Cl_2 (20 mL). The solution was washed with water (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 50%) afforded the title compound (518 mg, 79% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.55 (1H, br. s), 8.25 – 8.16 (2H, m), 7.86 – 7.78 (2H, m), 2.12 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.3, 145.4, 142.0, 125.0, 118.5, 24.2; m.p. 210–211 °C ($CDCl_3$) (Lit.[289] 209–211, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[290]

_N_-(3,4-Dihydronaphthalen-2-yl)acetamide (195)



The title compound was prepared following a modified literature procedure.[291] A flame-dried round-bottomed flask equipped with a Dean-Stark apparatus was charged with *β*-tetralone (820 μL, 6.20 mmol), acetamide (916 mg, 15.5 mmol), *p*-toluenesulfonic acid monohydrate (118 mg, 0.620 mmol) and toluene (40 mL). The mixture was heated at reflux for 16 h under a nitrogen atmosphere. The reaction was cooled to ambient temperature, quenched with saturated aq. $NaHCO_3$ (100 mL) and then extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude material. Purification of the residue by FCC (hexane/EtOAc 50%) afforded the title compound (1.12 g, 97% yield) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16 – 6.95 (5H, m), 6.81 (1H, br. s), 2.87 (2H, t, *J* = 8.0 Hz), 2.44 (2H, t, *J* = 8.0 Hz), 2.10 (3H, s); 13C NMR ($CDCl_3$, 100 MHz): δ 168.5, 134.9, 134.6, 132.6, 127.0, 126.7, 126.1, 125.7, 111.3, 27.9, 27.5, 24.7; m.p. 98–100 ˚C (hexane/EtOAc) (Lit.[291] 99–101 ˚C, *no recrystallisation solvent specified*). *The spectroscopic properties were consistent with the data available in the literature.*[291]

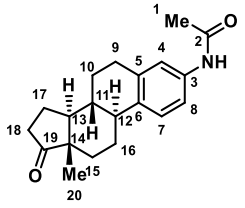
13*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate



The title compound was prepared following a literature procedure.[292] To a flame-dried round-bottomed flask was added estrone (2.00 g, 7.40 mmol) in dry CH_2Cl_2 (37 mL) under nitrogen. Pyridine (1.20 mL, 14.8 mmol) was added and the solution was cooled to 0 °C. Triflic anhydride (1.50 mL, 8.88 mmol) was added dropwise over 5 minutes. The solution was warmed to ambient temperature and was stirred

for 1.5 h. The reaction was quenched by the addition of water (20 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 30%) afforded the title compound (3.04 g, quantitative) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (1H, d, *J* = 8.5 Hz), 7.06 – 6.95 (2H, m), 2.98 – 2.93 (2H, m), 2.61 – 2.46 (1H, m), 2.44 – 2.35 (1H, m), 2.35 – 2.25 (1H, m), 2.22 – 2.00 (3H, m), 2.00 – 1.92 (1H, m), 1.69 – 1.38 (6H, m), 0.91 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 220.4, 147.7, 140.4, 139.4, 127.3, 121.3, 118.8 (q, *J* = 321.0 Hz), 118.4, 50.5, 47.9, 44.2, 37.8, 35.9, 31.6, 29.5, 26.2, 25.8, 21.7, 13.9; m.p. 85–87 °C (CH_2Cl_2) (Lit.[293] 87–89 °C, *no recrystallisation solvent specified*); $[\alpha]^{22}_D$ = + 114.6 (c = 0.20, CH_2Cl_2). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[293]

_N_-((8_R_,9_S_,13_S_,14_S_)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-_6H_-cyclopenta[_a_]phenanthren-3-yl)acetamide (60aj)



The title compound was prepared following a literature procedure.[19] An oven dried resealable tube was charged with (13*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*] phenanthrene-3-yl trifluoromethanesulfonate (805 mg, 2.00 mmol), the preceding acetanilide (177 mg, 3.00 mmol), $Pd_2(dba)_3$ (18.0 mg, 0.020 mmol), Me_4*t*-BuXPhos (48.0 mg, 0.100 mmol) and K_3PO_4 (1.06 g, 5.00 mmol). The tube was fitted with a rubber septum and purged with nitrogen before *t*-BuOH (deoxygenated with Ar for 10 minutes) was added and the tube was sealed with a Young's tap. The reaction mixture was heated at 110 °C for 18 h, cooled to ambient temperature and filtered over a pad of Celite®, washing with EtOAc and CH_2Cl_2/MeOH (1:1). The resulting solution was concentrated *in vacuo* and purification of the residue by FCC (toluene/EtOAC 40–50%) afforded the desired product (526 mg, 84%) as a colourless solid. ν_{max}/cm^{-1}: 3291 (m), 2936 (m), 2920 (m), 1734 (s), 1658 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (1H, s, N-H), 7.33-7.25 (2H, m, C**4**-H, C**8**-H), 7.17 (1H, d, *J* = 8.5 Hz, C**7**-H), 2.85-2.76 (2H, m, C**9**-H_2), 2.44 (1H, dd, *J* = 19.0, 8.5 Hz, C**18**-H_2), 2.38-2.28 (1H, m, C**16**-H_2), 2.24-2.14 (1H, m, C**12**-H), 2.05 (1H, dd, *J* = 19.0, 8.5 Hz, C**18**-H_2), 2.00 (3H, s, C**1**-H_3), 1.98-1.88 (2H, m, C**10**-H_2, C**17**-H_2), 1.78-1.70 (1H, m, C**15**-H_2), 1.61-1.28 (6H, m, C**10**-H_2, C**11**-H, C**13**-H, C**15**-H_2, C**16**-H_2, C**17**-H_2), 0.83 (3H, s, C**20**-H_3); ^{13}C NMR (101 MHz, DMSO-d_6): δ 219.6 (C**19**), 167.9 (C**2**), 136.9 (C**5**), 136.3 (C**3**), 134.3 (C**6**), 125.4 (C**7**), 119.1 (C**4**), 116.6 (C**8**), 49.6 (C**13**), 47.3 (C**14**), 43.6 (C**12**), 37.7 (C**11**), 35.3 (C**18**), 31.3 (C**15**), 29.1 (C**9**), 26.0 (C**10**), 25.3 (C**16**), 23.9 (C**1**), 21.1

(C**17**), 13.5 (C**20**); HRMS (ESI$^+$) calculated for $C_{20}H_{26}NO_2$ 312.1958. Found $[M+H]^+$ 312.1979; m.p. 230 °C (degradation) ($CDCl_3$); $[\alpha]^{20}_D$ = + 134.7 (c = 0.20, CH_2Cl_2).

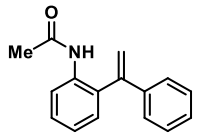
For heteroaromatic substrates **126a–d**, **131**, **134a** and **145** *see* Section **7.5.1**

For heteroaromatic substrates **126e** and **150a–c** *see* Section **7.6.2**

7.7.2 – α-Arylation of Styrenes with Acetanilide Substrates

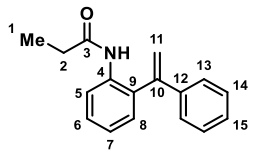
*For branched hydroarylation product **96aa'** see Section **7.4.3***

***N*-(2-(1-Phenylvinyl)phenyl)acetamide (104aa')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 10–40%) afforded the title compound (25.0 mg, 74%) as a colourless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (1H, s), 7.49 (1H, d, *J* = 8.0 Hz), 7.39 – 7.26 (4H, m), 7.24 – 7.13 (4H, m), 5.76 (1H, d, *J* = 1.0 Hz), 5.31 (1H, d, *J* = 1.0 Hz), 1.60 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.9, 146.3, 140.0, 135.5, 130.2, 128.1, 127.9, 127.6, 126.5, 125.9, 125.0, 116.7, 22.7; m.p. 120–122 °C (hexane/EtOAc). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[294]

***N*-(2-(1-Phenylvinyl)phenyl)propionamide (104ka')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (1st column: hexane/EtOAc 0–30%; 2nd column: hexane/EtOAc 30%) to afford the title compound (24.7 mg, 69%, 0.96:0.04 mixture of rotamers *A:B*) as golden plates. ν_{max}/cm^{-1}: 3415 (m), 3288 (m), 1668 (s), 1516 (s), 1448 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (1H, d, *J* = 8.0 Hz, C**5**-H), 7.38 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz, C**6**-H), 7.35 – 7.31 (5H, m, C**13**-H, C**14**-H, C**15**-H), 7.29 – 7.25 (1H, m, C**8**-H), 7.19 – 7.12 (1H, m, C**7**-H), 6.99 (1H, br. s, N-H), 5.88 (1H, d, *J* = 1.5 Hz, C**11**-H_2), 5.37 (1H, d, *J* = 1.5 Hz, C**11**-H_2), 2.01 (2H, q, *J* = 7.5 Hz, C**2**-H_2), 0.92 (3H, t, *J* = 7.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C**3**), 146.5 (C**10**), 139.3 (C**12**), 135.4 (C**4**), 131.8 (C**9**), 130.4 (C**8**), 129.0 (ArCH), 128.9 (ArCH), 128.7 (C**6**), 126.6 (ArCH), 124.2 (C**7**), 121.7 (C**5**),

117.4 (C**11**), 30.8 (C**2**), 9.4 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{18}NO$ 252.1383. Found $[M+H]^+$ 252.1386; m.p. 113–115 °C ($CDCl_3$).

Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (1H, d, *J* = 8.5 Hz, C**5**-H), 5.84 (1H, s, C**11**-H_2), 5.33 (1H, s, C**11**-H_2).

*The structure of compound **104ka'** was confirmed by single crystal X-ray diffraction of crystals obtained from $CDCl_3$ (Figure **9**).*

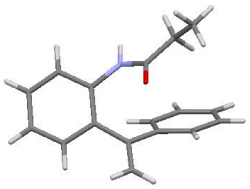
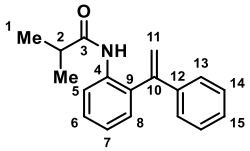


Figure 9

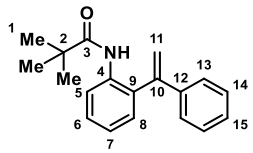
***N*-(2-(1-Phenylvinyl)phenyl)isobutyramide (104la')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 20%) to afford the title compound (30.7 mg, 81%, 0.98:0.02 mixture of rotamers *A:B*) as an orange oil. ν_{max}/cm^{-1}: 3418 (m), 2966 (m), 1676 (s), 1515 (s), 1444 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, d, *J* = 8.0 Hz, C**5**-H), 7.41 – 7.35 (1H, m, C**6**-H), 7.35 – 7.31 (5H, m, C**13**-H, C**14**-H, C**15**-H), 7.30 – 7.25 (1H, m, C**8**-H), 7.15 (1H, ddd, *J* = 8.0, 8.0, 1.0 Hz, C**7**-H), 7.03 (1H, s, N-H), 5.90 (1H, d, *J* = 1.5 Hz, C**11**-H_2), 5.38 (1H, d, *J* = 1.5 Hz, C**11**-H_2), 2.13 (1H, sept, *J* = 7.0 Hz, C**2**-H), 0.91 (6H, d, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8 (C**3**), 146.5 (C**10**), 139.2 (C**12**), 135.4 (C**4**), 131.7 (C**9**), 130.5 (C**8**), 129.0 (ArCH), 128.9 (ArCH), 128.7 (ArCH), 126.6 (ArCH), 124.1 (C**7**), 121.4 (C**5**), 117.5 (C**11**), 36.8 (C**2**), 19.2 (C**1**); HRMS: (ESI$^+$) calculated for $C_{18}H_{19}NONa$ 288.1359. Found $[M+Na]^+$ 288.1362.

Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1H, d, *J* = 8.5 Hz, C**5**-H), 5.86 (1H, d, *J* = 1.0 Hz, C**11**-H_2), 5.33 (1H, d, *J* = 1.0 Hz, C**11**-H_2).

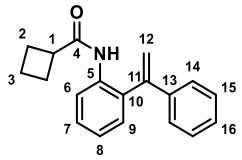
***N*-(2-(1-Phenylvinyl)phenyl)pivalamide (104ma')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 0–10%) to afford the title compound (26.0 mg, 65%, 0.97:0.03 mixture of rotamers *A:B*) as a brown oil. ν_{max}/cm^{-1}: 3431 (m), 2959 (m), 1686 (s), 1516 (s), 1300 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (1H, dd, *J* = 8.0, 1.0 Hz, C**5**-H), 7.40 – 7.36 (1H, m, C**6**-H), 7.37 – 7.30 (6H, m, C**13**-H, C**14**-H, C**15**-H, N-H), 7.29 – 7.24 (1H, m, C**8**-H), 7.14 (1H, ddd, *J* = 8.0, 8.0, 1.0 Hz, C**7**-H), 5.92 (1H, d, *J* = 1.5 Hz, C**11**-H_2), 5.38 (1H, d, *J* = 1.5 Hz, C**11**-H_2), 0.94 (9H, s, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4 (C**3**), 146.5 (C**10**), 138.8 (C**12**), 135.6 (C**4**), 131.7 (C**9**), 130.6 (C**8**), 129.1 (ArCH), 129.0 (ArCH), 128.8 (ArCH), 126.61 (ArCH), 124.1 (C**7**), 121.3 (C**5**), 117.4 (C**11**), 39.7 (C**2**), 27.3 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{21}NONa$ 302.1515. Found $[M+Na]^+$ 302.1518.

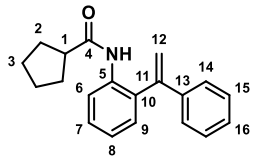
Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (1H, d, *J* = 8.0 Hz, C**5**-H), 5.88 (1H, s, C**11**-H_2), 5.33 (1H, s, C**11**-H_2).

***N*-(2-(1-Phenylvinyl)phenyl)cyclobutanecarboxamide (104na')**



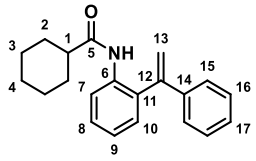
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (toluene/Et_2O 0–2%) to afford the title compound (22.9 mg, 57%) as a yellow oil. ν_{max}/cm^{-1}: 3411 (m), 2942 (m), 1680 (s), 1515 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, d, *J* = 7.5 Hz, C**6**-H), 7.41 – 7.35 (1H, m, C**7**-H), 7.34 – 7.31 (5H, m, C**14**-H, C**15**-H, C**16**-H), 7.30 – 7.24 (1H, m, C**9**-H), 7.14 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz, C**8**-H), 6.90 (1H, s, N-H), 5.87 (1H, d, *J* = 1.5 Hz, C**12**-H_2), 5.37 (1H, d, *J* = 1.5 Hz, C**12**-H_2), 2.79 (1H, app. p, *J* = 8.5 Hz, C**1**-H), 2.04 – 1.59 (6H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0 (C**4**), 146.4 (C**11**), 139.3 (C**13**), 135.4 (C**5**), 131.6 (C**10**), 130.5 (C**9**), 129.0 (C**15**), 129.0 (C**7**), 128.7 (C**16**), 126.6 (C**14**), 124.1 (C**8**), 121.3 (C**6**), 117.5 (C**12**), 40.8 (C**1**), 25.1 (C**2**), 17.9 (C**3**); HRMS: (ESI$^+$) calculated for $C_{19}H_{20}NO$ 278.1539. Found $[M+H]^+$ 278.1545.

***N*-(2-(1-Phenylvinyl)phenyl)cyclopentanecarboxamide (104oa')**



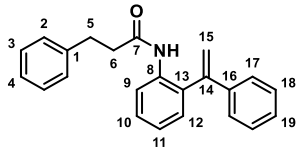
General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 0–5%) to afford the title compound (33.0 mg, 79%) as a yellow oil. ν_{max}/cm^{-1}: 3415 (m), 2952 (m), 1681 (s), 1514 (s), 1443 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, d, *J* = 7.5 Hz, C**6**-H), 7.42 – 7.28 (6H, m, C**7**-H, C**14**-H, C**15**-H, C**16**-H), 7.26 (1H, d, *J* = 7.5 Hz, C**9**-H), 7.13 (1H, dd, *J* = 7.5, 7.5 Hz, C**8**-H), 7.02 (1H, br s, N-H), 5.89 (1H, s, C**12**-H$_2$), 5.37 (1H, s, C**12**-H$_2$), 2.37 – 2.19 (1H, m, C**1**-H), 1.69 – 1.34 (8H, m, C**2**-H$_2$, C**3**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1 (C**4**), 146.5 (C**11**), 139.3 (C**13**), 135.6 (C**5**), 131.5 (C**10**), 130.4 (C**9**), 129.0 (ArCH), 128.9 (ArCH), 128.7 (ArCH), 126.6 (ArCH), 124.0 (C**8**), 121.4 (C**6**), 117.4 (C**12**), 47.0 (C**1**), 30.0 (cyclopentyl), 25.9 (cyclopentyl); HRMS: (ESI$^+$) calculated for $C_{20}H_{22}NO$ 292.1696. Found $[M+H]^+$ 292.1685.

***N*-(2-(1-Phenylvinyl)phenyl)cyclohexanecarboxamide (104pa')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 0–10%) to afford the title compound (31.2 mg, 71%) as a yellow powder. ν_{max}/cm^{-1}: 3418 (m), 2926 (m), 1679 (s), 1515 (s), 1279 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.41 – 7.36 (1H, m, C**8**-H), 7.34 – 7.30 (5H, m, C**15**-H, C**16**-H, C**17**-H), 7.29 – 7.25 (1H, m, C**10**-H), 7.14 (1H, ddd, *J* = 8.0, 8.0, 1.0 Hz, C**9**-H), 7.03 (1H, br. s, N-H), 5.89 (1H, d, *J* = 1.0 Hz, C**13**-H$_2$), 5.38 (1H, d, *J* = 1.0 Hz, C**13**-H$_2$), 1.94 – 1.78 (1H, m, C**1**-H), 1.74 – 1.62 (2H, m, cy), 1.63 – 1.49 (3H, m, cy), 1.22 – 1.01 (5H, m, cy); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0 (C**5**), 146.6 (C**12**), 139.3 (C**14**), 135.5 (C**6**), 131.6 (C**11**), 130.5 (ArCH), 129.0 (ArCH), 128.9 (ArCH), 128.7 (ArCH), 126.7 (C**9**), 124.1 (C**7**), 117.6 (C**13**), 46.6 (C**1**), 29.3 (Cy), 25.7 (Cy), 25.7 (Cy); HRMS: (ESI$^+$) calculated for $C_{21}H_{23}NONa$ 328.1672. Found $[M+Na]^+$ 328.1671; m.p. 57–59 °C ($CDCl_3$).

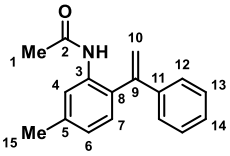
3-Phenyl-*N*-(2-(1-phenylvinyl)phenyl)propanamide (104qa')



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified

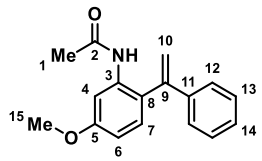
by FCC (hexane/EtOAc 0–10%) to afford the title compound (33.9 mg, 74%) as a yellow oil. ν_{max}/cm^{-1}: 3416 (m), 3026 (m), 2923 (s) 1669 (s), 1516 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (1H, d, *J* = 8.0 Hz, C**9**-H), 7.41 – 7.36 (1H, m, C**10**-H), 7.35 – 7.23 (8H, m, C**3**-H, C**12**-H, C**17**-H, C**18**-H, C**19**-H), 7.22 – 7.14 (2H, m, C**11**-H, C**4**-H), 7.12 – 7.08 (2H, m, C**2**-H), 6.95 (1H, s, N-H), 5.83 (1H, s, C**15**-H_2), 5.30 (1H, s, C**15**-H_2), 2.78 – 2.71 (2H, m, C**5**-H_2), 2.32 – 2.23 (2H, m, C**6**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1 (C**7**), 146.3 (C**14**), 140.6 (C**1**), 139.4 (C**16**), 135.2 (C**8**), 131.9 (C**13**), 130.4 (C**12**), 129.0 (ArCH), 128.9 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.3 (C**2**), 126.6 (ArCH), 126.3 (C**4**), 124.4 (C**11**), 121.8 (C**9**), 117.5 (C**15**), 39.4 (C**6**), 31.4 (C**5**); HRMS: (ESI$^+$) calculated for $C_{23}H_{22}NO$ 328.1696. Found $[M+H]^+$ 328.1696.

***N*-(5-Methyl-2-(1-phenylvinyl)phenyl)acetamide (104ca')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. Purification of the residue by FCC (toluene/EtOAc 10–30%) afforded the title compound (27.5 mg, 77%) as a colourless solid. ν_{max}/cm^{-1}: 2253 (m), 1686 (m), 1381 (m), 904 (m); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (1H, s, C**4**-H), 7.40 – 7.25 (5H, m, C**12**-H, C**13**-H, **14**-H), 7.15 (1H, d, *J* = 8.0 Hz, C**7**-H), 6.97 (1H, d, *J* = 8.0 Hz, C**6**-H), 6.90 (1H, s, N-H), 5.83 (1H, s, C**10**-H_2), 5.35 (1H, s, C**10**-H_2), 2.39 (3H, s, C**15**-H_3), 1.77 (3H, s, C**1**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.4 (C**2**), 146.8 (C**11**), 140.0 (C**9**), 139.2 (C**8**), 135.3 (C**5**), 130.5 (C**7**), 129.5 (C**3**), 129.2 (ArCH), 128.8 (ArCH), 126.9 (ArCH), 125.5 (C**6**), 122.8 (C**4**), 117.5 (C**10**), 24.7 (C**1**), 21.9 (C**15**); HRMS: (ESI$^+$) calculated for $C_{17}H_{18}NO$: 252.1383. Found $[M+H]^+$; 252.1383; m.p. 98–100 °C ($CDCl_3$).

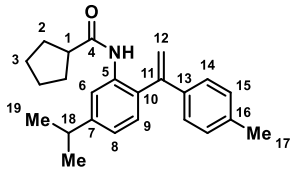
***N*-(5-Methoxy-2-(1-phenylvinyl)phenyl)acetamide (104ba')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 10–30%) to afford the title compound (24.9 mg, 65%, 0.97:0.03 mixture of rotamers *A:B*) as a brown oil. ν_{max}/cm^{-1}: 3280 (m), 2936 (m), 1676 (s), 1524 (s), 1239 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (1H, d, *J* = 2.5 Hz, C**4**-H), 7.38 – 7.28 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.16 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.01 (1H, br. s, N-H), 6.70 (1H, dd, *J* = 8.5, 2.5 Hz, C**6**-H), 5.81 (1H, d, *J* = 1.5 Hz, C**10**-H_2), 5.34 (1H, d, *J* = 1.5 Hz, C**10**-H_2), 3.84 (3H, s, C**15**-H_3), 1.79

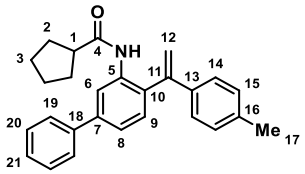
(3H, s, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2 (C**2**), 160.0 (C**5**), 146.2 (C**9**), 139.9 (C**11**), 136.4 (C**3**), 131.1 (C**7**), 128.9 (ArCH), 128.6 (C**14**), 126.8 (ArCH), 123.9 (C**8**), 117.2 (C**10**), 110.5 (C**6**), 106.6 (C**4**), 55.6 (C**15**), 24.5 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{17}NO_2Na$: 290.1151. Found $[M+Na]^+$ 290.1146.

***N*-(5-Isopropyl-2-(1-(*p*-tolyl)vinyl)phenyl)cyclopentanecarboxamide (104we')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/Et_2O 0–10%) to afford the title compound (38.6 mg, 78%) as a yellow oil. ν_{max}/cm^{-1}: 3414 (m), 2958 (m), 1683 (s), 1523 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (1H, s, C**6**-H), 7.23 (2H, d, *J* = 8.0 Hz, C**14**-H), 7.19 – 7.11 (3H, m, C**9**-H, C**15**-H), 7.07 (1H, s, N-H), 6.99 (1H, dd, *J* = 7.5, 2.0 Hz, C**8**-H), 5.81 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 5.30 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 2.95 (1H, hept, *J* = 7.0 Hz, C**18**-H), 2.35 (3H, s, C**17**-H$_3$), 2.34 – 2.23 (1H, m, C**1**-H), 1.67 – 1.42 (8H, m, C**3**-H$_2$, C**2**-H$_2$), 1.30 (6H, d, *J* = 7.0 Hz, C**19**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 149.8 (C**7**), 146.4 (C**11**), 138.6 (C**16**), 136.7 (C**13**), 135.5 (C**5**), 130.2 (C**9**), 129.6 (C**15**), 129.1 (C**10**), 126.7 (C**14**), 121.9 (C**8**), 119.4 (C**6**), 116.3 (C**12**), 47.0 (C**1**), 34.3 (C**18**), 30.0 (cyclopentyl), 25.9 (cyclopentyl), 24.0 (C**19**), 21.3 (C**17**); HRMS: (ESI$^+$) calculated for $C_{24}H_{30}NO$ 348.2322. Found $[M+H]^+$ 348.2332.

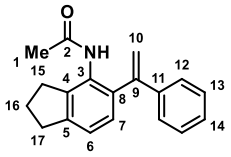
***N*-(4-(1-(*p*-Tolyl)vinyl)-[1,1'-biphenyl]-3-yl)cyclopentanecarboxamide (104xe')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/Et_2O 0–10%) to afford the title compound (38.3 mg, 70%) as a yellow oil. ν_{max}/cm^{-1}: 3412 (m), 2952 (m), 1683 (s), 1525 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (1H, d, *J* = 2.0 Hz, C**6**-H), 7.73 – 7.66 (2H, m, C**19**-H), 7.47 – 7.41 (2H, m, C**20**-H), 7.41 – 7.32 (3H, m, C**8**-H, C**9**-H, C**21**-H), 7.28 (2H, d, *J* = 8.0 Hz, C**14**-H), 7.17 (2H, d, *J* = 8.0 Hz, C**15**-H), 7.13 (1H, s, N-H), 5.87 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 5.37 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 2.37 (3H, s, C**17**-H$_3$), 2.38 – 2.25 (1H, m, C**1**-H), 1.69 – 1.46 (8H, m, C**3**-H$_2$, C**2**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3 (C**4**), 146.1 (C**11**), 141.7 (C**7**), 140.6 (C**18**), 138.8 (C**16**), 136.5 (C**13**), 136.0 (C**5**), 130.8 (C**10**), 130.5 (C**8**), 129.7 (C**15**), 128.8 (C**20**), 127.6 (C**21**), 127.3 (C**19**), 126.7 (C**14**), 122.5 (C**9**), 119.9 (C**6**), 116.6 (C**12**), 47.0 (C**1**), 30.1

(cyclopentyl), 25.9 (cyclopentyl), 21.3 (C**17**); HRMS: (ESI$^+$) calculated for $C_{27}H_{28}NO$ 382.2165. Found $[M+H]^+$ 382.2183.

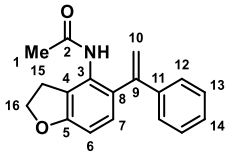
***N*-(5-(1-Phenylvinyl)-2,3-dihydro-1*H*-inden-4-yl)acetamide (104ja')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (1st column: hexane/EtOAc 10–40%; 2nd column: hexane/EtOAc 40%) to afford the title compound (33.1 mg, 83%, 0.92:0.08 mixture of rotamers *A:B*) as an off-white solid. ν_{max}/cm^{-1}: 3255 (m), 2952 (m), 1660 (s), 1524 (s), 1289 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.27 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.20 – 7.14 (2H, m, C**6**-H, C**7**-H), 6.51 (1H, br. s, N-H), 5.70 (1H, d, *J* = 1.5 Hz, C**10**-H$_2$), 5.31 (1H, d, *J* = 1.5 Hz, C**10**-H$_2$), 3.03 – 2.95 (2H, m, C**17**-H$_2$), 2.85 – 2.77 (2H, m, C**15**-H$_2$), 2.14 – 2.01 (2H, m, C**16**-H$_2$), 1.63 (3H, s, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (C**2**), 147.7 (C**9**), 146.1 (C**5**), 142.2 (C**4**), 140.7 (C**11**), 135.0 (C**8**), 130.6 (C**3**), 128.8 (C**6**), 128.8 (ArCH), 128.1 (ArCH), 126.5 (ArCH), 122.9 (C**7**), 116.5 (C**10**), 33.4 (C**17**), 32.0 (C**15**), 25.4 (C**16**), 22.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{19}NONa$ 300.1359. Found $[M+Na]^+$ 300.1356; m.p. 106–108 °C ($CDCl_3$).

Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (1H, s, N-H), 5.66 (1H, s, C**10**-H$_2$), 5.26 (1H, s, C**10**-H$_2$).

***N*-(5-(1-Phenylvinyl)-2,3-dihydrobenzofuran-4-yl)acetamide (104da')**

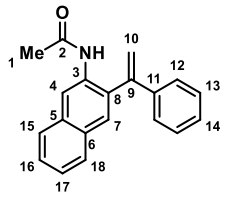


General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 30–50%) to afford the title compound (27.2 mg, 68%, 0.98:0.02 mixture of rotamers *A:B*) as an off-white solid. ν_{max}/cm^{-1}: 3259 (m), 2927 (m), 1746 (s), 1666 (s), 1462 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.13 (1H, d, *J* = 8.0 Hz, C**7**-H), 6.72 (1H, d, *J* = 8.0 Hz, C**6**-H), 6.52 (1H, s, N-H), 5.67 (1H, d, *J* = 1.5 Hz, C**10**-H$_2$), 5.29 (1H, d, *J* = 1.5 Hz, C**10**-H$_2$), 4.61 (2H, t, *J* = 8.5 Hz, C**16**-H$_2$), 3.15 (2H, t, *J* = 8.5 Hz, C**15**-H$_2$), 1.60 (3H, s, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (C**2**), 161.3 (C**5**), 147.2 (C**9**), 140.7 (C**11**), 131.4 (C**3**), 130.4 (C**7**), 128.9 (ArCH), 128.6 (C**8**), 128.2 (C**14**), 126.5 (ArCH), 124.8 (C**4**),

116.6 (C**10**), 107.3 (C**6**), 71.9 (C**16**), 29.8 (C**15**), 23.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{18}H_{17}NO_2Na$ 302.1151. Found $[M+Na]^+$ 302.1148; m.p. 143−145 °C ($CDCl_3$).

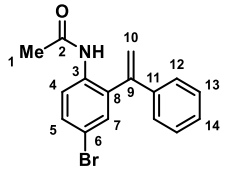
Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): 6.66 (1H, d, *J* = 8.0 Hz, C**6**-H), 5.63 (1H, s, C**10**-H_2), 5.24 (1H, s, C**10**-H_2).

***N*-(3-(1-Phenylvinyl)naphthalen-2-yl)acetamide (104fa')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (1st column: hexane/EtOAc 30–50%; 2nd column: hexane/EtOAc 10–30%) to afford the title compound (29.6 mg, 72%) as a brown solid. ν_{max}/cm^{-1}: 3416 (m), 3054 (m), 1673 (s), 1525 (s), 1483 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (1H, s, C**4**-H), 7.87 (1H, d, *J* = 8.0 Hz, C**15**-H), 7.82 – 7.75 (2H, m, C**7**-H, C**18**-H), 7.52 – 7.40 (2H, m, C**16**-H, C**17**-H), 7.39 – 7.31(5H, m, C**12**-H, C**13**-H, C**14**-H), 7.10 (1H, br. s, N-H), 5.96 (1H, s, C**10**-H_2), 5.50 (1H, s, C**10**-H_2), 1.84 (3H, s, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C**2**), 146.3 (C**9**), 139.3 (C**11**), 133.7 (C**5**), 132.9 (C**3**), 131.9 (C**8**), 130.3 (C**6**), 129.4 (ArCH), 129.0 (ArCH), 128.7 (ArCH), 127.8 (C**15**), 127.5 (ArCH), 126.6 (ArCH), 126.5 (C**16**), 125.4 (C**17**), 118.5 (C**4**), 117.8 (C**10**), 24.4 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{17}NONa$ 310.1202. Found $[M+Na]^+$ 310.1213; m.p. 101−103 °C ($CDCl_3$).

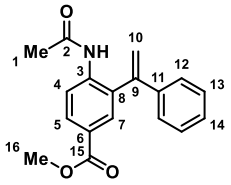
***N*-(4-Bromo-2-(1-phenylvinyl)phenyl)acetamide (104ya')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (10 mol%), **L-20c** (10 mol%). 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 10–30%) to afford the title compound (27.7 mg, 61%) as off-white needles. ν_{max}/cm^{-1}: 3286 (m), 3027 (m), 1670 (s), 1506 (s), 1293 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (1H, d, *J* = 9.0 Hz, C**4**-H), 7.48 (1H, dd, *J* = 9.0, 2.5 Hz, C**5**-H), 7.41 (1H, d, *J* = 2.5 Hz, C**7**-H), 7.39 – 7.28 (5H, m, C**12**-H, C**13**-H, C**14**-H), 6.90 (1H, br. s, N-H), 5.89 (1H, s, C**10**-H_2), 5.38 (1H, s, C**10**-H_2), 1.78 (3H, s, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C**2**), 145.3 (C**9**), 138.7 (C**11**), 134.5 (C**3**), 133.7 (C**8**), 132.9 (C**7**), 131.8 (C**5**), 129.2 (ArCH), 129.0 (C**14**), 126.6 (ArCH), 123.3 (C**4**), 118.2 (C**10**),

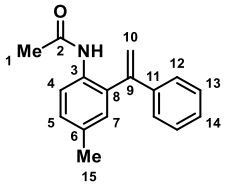
117.1 (C**6**), 24.4 (C**1**); HRMS: (ESI$^+$) calculated for $C_{16}H_{14}{}^{79}BrNONa$ 338.0151. Found $[M+Na]^+$ 338.0156; m.p. 118–120 °C ($CDCl_3$).

Methyl 4-acetamido-3-(1-phenylvinyl)benzoate (104za')



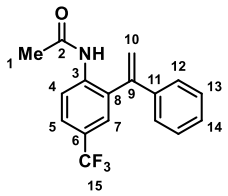
General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (1st column: hexane/EtOAc 30–50%; 2nd column: hexane/EtOAc 40–50%) to afford the title compound (22.2 mg, 58%) as a yellow oil. ν_{max}/cm^{-1}: 3332 (m), 2951 (m), 1710 (s), 1512 (s), 1256 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (1H, d, *J* = 8.5 Hz, C**4**-H), 8.04 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 7.95 (1H, d, *J* = 2.0 Hz, C**7**-H), 7.38 – 7.28 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.17 (1H, s, N-H), 5.94 (1H, d, *J* = 1.0 Hz, C**10**-H$_2$), 5.42 (1H, d, *J* = 1.0 Hz, C**10**-H$_2$), 3.90 (3H, s, C**16**-H$_3$), 1.83 (3H, s, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (C**2**), 166.7 (C**15**), 145.5 (C**9**), 139.6 (C**3**), 138.8 (C**11**), 131.8 (C**7**), 130.9 (C**8**), 130.6 (C**5**), 129.2 (ArCH), 129.0 (C**14**), 126.6 (ArCH), 125.6 (C**6**), 120.4 (C**4**), 118.4 (C**10**), 52.2 (C**16**), 24.6 (C**1**); HRMS: (ESI$^+$) calculated for $C_{18}H_{17}NO_3Na$ 318.1101. Found $[M+Na]^+$ 318.1098.

***N*-(4-Methyl-2-(1-phenylvinyl)phenyl)acetamide (104aaa')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 10–30%) to afford the title compound (25.4 mg, 71%) as a brown oil. ν_{max}/cm^{-1}: 3414 (m), 3024 (m), 1664 (s), 1514 (s), 1498 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.41 – 7.22 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.18 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 7.12 – 7.03 (1H, m, C**7**-H), 6.88 (1H, br. s, N-H), 5.84 (1H, s, C**10**-H$_2$), 5.35 (1H, s, C**10**-H$_2$), 2.34 (3H, s, C**1**-H$_3$), 1.77 (3H, s, C**15**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C**2**), 146.6 (C**9**), 139.6 (C**11**), 134.1 (C**6**), 132.7 (C**3**), 132.2 (C**8**), 130.8 (C**7**), 129.4 (C**5**), 128.9 (ArCH), 128.6 (C**14**), (ArCH), 122.2 (C**4**), 117.1 (C**10**), 24.3 (C**15**), 21.0 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{17}NONa$ 274.1202. Found $[M+Na]^+$ 274.1199.

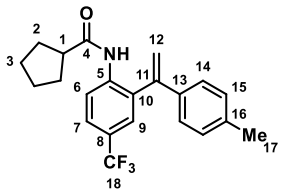
***N*-(2-(1-Phenylvinyl)-4-(trifluoromethyl)phenyl)acetamide (104ga')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 30–50%) to afford the title compound (8.31 mg, 19%) as a brown oil. ν_{max}/cm^{-1}: 3414 (m), 2925 (m), 1683 (s), 1520 (s), 1120 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.62 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 7.53 (1H, d, *J* = 2.0 Hz, C**7**-H), 7.39 – 7.35 (3H, m, C**13**-H, C**14**-H), 7.32 – 7.29 (2H, m, C**12**-H), 7.09 (1H, s, N-H), 5.95 (1H, d, *J* = 1.0 Hz, C**10**-H_2), 5.43 (1H, d, *J* = 1.0 Hz, C**10**-H_2), 1.83 (3H, s, C**1**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.3 (C**2**), 145.3 (C**9**), 138.5 (C**11**), 138.5 (C**3**), 131.5 (C**8**), 129.3 (C**13**), 129.1 (C**14**), 127.3 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C**7**), 126.6 (C**12**), 126.1 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, C**5**), 124.2 (q, $^1J_{C\text{-}F}$ = 270 Hz, C**15**), 121.2 (C**4**), 118.6 (C**10**), 24.6 (C**1**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -61.96; HRMS: (ESI^+) calculated for $C_{17}H_{14}F_3NONa$ 328.0920. Found $[M+Na]^+$ 328.0922.

*Note: C**6** was not observed by ^{13}C NMR analysis.*

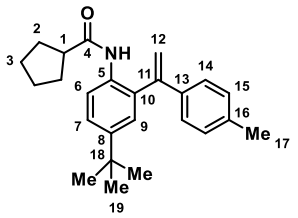
***N*-(2-(1-(*p*-Tolyl)vinyl)-4-(trifluoromethyl)phenyl)cyclopentanecarboxamide (104abe')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (10.0 mol%), **L-20c** (10.0 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (hexane/Et_2O 0–10%) to afford the title compound (21.9 mg, 43%) as a yellow solid. ν_{max}/cm^{-1}: 3413 (m), 2955 (m), 1701 (s), 1519 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (1H, d, *J* = 8.5 Hz, C**6**-H), 7.61 (1H, dd, *J* = 8.5, 2.0 Hz, C**7**-H), 7.51 (1H, d, *J* = 2.0 Hz, C**9**-H), 7.21 – 7.11 (5H, m, C**14**-H, C**15**-H, N-H), 5.91 (1H, d, *J* = 1.0 Hz, C**12**-H_2), 5.36 (1H, d, *J* = 1.0 Hz, C**12**-H_2), 2.36 (3H, s, C**17**-H_3), 2.35 – 2.26 (1H, m, C**1**-H), 1.77 – 1.39 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5 (C**4**), 145.2 (C**11**), 139.3 (C**16**), 138.8 (C**5**), 135.5 (C**13**), 131.4 (C**10**), 129.9 (C**15**), 127.3 (C**9**), 126.5 (C**14**), 126.0 (C**7**), 125.7 (q, *J* = 18.2 Hz, C**8**), 120.7 (C**6**), 117.6 (C**12**), 47.1 (C**1**), 30.0 (cyclopentyl), 25.9 (cyclopentyl), 21.3 (C**17**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -61.9; HRMS: (ESI^+) calculated for $C_{22}H_{23}NOF_3$ 374.1726. Found $[M+H]^+$ 374.1734. m.p. 34–36 °C ($CDCl_3$).

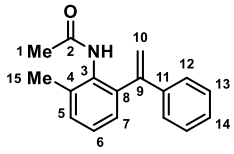
*Note: C**18** was not observed by ^{13}C NMR analysis.*

***N*-(4-(tert-Butyl)-2-(1-(*p*-tolyl)vinyl)phenyl)cyclopentanecarboxamide (104ace')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/Et$_2$O 0–10%) to afford the title compound (48.8 mg, 94%) as a yellow oil. ν_{max}/cm^{-1}: 3311 (m), 2957 (m), 1683 (s), 1511 (s); ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.13 (1H, d, *J* = 8.5 Hz, C**6**-H), 7.38 (1H, dd, *J* = 8.5, 2.5 Hz, C**7**-H), 7.26 – 7.23 (2H, m, C**14**-H), 7.22 (1H, s, C**9**-H), 7.14 (2H, d, *J* = 8.0 Hz, C**15**-H), 6.98 (1H, s, N-H), 5.84 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 5.30 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 2.35 (3H, s, C**17**-H$_3$), 2.33 – 2.24 (1H, m, C**1**-H), 1.73 – 1.40 (8H, m, C**3**-H$_2$, C**2**-H$_2$), 1.32 (9H, s, C**19**-H$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 174.1 (C**4**), 146.9 (C**8**), 146.8 (C**11**), 138.6 (C**16**), 136.5 (C**13**), 133.0 (C**5**), 131.4 (C**10**), 129.6 (C**15**), 127.2 (C**9**), 127.2 (C**14**), 125.7 (C**7**), 121.1 (C**6**), 116.2 (C**12**), 46.9 (C**1**), 34.5 (C**18**), 31.5 (C**19**), 30.1 (cyclopentyl), 25.9 (cyclopentyl), 21.3 (C**17**); HRMS: (ESI$^+$) calculated for $C_{25}H_{32}NO$ 362.2478. Found $[M+H]^+$ 362.2482.

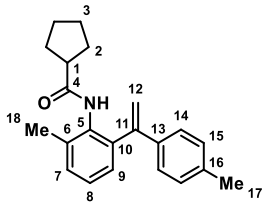
***N*-(5-Methyl-2-(1-phenylvinyl)phenyl)acetamide (104ea')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. Purification of the residue by FCC (1st column: hexane/EtOAc 10–40%; 2nd column: hexane/Et$_2$O 60–70%) afforded the title compound (20.0 mg, 56%, 0.86:0.14 mixture of rotamers *A:B*) as an off-white solid. ν_{max}/cm^{-1}: 3250 (m), 3023 (m), 1659 (s), 1521 (s), 1444 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36 – 7.27 (6H, m, ArCH), 7.25 – 7.20 (2H, m, ArCH), 6.41 (1H br. s, N-H), 5.73 (1H, d, *J* = 1.5 Hz, C**10**-H$_2$), 5.32 (d, *J* = 1.5 Hz, C**10**-H$_2$), 2.25 (3H, s, C**1**-H$_3$), 1.67 (3H, s, C**15**-H$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 168.4 (C**2**), 147.9 (C**9**), 140.5 (C**8**), 138.9 (C**11**), 136.7 (C**4**), 133.2 (C**3**), 130.8 (C**5**), 128.8 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.4 (ArCH), 126.5 (ArCH), 116.6 (C**10**), 22.9 (C**1**), 18.7 (C**15**); HRMS: (ESI$^+$) calculated for $C_{17}H_{17}NONa$ 274.1202. Found $[M+Na]^+$ 274.1207; m.p. 108–110 °C (CDCl$_3$).

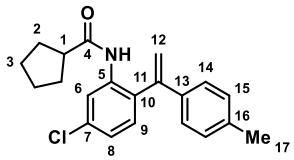
Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.26 (1H, s, N-H), 5.69 (1H, d, *J* = 1.0 Hz, C**10**-H$_2$), 5.28 (1H, d, *J* = 1.0 Hz, C**10**-H$_2$).

***N*-(2-Methyl-6-(1-(*p*-tolyl)vinyl)phenyl)cyclopentanecarboxamide (104ade')**



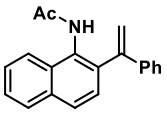
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (10 mol%), **L-20c** (10 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (hexane/EtOAC 0–10%) to afford the title compound (22.9 mg, 50%) as a yellow oil. ν_{max}/cm^{-1}: 3263 (m), 2953 (m), 1652 (s), 1511 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.20 (1H, m, C**7**-H), 7.20 – 7.12 (4H, m, C**8**-H, C**9**-H, C**14**-H), 7.13 – 7.03 (2H, m, C**15**-H), 6.46 (1H, s, N-H), 5.69 (1H, d, *J* = 1.5 Hz, C**12**-H_2), 5.19 (1H, d, *J* = 1.5 Hz, C**12**-H_2), 2.31 (3H, s, C**17**-H_3), 2.27 – 2.22 (1H, m, C**1**-H), 2.20 (3H, s, C**18**-H_3), 1.68 – 1.35 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0 (C**4**), 147.5 (C**11**), 138.8 (C**10**), 138.0 (C**16**), 137.2 (C**13**), 136.4 (C**6**), 133.3 (C**5**), 130.6 (C**7**), 129.4 (C**15**), 128.2 (C**9**), 127.0 (C**8**), 126.3 (C**14**), 115.3 (C**12**), 45.9 (C**1**), 30.2 (cyclopentyl), 25.9 (cyclopentyl), 21.3 (C**17**), 18.8 (C**18**); HRMS: (ESI^+) calculated for $C_{22}H_{26}NO$ 320.2009. Found $[M+H]^+$ 320.2010.

***N*-(5-Chloro-2-(1-(*p*-tolyl)vinyl)phenyl)cyclopentanecarboxamide (104aee')**



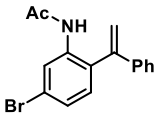
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (10 mol%), **L-20c** (10 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (hexane/Et_2O 0–10%) to afford the title compound (15.8 mg, 36%) as a yellow wax. ν_{max}/cm^{-1}: 3411 (m), 2953 (m), 1693 (s), 1571 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (1H, d, *J* = 2.0 Hz, C**6**-H), 7.22 – 7.17 (2H, m, C**14**-H), 7.16 – 7.13 (3H, m, C**9**-H, C**15**-H), 7.09 (1H, dd, *J* = 8.0, 2.0 Hz, C**8**-H), 7.06 (1H, s, N-H), 5.85 (1H, d, *J* = 1.0 Hz, C**12**-H_2), 5.30 (1H, d, *J* = 1.0 Hz, C**12**-H_2), 2.35 (3H, s, C**17**-H_3), 2.33 – 2.25 (1H, m, C**1**-H), 1.68 – 1.44 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3 (C**4**), 145.4 (C**11**), 139.0 (C**16**), 136.6 (C**5**), 136.0 (C**13**), 134.5 (C**7**), 131.2 (C**9**), 129.8 (C**15**), 129.7 (C**10**), 126.6 (C**14**), 123.9 (C**8**), 120.9 (C**6**), 117.0 (C**12**), 47.0 (C**1**), 30.0 (cyclopentyl), 25.9 (cyclopentyl), 21.3 (C**17**); HRMS: (ESI^+) calculated for $C_{21}H_{23}NOCl$ 340.1463. Found $[M+H]^+$ 340.1464.

***N*-(2-(1-Phenylvinyl)naphthalen-1-yl)acetamide (104afa')**



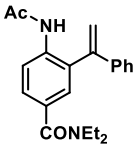
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^1H NMR analysis of the crude material. *Characteristic ^1H NMR peaks:* ^1H NMR (400 MHz, $CDCl_3$): δ 6.72 (1H, br. s), 5.82 (1H, d, *J* = 1.0 Hz), 5.39 (1H, d, *J* = 1.0 Hz).

***N*-(5-Bromo-2-(1-phenylvinyl)phenyl)acetamide (104ia')**



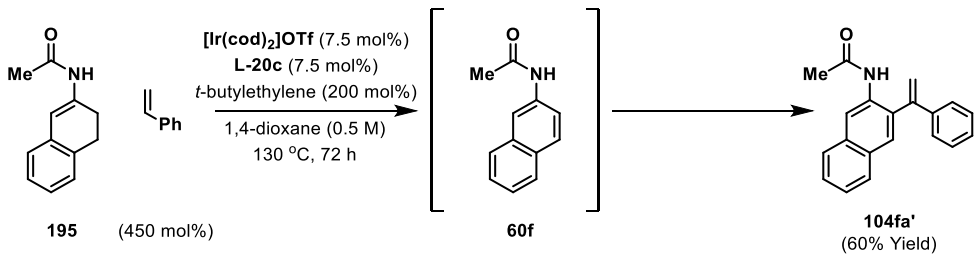
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^1H NMR analysis of the crude material. *Characteristic ^1H NMR peaks:* ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (1H, s), 5.87 (1H, s), 5.36 (1H, s), 1.78 (3H, s).

4-Acetamido-*N*,*N*-diethyl-3-(1-phenylvinyl)benzamide (104aga')



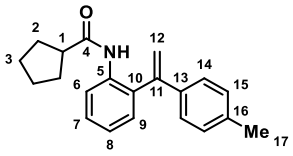
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^1H NMR analysis of the crude material. *Characteristic ^1H NMR peaks:* ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (1H, s), 5.34 (1H, s), 1.78 (1H, s), 0.86 – 0.66 (6H, m).

Tandem dehydrogenation/C–H arylation process depicted in Scheme 86



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (1st column: hexane/EtOAc 30–50%; 2nd column: hexane/EtOAc 10–30%) to afford the title compound (24.6 mg, 60%) as a brown solid. Data for **104fa'** is the same as described previously.

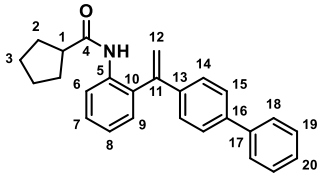
***N*-(2-(1-(*p*-Tolyl)vinyl)phenyl)cyclopentanecarboxamide (104oe')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 0–5%) to afford the title compound (33.5 mg, 77%, 0.93:0.07 mixture of rotamers *A:B*) as an orange oil. ν_{max}/cm^{-1}: 3418 (m), 2953 (m), 1682 (s) 1512 (s), 1445 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.52 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, C**7**-H), 7.45 – 7.34 (3H, m, C**9**-H, C**14**-H), 7.32 – 7.24 (3H, m, C**8**-H, C**15**-H), 7.22 (1H, s, N-H), 6.01 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 5.46 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 2.50 (3H, s, C**17**-H$_3$), 2.49 – 2.41 (1H, m, C**1**-H), 1.84 – 1.56 (8H, m, C**2**-H$_2$, C**3**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 146.3 (C**11**), 138.7 (C**16**), 136.4 (C**13**), 135.6 (C**5**), 131.7 (C**10**), 130.4 (C**9**), 129.6 (C**15**), 128.8 (C**7**), 126.6(C**14**), 123.9 (C**8**), 121.2 (C**6**), 116.4 (C**12**), 47.0 (C**1**), 30.1 (C**2**), 25.9 (C**3**), 21.3 (C**17**); HRMS: (ESI$^+$) calculated for $C_{21}H_{24}NO$ 306.1852. Found $[M+H]^+$ 306.1861.

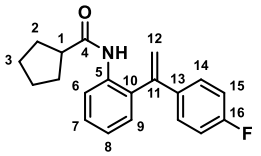
Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (1H, d, *J* = 8.5 Hz, C**6**-H), 5.97 (1H, s, C**12**-H$_2$), 5.42 (1H, s, C**12**-H$_2$).

***N*-(2-(1-([1,1'-Biphenyl]-4-yl)vinyl)phenyl)cyclopentanecarboxamide (104ok')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (1st column: hexane/EtOAc 0–5%; 2nd column: hexane/EtOAc 5%) to afford the title compound (32.5 mg, 62%) as an off-white powder. ν_{max}/cm^{-1}: 3415 (m), 3029 (m), 2953 (m), 1684 (s), 1515 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (1H, d, *J* = 8.5 Hz, C**6**-H), 7.65 – 7.54 (4H, m, ArCH), 7.52 – 7.34 (6H, m, ArCH), 7.30 (1H, dd, *J* = 7.5, 1.5 Hz, C**9**-H), 7.16 (1H, dd, *J* = 7.5, 7.5 Hz, C**8**-H), 7.07 (1H, br. s, N-H), 5.96 (1H, s, C**12**-H$_2$), 5.40 (1H, s, C**12**-H$_2$), 2.34 (1H, app. p, *J* = 7.5 Hz, C**1**-H), 1.68 – 1.36 (8H, m, C**2**-H$_2$, C**3**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 146.1 (C**11**), 141.6 (ArCH), 140.5 (ArCH), 138.1 (C**13**), 135.6 (C**5**), 131.5 (C**10**), 130.5 (C**9**), 129.0 (ArCH), 129.0 (ArCH), 127.7 (ArCH), 127.7 (ArCH), 127.1 (ArCH), 127.1 (ArCH), 124.1 (C**8**), 121.5 (C**6**), 117.3 (C**12**), 47.0 (C**1**), 30.1 (C**2**), 25.9 (C**3**); HRMS: (ESI$^+$) calculated for $C_{26}H_{25}NONa$ 390.1828. Found $[M+Na]^+$ 390.1829; m.p. 100−102 °C ($CDCl_3$).

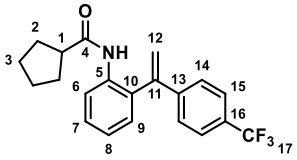
***N*-(2-(1-(4-Fluorophenyl)vinyl)phenyl)cyclopentanecarboxamide (104on')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 0–10%) to afford the title compound (33.2 mg, 75%, 0.96:0.04 mixture of rotamers *A:B*) as a yellow oil. ν_{max}/cm^{-1}: 3062 (m), 2953 (m), 1666 (s), 1506 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.37 (1H, ddd, *J* = 8.0, 8.0, 2.0 Hz, C**7**-H), 7.33 – 7.27 (2H, m, C**14**-H), 7.25 – 7.21 (1H, m, C**9**-H), 7.18 – 7.09 (1H, m, C**8**-H), 7.06 – 6.97 (3H, m, C**15**-H, N-H), 5.85 (1H, s, C**12**-H_2), 5.34 (1H, s, C**12**-H_2), 2.42 – 2.26 (1H, m, C**1**-H), 1.70 – 1.37 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 163.0 (d, $^1J_{C\text{-}F}$ = 248.5 Hz, C**16**), 145.4 (C**11**), 135.5 (C**5**),135.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz, C**13**), 131.4 (C**10**), 130.3 (C**9**), 129.0 (C**7**), 128.4 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, C**14**), 124.1 (C**8**), 121.6 (C**6**), 117.0 (C**12**), 115.8 (d, $^2J_{C\text{-}F}$ = 21.5 Hz, C**15**), 46.97 (C**1**), 30.10 (C**2**), 25.90 (C**3**); HRMS: (ESI^+) calculated for $C_{20}H_{21}FNO$ 310.1602. Found $[M+H]^+$ 310.1606.

Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): 8.12 (1H, d, *J* = 8.5 Hz, C**6**-H), 5.81 (1H, s, C**12**-H_2), 5.29 (1H, s, C**12**-H_2), 1.90 (1H, app. p, *J* = 7.5 Hz, C**1**-H).

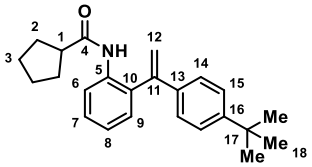
***N*-(2-(1-(4-(Trifluoromethyl)phenyl)vinyl)phenyl)cyclopentanecarboxamide (104oo')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (10 mol%), **L-20c** (10 mol%) and 1,4-dioxane (1.0 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 0–10%) to afford the title compound (29.5 mg, 57%, 0.85:0.15 mixture of rotamers *A:B*) as a yellow oil. ν_{max}/cm^{-1}: 3282 (m), 2956 (m), 1658 (s), 1518 (s), 1322 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (1H, d, *J* = 8.0 Hz, C**6**-H, *A*+*B*), 7.58 (1.7H, d, *J* = 8.0 Hz, C**15**-H, *A*), 7.52 (0.3H, d, *J* = 8.0 Hz, C**15**-H, *B*), 7.43 (1.7H, d, *J* = 8.0 Hz, C**14**-H, *A*+*B*), 7.40 – 7.37 (0.85H, m, C**7**-H, *A*), 7.31 (0.15H, dd, *J* = 7.5, 7.5 Hz, C**7**-H, *B*), 7.24 (1H, m, C**9**-H, *A*+*B*), 7.16 (0.85H, dd, *J* = 7.5, 7.5 Hz, C**8**-H, *A*), 7.08 (0.15H, dd, *J* = 7.5, 7.5 Hz, C**8**-H, *B*), 6.91 (1H, s, N-H, *A*+*B*), 5.99 (1H, s, C**12**-H_2, *A*+*B*), 5.50 (1H, s, C**12**-H_2, *A*+*B*), 2.68 (0.15H, app. p, *J* = 8.0 Hz, C**1**-H, *B*), 2.31 (0.85H, app. p, *J* = 8.0 Hz, C**1**-H, *A*), 1.98 – 1.85 (0.85H, m, cyclopentyl, *A*), 1.84 – 1.75 (0.15H m, cyclopentyl, *B*), 1.68 – 1.42 (5.95H, m, cyclopentyl, *A*), 1.29 – 1.23 (1.05H, m, cyclopentyl, *B*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0 (C**4**, *A*), 173.9 (C**4**, *B*), 145.3 (C**11**, *A*), 145.27 (C**11**, *B*), 144.11 (C**13**, *B*), 142.68 (C**13**,

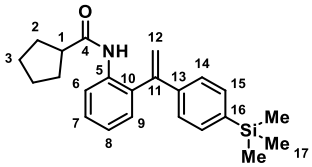
A), 135.22 (C**5**, *A*+*B*), 130.95 (C**10**, *A*+*B*), 130.93 (C**16**, *A*+*B*), 130.58 (C**9**, *B*), 130.30 (C**9**, *A*), 129.14 (C**7**, *A*), 128.93 (C**7**, *B*), 126.75 (C**14**, *A*+*B*), 125.7 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz, C**15**, *A*+*B*), 124.3 (C**8**, *A*+*B*), 122.6 (C**17**, *A*+*B*), 122.0 (C**6**, *A*+*B*), 119.6 (C**12**, *B*), 119.2 (C**12**, *A*), 46.7 (C**1**, *A*+*B*), 30.5 (C**2**, *B*), 29.9 (C**2**, *A*), 26.0 (C**3**, *B*), 25.7 (C**3**, *A*); ^{19}F NMR (377 MHz, $CDCl_3$): δ -62.61; HRMS: (ESI$^+$) calculated for $C_{21}H_{21}F_3NO$ 360.1570. Found $[M+H]^+$ 360.1576.

***N*-(2-(1-(4-(*tert*-Butyl)phenyl)vinyl)phenyl)cyclopentanecarboxamide (104op')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (1.0 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (toluene/Et_2O 0–2%) to afford the title compound (39.6 mg, 80%) as a yellow oil. ν_{max}/cm^{-1}: 3415 (m), 2958 (m), 1686 (s), 1513 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.39 – 7.32 (3H, m, C**15**-H, C**7**-H), 7.29 – 7.24 (3H, m, C**14**-H, C**9**-H), 7.19 – 7.09 (1H, m, C**8**-H), 7.00 (1H, s, N-H), 5.85 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 5.33 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 2.32 – 2.23 (1H, m, C**1**-H), 1.63 – 1.51 (4H, m, C**3**-H$_2$), 1.47 – 1.40 (4H, m, C**2**-H$_2$), 1.31 (9H, s, C**18**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1 (C**4**), 152.0 (C**16**), 146.3 (C**11**), 136.3 (C**13**), 135.6 (C**5**), 131.6 (C**10**), 130.5 (C**9**), 128.9 (C**7**), 126.4 (C**14**), 125.9 (C**15**), 123.9 (C**8**), 121.2 (C**6**), 116.7 (C**12**), 47.0 (C**1**), 34.8 (C**17**), 31.4 (C**18**), 30.0 (C**3**), 25.8 (C**2**); HRMS: (ESI$^+$) calculated for $C_{24}H_{30}NO$ 348.2322. Found $[M+H]^+$ 348.2334.

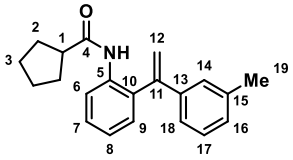
***N*-(2-(1-(4-(Trimethylsilyl)phenyl)vinyl)phenyl)cyclopentanecarboxamide (104oq')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (toluene/Et_2O 0–2%) to afford the title compound (27.4 mg, 53%) as a yellow oil. ν_{max}/cm^{-1}: 3418 (m), 2954 (m), 1682 (s), 1516 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.52 – 7.46 (2H, m, C**15**-H), 7.41 – 7.34 (1H, m, C**7**-H), 7.34 – 7.23 (3H, m, C**9**-H, C**14**-H), 7.14 (1H, ddd, *J* = 7.5, 7.5, 1.0 Hz, C**8**-H), 6.98 (1H, s, N-H), 5.90 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 5.38 (1H, d, *J* = 1.5 Hz, C**12**-H$_2$), 2.33 – 2.20 (1H, m, C**1**-H), 1.60 – 1.42 (8H, m, C**2**-H$_2$, C**3**-H$_2$), 0.26 (9H, s, C**17**-H$_3$); ^{13}C NMR (101 M Hz, $CDCl_3$): δ 174.0 (C**4**), 146.5 (C**11**), 141.2 (C**16**), 139.5 (C**13**), 135.4 (C**5**), 133.9 (C**15**), 131.3 (C**7**), 130.3 (C**9**), 128.8 (C**10**), 125.7 (C**14**), 123.9 (C**8**), 121.3 (C**6**), 117.4 (C**12**), 46.9

(C**1**), 29.8 (C**3**), 25.7 (C**2**), -1.2 (C**17**); HRMS: (ESI$^+$) calculated for $C_{23}H_{30}NOSi$ 364.2091. Found $[M+H]^+$ 364.2091.

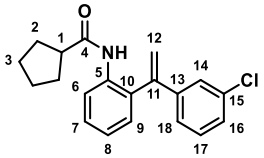
***N*-(2-(1-(*m*-Tolyl)vinyl)phenyl)cyclopentanecarboxamide (104or')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 0–10%) to afford the title compound (30.5 mg, 70%, 0.93:0.07 mixture of rotamers *A:B*) as a yellow oil. ν_{max}/cm^{-1}: 3414 (m), 2953 (m), 1682 (s), 1515 (s), 1446 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.37 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, C**7**-H), 7.29 – 7.18 (2H, m, C**9**-H, ArCH), 7.17 – 7.10 (4H, m, ArCH), 7.05 (1H, br. s, N-H), 5.86 (1H, s, C**12**-H$_2$), 5.35 (1H, s, C**12**-H$_2$), 2.38 – 2.25 (4H, m, C**1**-H, C**19**-H$_3$), 1.69 – 1.42 (8H, m, C**2**-H$_2$, C**3**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 146.7 (C**11**), 139.3 (C**13**), 138.7 (C**15**), 135.6 (C**5**), 131.7 (C**10**), 130.4 (C**9**), 129.5 (ArCH), 128.9 (C**7**), 128.9 (ArCH), 127.3 (ArCH), 124.0 (C**8**), 123.8 (ArCH), 121.3 (C**6**), 117.3 (C**12**), 47.0 (C**1**), 30.0 (C**2**), 25.9 (C**3**), 21.5 (C**19**); HRMS: (ESI$^+$) calculated for $C_{21}H_{24}NO$ 306.1852. Found $[M+H]^+$ 306.1864.

Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): 8.14 (1H, d, *J* = 8.5 Hz, C**6**-H), 5.83 (1H, s, C**12**-H$_2$), 5.31 (1H, s, C**12**-H$_2$).

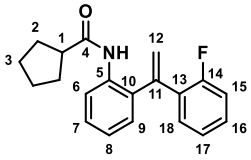
***N*-(2-(1-(3-Chlorophenyl)vinyl)phenyl)cyclopentanecarboxamide (104os')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (10 mol%), **L-20c** (10 mol%) and 1,4-dioxane (1.0 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 0–5%) to afford the title compound (29.8 mg, 64%, 0.95:0.05 mixture of rotamers *A:B*) as a yellow oil. ν_{max}/cm^{-1}: 3290 (m), 3062 (m), 2954 (s), 1663 (s), 1515 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.43 – 7.34 (2H, m, C**7**-H, C**14**-H), 7.32 – 7.26 (1H, m, C**17**-H), 7.26 – 7.20 (2H, m, C**9**-H, C**16**-H), 7.18 – 7.10 (2H, m, C**8**-H, C**18**-H), 6.98 (1H, s, N-H), 5.90 (1H, s, C**12**-H$_2$), 5.42 (1H, s, C**12**-H$_2$), 2.41 – 2.28 (1H, m, C**1**-H), 1.72 – 1.35 (8H, m, C**2**-H$_2$, C**3**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 145.4 (C**11**), 141.3 (C**13**), 135.5 (C**5**), 135.0 (C**15**), 131.0 (C**10**), 130.4 (ArCH), 130.2 (ArCH), 129.2 (ArCH), 128.7 (C**17**), 126.6 (ArCH), 125.0 (ArCH), 124.2 (C**8**), 121.8 (C**6**), 118.5 (C**12**), 47.0 (C**1**), 30.1 (C**2**), 25.9 (C**3**); HRMS: (ESI$^+$) calculated for $C_{20}H_{21}ClNO$ 326.1306. Found $[M+H]^+$ 326.1303.

Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): 8.37 (1H, d, *J* = 8.0 Hz, C**6**-H), 5.43 (1H, s, C**12**-H_2), 1.91 (1H, app. p, *J* = 7.5 Hz, C**1**-H).

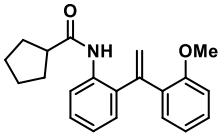
***N*-(2-(1-(2-Fluorophenyl)vinyl)phenyl)cyclopentanecarboxamide (104og')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (10 mol%) and **L-20c** (10 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The crude material was purified by FCC (2 columns; hexane/EtOAc 0–10%) to afford the title compound (22.2 mg, 50%, 0.97:0.03 mixture of rotamers *A:B*) as an orange oil. ν_{max}/cm^{-1}: 3288 (m), 2952 (m) 1665 (s), 1514 (s), 1445 (s); *Signals for rotamer A*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.34 (1H, ddd, *J* = 8.0, 8.0, 1.5 Hz, C**7**-H), 7.31 – 7.26 (1H, m, C**17**-H), 7.25 – 7.17 (2H, m, C**9**-H, N-H), 7.15 – 7.05 (4H, m, C**8**-H, C**15**-H, C**16**-H, C**18**-H), 5.95 (1H, s, C**12**-H_2), 5.61 (1H, s, C**12**-H_2), 2.42 (1H, app. p, *J* = 7.5 Hz, C**1**-H), 1.80 – 1.45 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 160.3 (d, $^{1}J_{C\text{-}F}$ = 249.5 Hz, C**14**), 140.8 (C**11**), 135.2 (C**5**), 132.0 (C**10**), 130.4 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz, C**17**), 129.9 (d, $^{3}J_{C\text{-}F}$ = 3.0 Hz, ArCH), 129.84 (C**9**), 128.3 (C**7**), 127.7 (d, $^{2}J_{C\text{-}F}$ = 12.0 Hz, C**13**), 124.6 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz, ArCH), 124.0 (C**8**), 122.4 (d, ^{4}J = 6.5 Hz, C**12**), 121.6 (C**6**), 116.3 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz, C**15**), 47.0 (C**1**), 30.2 (C**3**), 26.0 (C**2**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -114.17 (–) -114.33 (m); HRMS: (ESI^+) calculated for $C_{20}H_{21}FNO$ 310.1612. Found $[M+H]^+$ 310.1608.

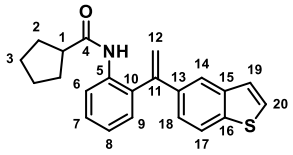
Characteristic signals for rotamer B: ^{1}H NMR (400 MHz, $CDCl_3$): 8.36 (1H, d, *J* = 8.5 Hz, C**6**-H), 5.98 (1H, s, C**12**-H_2), 5.98 (1H, s, C**12**-H_2).

***N*-(2-(1-(2-Methoxyphenyl)vinyl)phenyl)cyclopentanecarboxamide (104ot')**



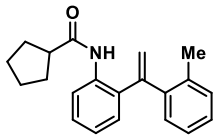
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (1H, d, *J* = 8.0 Hz), 5.76 (1H, s), 5.49 (1H, s).

***N*-(2-(1-(Benzo[*b*]thiophen-5-yl)vinyl)phenyl)cyclopentanecarboxamide (104ou')**



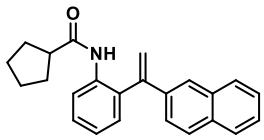
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 76 h. The crude material was purified by FCC (toluene/EtOAc 0–10%) to afford the title compound (25.3 mg, 51%) as a yellow oil. ν_{max}/cm^{-1}: 3311 (m), 2952 (m), 1678 (s), 1513 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.85 (1H, d, *J* = 8.5 Hz, C**17**-H), 7.68 (1H, d, *J* = 1.5 Hz, C**14**-H), 7.48 – 7.43 (1H, m, C**18**-H), 7.44 – 7.36 (2H, m, C**7**-H, C**19**-H), 7.33 – 7.27 (2H, m, C**9**-H, C**20**-H), 7.16 (1H, dd, *J* = 8.0, 1.5 Hz, C**8**-H), 7.09 (1H, s, N-H), 5.96 (1H, d, *J* = 1.0 Hz, C**12**-H_2), 5.41 (1H, d, *J* = 1.0 Hz, C**12**-H_2), 2.25 (1H, p, *J* = 7.5 Hz, C**1**-H), 1.57 – 1.31 (8H, m, C**2**-H_2, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2 (C**4**), 146.5 (C**11**), 140.2 (C**15**), 140.0 (C**16**), 135.7 (C**13**), 135.7 (C**5**), 131.7 (C**10**), 130.5 (C**9**), 129.0 (C**7**), 127.6 (C**18**), 124.2 (C**20**), 124.1 (C**8**), 122.9 (C**17**), 122.7 (C**19**), 122.0 (C**14**), 121.5 (C**6**), 117.2 (C**12**), 47.0 (C**1**), 30.0 (cyclopentyl), 25.8 (cyclopentyl); HRMS: (ESI^+) calculated for $C_{22}H_{21}NOS$ 348.1417. Found $[M+H]^+$ 348.1432.

***N*-(2-(1-(*o*-Tolyl)vinyl)phenyl)cyclopentanecarboxamide (104ov')**



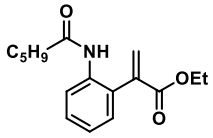
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (1H, d, *J* = 8.0 Hz), 5.58 (1H, d, *J* = 1.5 Hz), 5.54 (1H, d, *J* = 1.5 Hz,).

***N*-(2-(1-(Naphthalen-2-yl)vinyl)phenyl)cyclopentanecarboxamide (104ow')**



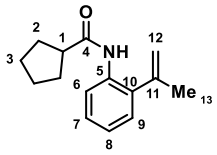
General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (1H, d, *J* = 8.0 Hz), 6.02 (1H, s), 5.44 (1H, s).

Ethyl 2-(2-(cyclopentanecarboxamido)phenyl)acrylate (104ox')



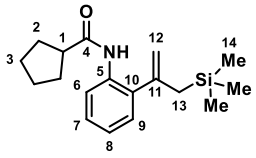
General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (1H, s), 5.88 (1H, s), 5.84 (1H, s).

***N*-(2-(Prop-1-en-2-yl)phenyl)cyclopentanecarboxamide (198)**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (2.60 mg, 11%) as a colourless oil. ν_{max}/cm^{-1}: 3228 (m), 2960 (m), 1644 (s), 1530 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.61 (1H, s, N-H), 7.37 – 7.19 (1H, m, C**7**-H), 7.13 (1H, dd, *J* = 8.0, 1.5 Hz, C**9**-H), 7.10 – 6.95 (1H, m, C**8**-H), 5.40 (1H, s, C**12**-H$_2$), 5.03 (1H, d, *J* = 1.0 Hz, C**12**-H$_2$), 2.74 – 2.59 (1H, m, C**1**-H), 2.07 (3H, s, C**13**-H$_3$), 1.97 – 1.81 (4H, m, C**2**-H$_2$), 1.81 – 1.73 (2H, m, C**3**-H$_2$), 1.68 – 1.59 (2H, m, C**3**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3 (C**4**), 143.3 (C**11**), 134.3 (C**5**), 133.2 (C**10**), 128.1 (C**7**), 127.7 (C**9**), 123.6 (C**8**), 120.8 (C**6**), 116.9 (C**12**), 47.3 (C**1**), 30.5 (C**2**), 26.0 (C**3**), 24.6 (C**13**); HRMS: (ESI$^+$) calculated for $C_{15}H_{19}NO$ 230.1539 Found $[M+H]^+$ 230.1530.

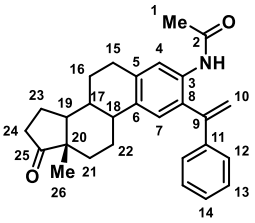
***N*-(2-(3-(Trimethylsilyl)prop-1-en-2-yl)phenyl)cyclopentanecarboxamide (1004oad')**



General Procedure U: The reaction was carried out with Ir(cod)$_2$OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (1.05 mg, 4%) as a colourless oil. ν_{max}/cm^{-1}: 2956 (m), 2926 (m), 2925 (s), 1701 (s), 1279 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (1H, d, *J* = 8.0 Hz, C**6**-H), 7.27 – 7.23 (1H, m, C**9**-H), 7.21 (1H, s, N-H), 7.16 (1H, dd, *J* = 8.0, 1.5 Hz, C**7**-H), 7.08 – 7.01 (1H, m, C**8**-H), 5.22 (1H, d, *J* = 2.0 Hz, C**12**-H$_2$), 4.95 (1H, d, *J* = 2.0 Hz, C**12**-H$_2$), 2.74 – 2.60 (2H, m, C**1**-H), 1.90 (4H, ddd, *J* = 9.0, 7.0, 3.5 Hz, C**2**/**3**-H$_2$), 1.82 – 1.74 (2H, m, C**2**/**3**-H$_2$), 1.64 (2H, ddd, *J* = 14.0, 7.0, 5.5 Hz, C**2**/**3**-H$_2$), 1.34 – 1.26 (2H, m, C**13**-H$_2$), -0.05 (9H, s, C**14**-H$_3$); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 174.2 (C**4**), 145.4 (C**5**), 135.2 (C**11**), 133.5 (C**10**), 128.2 (C**7**), 128.1 (C**9**), 123.4 (C**8**), 120.5 (C**6**), 114.0 (C**12**), 47.5 (C**1**), 29.5 (C**13**), 26.2 (C**2**/**3**), 26.1 (C**2**/**3**), -1.3 (C**14**); HRMS: (ESI^+) calculated for $C_{18}H_{27}NOSi$ 302.1935. Found $[M+H]^+$ 302.1925.

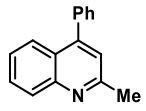
***N*-((13S)-13-Methyl-17-oxo-2-(1-phenylvinyl)-7,8,9,11,12,13,14,15,16,17-decahydro-*6H*-cyclopenta[a]phenanthren-3-yl)acetamide (104aja')**



General Procedure U: The reaction was carried out with $Ir(cod)_2OTf$ (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 72 h. Purification of the residue by FCC (hexane/EtOAc 5–10%) afforded the title compound (23.1 mg, 56%) as an orange oil. ν_{max}/cm^{-1}: 3313 (m), 2929 (m), 1735 (s), 1679 (s), 1514 (s); ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (1H, s, C**4**-H), 7.38 – 7.28 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.18 (1H, s, C**7**-H), 6.84 (1H, s, N-H), 5.81 (1H, s, C**10**-H_2), 5.33 (1H, s, C**10**-H_2), 3.02 – 2.89 (2H, m, C**16**-H_2), 2.51 (1H, dd, *J* = 19.0, 8.5 Hz, C**24**-H_2), 2.42 – 2.25 (2H, m, C**22**-H_2, C**18**-H_2), 2.20 – 2.01 (3H, m, C**15**-H_2, C**23**-H_2, C**24**-H_2), 1.94 (1H, dd, *J* = 12.0, 4.0 Hz, C**21**-H_2), 1.76 (3H, s, C**1**-H_3), 1.70 – 1.58 (3H, m, C**17**-H, C**23**-H_2), 1.56 – 1.41 (6H, m, C**15**-H_2, C**17**-H, C**19**-H, C**21**-H_2, C**22**-H_2, C**23**-H_2), 0.92 (3H, s, C**26**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 221.0 (C**25**), 168.2 (C**2**), 146.8 (C**9**), 139.8 (C**11**), 137.3 (C**5**), 136.1 (C**6**), 132.9 (C**3**), 129.9 (C**8**), 128.9 (ArCH), 128.6 (C**14**), 127.3 (C**7**), 126.7 (ArCH), 122.4 (C**4**), 117.1 (C**10**), 50.6 (C**19**), 48.1 (C**20**), 44.3 (C**18**), 38.3 (C**17**), 36.0 (C**24**), 31.7 (C**21**), 29.6 (C**16**), 26.6 (C**15**), 25.9 (C**22**), 24.3 (C**1**), 21.7 (C**23**), 14.0 (C**26**); HRMS: (ESI^+) calculated for $C_{28}H_{32}NO_2$ 414.2428. Found $[M+H]^+$ 414.2427.

7.7.3 – Product Derivatisations

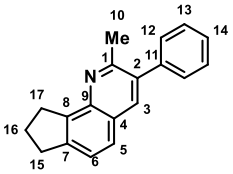
2-Methyl-4-phenylquinoline (199a)



General Procedure V: The residue was purified by FCC (hexane/EtOAc 30%) to afford the title compound (91.6 mg, quantitative) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (1H, d, *J* = 9.0 Hz), 7.86 (1H, dd, *J* = 9.0, 1.5 Hz,), 7.69 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz), 7.55 – 7.47 (5H, m), 7.44 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz), 7.24 (1H, s), 2.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 148.7, 148.5, 138.3, 129.6, 129.5, 129.2, 128.7, 128.5, 125.9, 125.8, 125.2, 122.4, 25.5; m.p. 95–97 °C ($CDCl_3$)

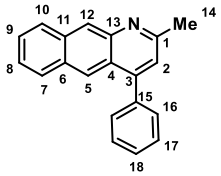
(Lit.[295] 92–94 °C, *recrystallisation solvent not specified*). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[295]

2-Methyl-3-phenyl-8,9-dihydro-*7H*-cyclopenta[*h*]quinoline (199b)



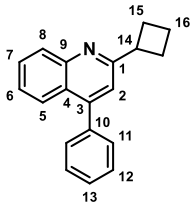
General Procedure V: The crude material was purified by FCC (hexane/EtOAc 30%) to afford the title compound (11.2 mg, 60%) as a colourless oil. ν_{max}/cm^{-1}: 3030 (m), 2573 (s) 1590 (s), 1407 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* = 8.5 Hz, C**5**-H), 7.54 – 7.43 (5H, m, C**12**-H, C**13**-H, C**14**-H), 7.33 (1H, d, *J* = 8.5 Hz, C**6**-H), 7.16 (1H, s, C**3**-H), 3.48 (2H, t, *J* = 7.5 Hz, C**17**-H_2), 3.13 (2H, t, *J* = 7.5 Hz, C**15**-H_2), 2.77 (3H, s, C**10**-H_3), 2.27 (2H, app. p, *J* = 7.5 Hz, C**16**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2 (C**1**), 148.8 (C**2**), 145.8 (C**4**), 145.3 (C**7**), 141.3 (C**8**), 139.0 (C**11**), 129.6 (C**12**/**13**), 128.5 (C**12**/**13**), 128.2 (C**14**), 124.5 (C**5**), 124.0 (C**9**), 123.0 (C**6**), 121.3 (C**3**), 34.3 (C**15**), 31.3 (C**17**), 25.8 (C**10**), 25.1 (C**16**); HRMS: (ESI$^+$) calculated for $C_{19}H_{18}N$ 260.1434. Found $[M+H]^+$ 260.1437.

2-Methyl-4-phenylbenzo[*g*]quinoline (199c)



General Procedure V: The crude material was purified by FCC (hexane/EtOAc 20–30%) to afford the title compound (19.0 mg, 82%) as an orange oil. ν_{max}/cm^{-1}: 3057 (m), 2923 (m) 1596 (m), 1334 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, s, C**12**-H), 8.40 (1H, s, C**5**-H), 8.07 (1H, d, *J* = 8.5 Hz, C**10**-H), 7.89 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.64 – 7.54 (5H, m, C**16**-H, C**17**-H, C**18**-H), 7.54 – 7.38 (2H, m, C**9**-H, C**8**-H), 7.20 (1H, s, C**2**-H), 2.83 (3H, s, C**14**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7 (C**1**), 148.7 (C**13**), 145.0 (C**3**), 138.4 (C**15**), 133.9 (C**11**), 131.5 (C**6**), 129.7 (ArCH), 128.8 (ArCH), 128.6 (C**18**), 128.6 (C**7**), 128.3 (C**10**), 126.6 (C**12**), 126.5 (C**9**), 125.7 (C**8**), 125.3 (C**5**), 124.3 (C**4**), 122.0 (C**2**), 25.9 (C**14**); HRMS: (ESI$^+$) calculated for $C_{20}H_{16}N$ 270.1277. Found $[M+H]^+$ 270.1290.

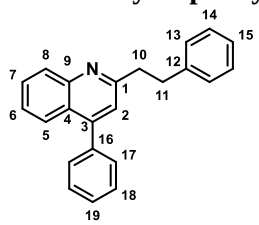
2-Cyclobutyl-4-phenylquinoline (199d)



General Procedure V: The crude material was purified by FCC (EtOAc 100%) to afford the title compound (21.5 mg, 98%) as an orange oil. ν_{max}/cm^{-1}: 3059 (m), 2935 (m) 1591 (m), 1443 (m); ^{1}H

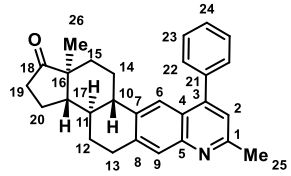
NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 8.5 Hz, C**5**-H), 7.86 (1H, d, *J* = 8.5 Hz, C**8**-H), 7.75 – 7.65 (1H, m, C**6**-H), 7.56 – 7.48 (5H, m, C**11**-H, C**12**-H, C**13**-H), 7.46 – 7.40 (1H, m, C**7**-H), 7.35 – 7.26 (1H, m, C**2**-H), 3.91 (1H, app. p, *J* = 9.0 Hz, C**14**-H), 2.55 – 2.40 (4H, m, C**15**-H_2), 2.21 – 2.07 (1H, m, C**16**-H_2), 2.03 – 1.89 (1H, m, C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7 (C**3**), 148.7 (C**9**), 148.4 (C**1**), 138.6 (C**10**), 129.7 (ArCH), 129.5 (C**5**), 129.3 (C**6**), 128.7 (ArCH), 128.4 (C**13**), 125.9 (C**7**), 125.7 (C**8**), 125.5 (C**4**), 120.0 (C**2**), 42.9 (C**14**), 28.5 (C**15**), 18.5 (C**16**); HRMS: (ESI^+) calculated for $C_{19}H_{18}N$ 260.1434. Found $[M+H]^+$ 260.1437.

2-Phenethyl-4-phenylquinoline (199e)



General Procedure V: The crude material was purified by FCC (hexane/EtOAc 20%) to afford the title compound (22.3 mg, 86%) as a yellow oil; ν_{max}/cm^{-1}: 3059 (m), 2924 (m) 1592 (m), 1490 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (1H, d, *J* = 7.5 Hz, C**8**-H), 7.88 (f1H, dd, *J* = 8.5, 1.5 Hz, C**5**-H), 7.72 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, C**7**-H), 7.56 – 7.42 (6H, m, C6-H, ArCH), 7.34 – 7.24 (4H, m, ArCH), 7.25 – 7.19 (1H m, ArCH), 7.17 (1H, s, C**2**-H), 3.37 – 3.30 (2H, m, C**10**-H_2), 3.24 – 3.16 (2H, m, C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.4 (C**1**), 148.6 (C**9**), 148.6 (C**3**), 141.7 (C**12**), 138.3 (C**16**), 129.6 (ArCH), 129.4 (C**8**), 129.4 (C**7**), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 126.1 (C**6**), 126.0 (C**5**), 125.8 (ArCH), 125.5 (C**4**), 122.0 (C**2**), 41.2 (C**10**), 36.2 (C**11**); HRMS: (ESI+) calculated for $C_{23}H_{20}N$ 310.1590 Found $[M+H]^+$ 310.1604.

(13a*S*)-8,13a-Dimethyl-10-phenyl-2,3,3a,3b,4,5,11b,12,13,13a-decahydro-1*H*-cyclopenta[5,6]naphtho[1,2-*g*]quinolin-1-one (199f)



General Procedure V: The crude material was purified by FCC (EtOAc/MeOH 0–20%) to afford the title compound (13.6 mg, 61%) as a colourless solid. ν_{max}/cm^{-1}: 2928 (m), 2859 (m), 1738 (s), 1591 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (1H, s, C**9**-H), 7.76 (1H, s, C**6**-H), 7.60 – 7.44 (5H, m, C**22**-H, C**23**-H, C**24**-H), 7.14 (1H, s, C**2**-H), 3.23 – 3.06 (2H, m, C**13**-H_2), 2.74 (3H, s, C**25**-H_3), 2.51 (1H, dd, *J* = 18.0, 8.5 Hz, C**20**-H_2), 2.43 – 2.33 (1H, m, C**10**-H), 2.33 – 2.22 (1H, m, C**14**-H_2), 2.21 – 2.02 (3H, m, C**12**-H_2, C**19**-H_2, C**20**-H_2), 1.92 (1H, ddd, *J* = 13.0, 13.0, 3.0 Hz, C**15**-H_2), 1.73 – 1.38 (5H, m, C**11**-H, C**12**-H_2, C**14**-H_2, C**15**-H_2, C**17**-H), 0.90 (3H, s, C**26**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 220.7 (C**18**), 158.0 (C**1**), 148.2 (C**3**), 146.9 (C**5**), 139.3 (C**8**), 138.9 (C**7**), 138.4 (C**21**), 129.4 (ArCH), 128.6 (ArCH), 128.3 (C**24**), 127.6 (C**9**), 123.3 (C**4**), 121.6 (C**2**), 121.3 (C**6**), 50.8 (C**17**), 47.9 (C**16**), 44.6

(C**10**), 38.1 (C**11**), 35.9 (C**20**), 31.4 (C**15**), 29.5 (C**13**), 26.5 (C**12**), 25.6 (C**14**), 25.2 (C**25**), 21.7 (C**19**), 13.8 (C**26**); HRMS: (ESI$^+$) calculated for $C_{28}H_{30}NO$ 396.2322. Found. $[M+H]^+$ 396.2317. m.p. 293–295 °C (hexane/EtOAc); $[\alpha]^{20}_D$ = + 134.7 (c = 0.20, CH_2Cl_2).

*The structure of compound **199f** was confirmed by single crystal X-ray diffraction of crystals obtained from* hexane/EtOAc *(Figure **10**).*

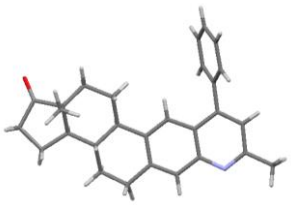
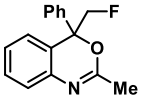


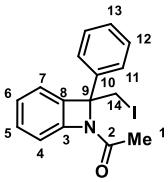
Figure 10

4-(Fluoromethyl)-2-methyl-4-phenyl-4*H*-benzo[*d*][1,3]oxazine (200)



The title compound was prepared following a literature procedure.[228] An oven-dried Schlenk tube was charged with *N*-(2-(1-phenylvinyl)phenyl)acetamide **104aa'** (50.0 mg, 0.21 mmol) and SelectFluor (82.0 mg, 0.23 mmol) and purged with nitrogen. Dry MeCN (2 mL) was added and the tube was sealed with a Young's tap and stirred at ambient temperature overnight. The solution was taken up in EtOAc before the solvent was removed *in vacuo*. Purification of the residue by FCC (hexane/EtOAc 10–20%) afforded the title compound (43.6 mg, 81% yield) as colourless cubes. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (6H, m), 7.31 – 7.21 (2H, m), 7.22 – 7.10 (1H, m), 4.92 (2H, d, *J* = 47.0 Hz), 2.24 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 139.5, 139.2, 139.2 (d, $^3J_{C\text{-}F}$ = 3.0 Hz), 129.7, 129.0, 128.7, 126.6, 126.4, 125.1, 124.8, 123.5, 84.4 (d, $^1J_{C\text{-}F}$ = 186.5 Hz), 82.2 (d, $^2J_{C\text{-}F}$ = 18.5 Hz), 21.9; ^{19}F NMR (377 MHz, $CDCl_3$): δ -219.4 (t, $^1J_{F\text{-}H}$ = 47.5 Hz); m.p. 86–88 °C ($CDCl_3$). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[228]

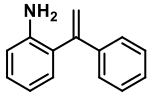
1-(8-(Iodomethyl)-8-phenyl-7-azabicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethan-1-one (201)



The title compound was prepared following a literature procedure.[229] To a solution of *N*-(2-(1-phenylvinyl)phenyl)acetamide **104aa'** (55.0 mg, 0.23 mmol) and $NaHCO_3$ (58.0 mg, 0.69 mmol) in dry MeCN (3 mL) under nitrogen at 0 °C was added I_2 (176 mg, 0.70 mmol) portion-wise over 15 minutes. The resulting solution was stirred overnight before being quenched with an aq. solution of $Na_2S_2O_3$ (10%) until the solution turned colourless. The solution was concentrated *in vacuo* before being

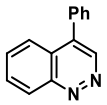
extracted with diethyl ether (3 × 10 mL). The organic extracts were combined, dried and concentrated *in vacuo* to afford the title compound (36.8 mg, 44%) as an orange oil. ν_{max}/cm^{-1}: 3029 (m), 2925 (m) 1645 (m), 1257 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (6H, m, C**11**-H, C**12**-H, 2 × ArCH), 7.24 – 7.16 (2H, m, 2× ArCH), 7.05 – 6.99 (1H, m, C**7**-H), 3.90 (2H, s, C**14**-H_2), 2.25 (3H, s, C**1**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6 (C**2**), 140.6 (C**10**), 138.9 (C**3**), 129.7 (C**5**), 128.7 (ArCH), 128.6 (ArCH), 126.5 (C**6**), 126.2 (ArCH), 126.0 (C**8**), 124.9 (ArCH), 124.8 (C**7**), 81.6 (C**9**), 22.1 (C**14**), 13.5 (C**1**); HRMS: (ESI^+) calculated for $C_{16}H_{15}INO$ 364.0193. Found $[M+H]^+$ 364.0205.

2-(1-Phenylvinyl)aniline (202)



To a reaction tube was added **104aa'** (50 mg, 0.188 mmol), aq. HCl (3 M, 14 mL) and 1,4-dioxane (0.8 mL). The reaction tube was sealed and heated at reflux for 3 h. The reaction was cooled to ambient temperature before being quenched by the addition of saturated aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC (hexane/Et_2O 50%) to afford the title compound (34.6 mg, 99%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.36 (2H, m), 7.36 – 7.29 (3H, m), 7.17 (1H, ddd, J = 8.0, 7.5, 1.5 Hz), 7.12 (1H, dd, *J* = 8.0, 1.5 Hz), 6.80 (1H, td, *J* = 7.5, 1.0 Hz), 6.70 (1H, dd, *J* = 8.0, 1.0 Hz), 5.81 (1H, d, *J* = 1.5 Hz), 5.37 (1H, d, *J* = 1.5 Hz), 3.56 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.3, 144.1, 139.8, 131.0, 128.9, 128.7, 128.2, 127.5, 126.8, 118.5, 116.3, 115.7; m.p. = 74–75 °C ($CDCl_3$) (Lit.[296] 80–82 °C, *no recrystallisation solvent specified*); *The spectroscopic proprieties were consistent with the data available in literature.*[296]

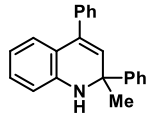
Phenylcinnoline (203)



The title compound was prepared following a literature procedure.[297] To a Schlenk tube was added **104aa'** (100 mg, 0.512 mmol) and aq. HCl (2 M, 1.4 mL) under nitrogen and the reaction was cooled to -5 °C. $NaNO_2$ (88.3 mg, 1.28 mmol) was added and the solution was stirred for 15 mins. Aq. H_3PO_2 (50%, 1 mL) was added and the resulting solution was stirred for 3 h at -5 °C before the reaction was warmed to ambient temperature and stirred for a further 3 h. The reaction was quenched by the addition of water (15 mL) and extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FCC (hexane/Et_2O 50%) to afford the title compound (106 mg, quantitative) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (1H, s), 8.59 (1H, dd, *J* = 8.5, 1.5 Hz), 7.98 (1H, d, *J* = 8.5 Hz,), 7.84 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz), 7.71 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz), 7.60 – 7.49 (5H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.6, 144.6, 135.2, 134.3,

131.3, 130.5, 130.2, 129.9, 129.3, 129.1, 124.7, 124.5. *The spectroscopic properties for this compound were consistent with the data available in the literature.*[298]

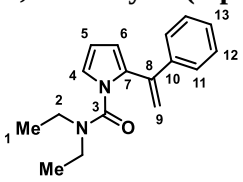
2-Methyl-2,4-diphenyl-1,2-dihydroquinoline (204)



The title compound was prepared following a modified literature procedure.[299] To a resealable Schlenk tube was added **104aa'** (100 mg, 0.512 mmol), TsOH (5.2 mg, 0.027 mmol), 2-acetophenone (78 μL, 0.666 mmol), Na_2SO_4 (145 mg, 1.02 mmol) and toluene (0.8 mL) under nitrogen. The tube was sealed and heated to 110 °C for 24 h. The solution was cooled to ambient temperature and quenched by the addition of water (15 mL) and extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by FCC (toluene/hexane 10%) afforded the title compound (148 mg, 97%) as colourless plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (2H, dd, *J* = 8.0, 1.5 Hz), 7.46 – 7.31 (7H, m), 7.30 – 7.18 (1H, m), 7.04 (1H, ddd, *J* = 8.0, 1.5, 1.5 Hz), 6.91 (1H, dd, *J* = 8.0, 1.5 Hz,), 6.61 – 6.52 (2H, m), 5.64 (1H, s), 4.21 (1H, br. s), 1.78 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 142.9, 139.5, 135.9, 129.2, 129.1, 129.1, 128.5, 128.3, 127.5, 127.0, 126.3, 125.5, 120.6, 117.6, 113.6, 57.3, 30.2; m.p. = 114–116 °C ($CDCl_3$) (Lit.[28] 113–115 °C, *no recrystallisation solvent specified*). *The spectroscopic properties for this compound were consistent with the data available in the literature.*[30]

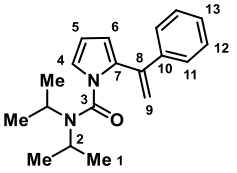
7.7.4 – α-Arylation of Styrenes with Pyrrole Substrates

***N,N*-Diethyl-2-(1-phenylvinyl)-*1H*-pyrrole-1-carboxamide (128ba')**



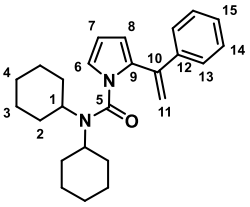
General Procedure W: The reaction was carried out with **126b** (0.143 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 48 h. The residue was purified by FCC (hexane/EtOAc 0–10%) to afford the title compound (11.0 mg, 29%) as a colourless oil. ν_{max}/cm^{-1}: 2974 (m), 2934 (m), 1687 (s), 1425 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.27 (5H, m, C**11**-H, C**12**-H, C**13**-H), 7.06 – 6.75 (1H, m, C**4**-H), 6.30 – 6.27 (1H, m, C**6**-H), 6.24 – 6.12 (1H, m, C**5**-H), 5.38 (1H, d, *J* = 1.0 Hz, C**9**-H_2), 5.35 (1H, d, *J* = 1.0 Hz, C**9**-H_2), 3.14 (4H, q, *J* = 7.0 Hz, C**2**-H_2), 0.94 (6H, t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.7 (C**3**), 141.1 (C**10**), 140.9 (C**8**), 134.1 (C**7**), 128.2 (ArCH), 128.1 (C**13**), 127.7 (ArCH), 121.6 (C**4**), 114.0 (C**9**), 112.6 (C**6**), 109.4 (C**5**), 42.1 (C**2**), 12.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{17}H_{21}N_2O$ 269.1648. Found $[M+H]^+$ 269.1648.

***N,N*-Diisopropyl-2-(1-phenylvinyl)-*1H*-pyrrole-1-carboxamide (128aa')**



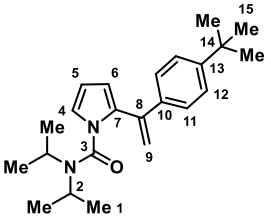
General Procedure W: The reaction was carried out with **126a** (0.143 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 48 h. The crude material was purified by FCC (hexane/EtOAc 0–4%) to afford the title compound (31.2 mg, 74%) as a colourless oil. ν_{max}/cm^{-1}: 2969 (m), 2933 (m), 1687 (s) 1432 (s), 1324 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.35 (2H, m, C**11**-H), 7.34 – 7.27 (3H, m, C**12**-H, C**13**-H), 6.84 – 6.77 (1H, m, C**4**-H), 6.22 – 6.17 (2H, m, C**5**-H, C**6**-H), 5.40 (1H, d, *J* = 1.0 Hz, C**9**-H), 5.34 (d, *J* = 1.0 Hz, 1H, C**9**-H), 3.56 – 3.39 (2H, m, C**2**-H), 1.22 – 1.10 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.0 (C**3**), 141.3 (C**10**), 141.0 (C**8**), 134.1 (C**7**), 128.2 (C**12**), 128.1 (C**11**), 127.9 (C**13**), 121.1 (C**4**), 113.9 (C**9**), 112.2 (ArCH), 109.2 ArCH), 48.4 (C**2**), 20.5 (C**1**); HRMS: (ESI^+) calculated for $C_{19}H_{25}N_2O$ 297.1961. Found $[M+H]^+$ 297.1967.

***N,N*-Dicyclohexyl-2-(1-phenylvinyl)-*1H*-pyrrole-1-carboxamide (128ca')**



General Procedure W: The reaction was carried out with **126c** (0.143 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 48 h. The crude material was purified by FCC (hexane/Et_20 5–10%) to afford the title compound (26.7 mg, 50%) as a red oil. ν_{max}/cm^{-1}: 2928 (m), 2853 (m), 1682 (s) 1427 (s), 1308 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.35 (2H, m, C**13**-H), 7.33 – 7.27 (3H, m,C**14**-H, C**15**-H), 6.80 – 6.75 (1H, m, C**6**-H), 6.22 – 6.16 (2H, m, C**7**-H, C**8**-H), 5.41 (1H, s, C**11**-H_2), 5.32 (1H, s, C**11**-H_2), 3.05 – 2.87 (2H, m,C**1**-H), 1.84 – 1.00 (20H, m, Cy); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.5 (C**5**), 141.4 (C**12**), 140.9 (C**10**), 133.9 (C**9**), 128.1 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 121.0 (C**6**), 113.7 (C**11**), 112.2 (C**7**/**8**), 109.2 (C**7**/**8**), 58.1 (C**1**), 30.3 (Cy), 26.1 (Cy), 25.3 (Cy); HRMS: (ESI^+) calculated for $C_{25}H_{33}N_2O$ 377.2587. Found $[M+H]^+$ 377.2594.

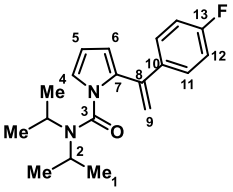
2-(1-(4-(*tert*-Butyl)phenyl)vinyl)-*N,N*-diisopropyl-*1H*-pyrrole-1-carboxamide (128ap')



General Procedure W: The reaction was carried out with **126a** (0.1 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 72 h. The crude material was purified by FCC

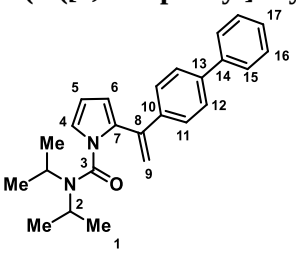
(hexane/EtOAc 0–3%) to afford the title compound (25.4 mg, 72%) as an orange oil. ν_{max}/cm^{-1}: 2964 (m), 2932 (m), 1689 (s), 1325 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.28 (4H, m, C**11**-H, C**12**-H), 6.80 (1H, dd, *J* = 3.0, 1.5 Hz, C**4**-H), 6.26 – 6.10 (2H, m, C**5**-H, C**6**-H), 5.37 (1H, d, *J* = 1.5 Hz, C**9**-H_2), 5.33 (1H, d, *J* = 1.5 Hz, C**9**-H_2), 3.48 (2H, br. s, C**2**-H), 1.31 (9H, s, C**15**-H_3), 1.17 – 1.05 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.0 (C**3**), 150.8 (C**13**), 140.9 (C**8**), 138.3 (C**10**), 134.4 (C**7**), 127.7 (C**11**), 125.2 (C**12**), 120.9 (C**4**), 113.5 (C**9**), 112.1 (C**5**), 109.2 (C**6**), 48.2 (C**2**), 34.7 (C**14**), 31.5 (C**15**), 20.5 (C**1**); HRMS: (ESI$^+$) calculated for $C_{23}H_{32}N_2ONa$ 375.2407. Found $[M+Na]^+$ 375.2398.

2-(1-(4-Fluorophenyl)vinyl)-*N*,*N*-diisopropyl-*1H*-pyrrole-1-carboxamide (128an')



General Procedure W: The reaction was carried out with **126a** (0.1 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 0–4%) to afford the title compound (19.6 mg, 62%) as an orange oil. ν_{max}/cm^{-1}: 2969 (m), 2931 (m), 1688 (s), 1507 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (2H, m, C**11**-H), 6.99 (2H, dd, *J* = 8.5, 1.5 Hz, C**12**-H), 6.84 – 6.77 (1H, m, C**4**-H), 6.21 – 6.18 (1H, m, C**5**-H), 6.18 – 6.13 (1H, m, C**6**-H), 5.36 (1H, s, C**9**-H_2), 5.29 (1H, s, C**9**-H_2), 3.54 – 3.41 (2H, m, C**2**-H), 1.17 (12H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.70 (d, $^{1}J_{C\text{-}F}$ = 246.5 Hz, C**13**), 152.0 (C**3**), 140.0 (C**8**), 137.4 (C**10**), 133.9 (C**7**), 129.70 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, C**11**), 121.2 (C**4**), 115.05 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz, C**12**), 113.8 (C**9**), 112.3 (C**6**), 109.3 (C**5**), 48.6 (C**2**), 20.5 (C**1**); HRMS: (ESI$^+$) calculated for $C_{19}H_{23}N_2OFNa$ 337.1687. Found $[M+Na]^+$ 337.1702.

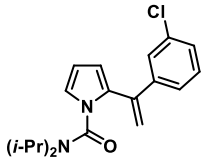
2-(1-([1,1'-Biphenyl]-4-yl)vinyl)-*N*,*N*-diisopropyl-*1H*-pyrrole-1-carboxamide (128ak')



General Procedure W: The reaction was carried out with **126a** (0.1 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 72 h. The crude material was purified by FCC (hexane/EtOAc 0–4%) to afford the title compound (13.4 mg, 36%) as an orange oil. ν_{max}/cm^{-1}: 2969 (m), 2935 (m), 1688 (s), 1326 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.50 (4H, m, C**15**-H, C**16**-H), 7.49 – 7.40 (4H, m, C**11**-H, C**12**-H), 7.38 – 7.32 (1H, m, C**17**-H), 6.83 (1H, dd, *J* = 3.0, 1.5 Hz, C**4**-H), 6.30 – 6.16 (2H, m, C**5**-H, C**6**-H), 5.43 (1H, d, *J* = 1.0 Hz, C**9**-H_2), 5.41 (1H, d, *J* = 1.0 Hz, C**9**-H_2), 3.51 (2H, br. ap. s, C**2**-H), 1.17 (12H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.0 (C**3**), 141.0 (C**8**), 140.8 (C**14**), 140.6 (C**13**), 140.3 (C**10**), 134.0 (C**7**), 128.9 (C**11**), 128.5 (C**12**), 127.4

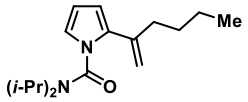
(C**15**), 127.2 (C**16**), 127.0 (C**17**), 121.1 (C**4**), 114.0 (C**9**), 112.3 (C**5**), 109.3 (C**6**), 49.0 (C**2**), 20.5 (C**1**); HRMS: (ESI$^+$) calculated for $C_{25}H_{28}N_2ONa$ 395.2094. Found $[M+Na]^+$ 395.2098.

2-(1-(3-Chlorophenyl)vinyl)-*N*,*N*-diisopropyl-*1H*-pyrrole-1-carboxamide (128as')



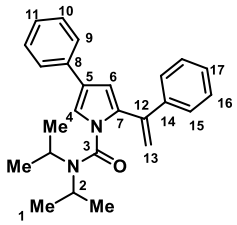
General Procedure W: The reaction was carried out with **126a** (0.1 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 – 6.13 (1H, m), 5.34 (1H, s), 5.25 (1H, s), 3.76 (2H, h, *J* = 6.5 Hz), 1.28 (6H, d, *J* = 6.5 Hz).

2-(Hex-1-en-2-yl)-*N*,*N*-diisopropyl-1*H*-pyrrole-1-carboxamide (128ac')



General Procedure W: The reaction was carried out with **126a** (0.1 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 72 h. The title product was observed by ^{1}H NMR analysis of the crude material. *Characteristic ^{1}H NMR peaks:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (1H, dd, *J* = 3.0, 1.0 Hz), 6.18 – 6.14 (1H, m), 5.11 (1H, s), 4.96 (1H, d, *J* = 1.0 Hz), 3.40 (2H, p, *J* = 6.5 Hz), 2.41 – 2.30 (2H, m), 0.91 (3H, t, *J* = 7.0 Hz).

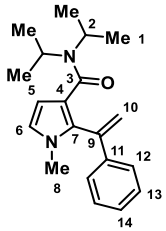
***N*,*N*-Diisopropyl-3-phenyl-2-(1-phenylvinyl)-1*H*-pyrrole-1-carboxamide (128ea')**



General Procedure W: The reaction was carried out with **126e** (0.1 mmol), $[Ir(cod)_2]OTf$ (10 mol%) and (*S*,*S*)-f-Binaphane (10 mol%) and was run for 72 h. The crude material was purified by FCC (1st column, $AgNO_3$ treated silica^{300}: toluene/CH_2Cl_2/Et_2O 75:25:1; 2nd column: hexane/Et_2O 10%) to afford the title compound (18.5 mg, 50%) as an orange oil. ν_{max}/cm^{-1}: 2956 (m), 2928 (m), 1687 (s), 1432 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.48 (2H, m, C**9**-H), 7.45 – 7.40 (2H, m, C**10**-H), 7.37 – 7.30 (5H, m, C**15**-H, C**16**-H, C**17**-H), 7.20 (1H, t, *J* = 7.5 Hz, C**11**-H), 7.10 (1H, d, *J* = 2.0 Hz, C**4**-H), 6.52 (1H, d, *J* = 2.0 Hz, C**6**-H), 5.46 (1H, s, C**13**-H_2), 5.40 (1H, s, C**13**-H_2), 3.60 – 3.51 (2H, m, C**2**-H), 1.19 (12H, d, *J* = 6.5 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6 (C**3**), 140.9 (C**14**), 140.7 (C**8**), 134.8 (C**7**), 134.6 (C**12**), 128.7 (C**15**/**16**), 128.2 (C**15**/**16**), 128.0 (C**10**), 127.9 (C**17**), 126.1 (C**11**), 125.3 (C**5**),

125.3 (C**9**), 117.2 (C**4**), 114.2 (C**13**), 110.2 (C**6**), 30.3 (C**2**), 29.7 (C**2**), 20.4 (C**1**); HRMS: (ESI$^+$) calculated for $C_{25}H_{29}N_2O$ 373.2274. Found $[M+H]^+$ 373.2293.

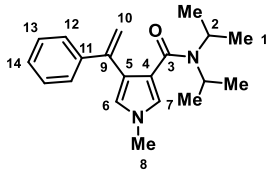
***N*,*N*-Diisopropyl-1-methyl-2-(1-phenylvinyl)-1*H*-pyrrole-3-carboxamide (205a', C2)**



General Procedure W: The reaction was carried out with **150** (0.143 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 48 h. The crude material was purified by FCC (hexane/EtOAc 20–30%) to afford the title compound (6.7 mg, 22%) as a yellow oil. ν_{max}/cm^{-1}: 2954 (m), 2927 (m), 1621 (s), 1498 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.27 (5H, m, C**12**-H, C**13**-H, C**14**-H), 6.56 (1H, d, *J* = 3.0 Hz, C**6**-H), 6.14 (1H, d, *J* = 3.0 Hz, C**5**-H), 5.71 (1H, d, *J* = 1.5 Hz, C**10**-H_2), 5.42 (1H, d, *J* = 1.5 Hz, C**10**-H_2), 4.38 – 4.18 (1H, m, C**2**-H), 3.57 – 3.25 (1H, m, C**2**-H), 3.22 (3H, s, C**8**-H_3), 1.50 – 0.77 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0 (C**3**), 140.7 (C**11**), 139.5 (C**9**), 131.4 (C**7**), 128.6 (C**12**/**13**), 127.9 (C**14**), 127.0 (C**12**/**13**), 122.3 (C**4**), 122.2 (C**6**), 118.5 (C**10**), 106.6 (C**5**), 35.0 (C**8**), 20.9 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{27}N_2O$ 311.2118. Found $[M+H]^+$ 311.2131.

*Note: C**2** was not observed by ^{13}C NMR analysis.*

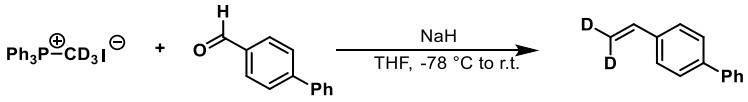
***N*,*N*-Diisopropyl-1-methyl-4-(1-phenylvinyl)-1*H*-pyrrole-3-carboxamide (205a', C4)**



General Procedure W: The reaction was carried out with **150** (0.143 mmol), $[Ir(cod)_2]OTf$ (7.5 mol%) and (*S*,*S*)-f-Binaphane (7.5 mol%) and was run for 48 h. The crude material was purified by FCC (hexane/EtOAc 20–30%) to afford the title compound (11.6 mg, 37%) as a yellow oil. ν_{max}/cm^{-1}: 2957 (m), 2929 (m), 1616 (s), 1443 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (2H, m, C**12**-H), 7.32 – 7.25 (3H, m, C**13**-H, C**14**-H), 6.62 (1H, d, *J* = 2.5 Hz, C**7**-H), 6.37 (1H, d, *J* = 2.5 Hz, C**6**-H), 5.31 (1H, d, *J* = 1.5 Hz, C**10**-H_2), 5.20 (1H, d, *J* = 1.5 Hz, C**10**-H_2), 4.32 – 4.05 (1H, m, C**2**-H), 3.58 (3H, s, C**8**-H_3), 3.47 – 3.15 (1H, m, C**2**-H), 1.38 – 0.79 (12H, m, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6 (C**3**), 142.7 (C**9**), 142.5 (C**11**), 128.1 (C**12**/**13**), 128.1 (C**12**/**13**) 127.5 (C**14**), 123.2 (C**5**), 122.0 (C**6**), 121.3 (C**4**), 120.7 (C**7**), 112.3 (C**10**), 51.0 (C**2**), 45.6 (C**2**), 36.3 (C**8**), 20.8 (C**1**); HRMS: (ESI$^+$) calculated for $C_{20}H_{27}N_2O$ 311.2118. Found $[M+H]^+$ 311.2127.

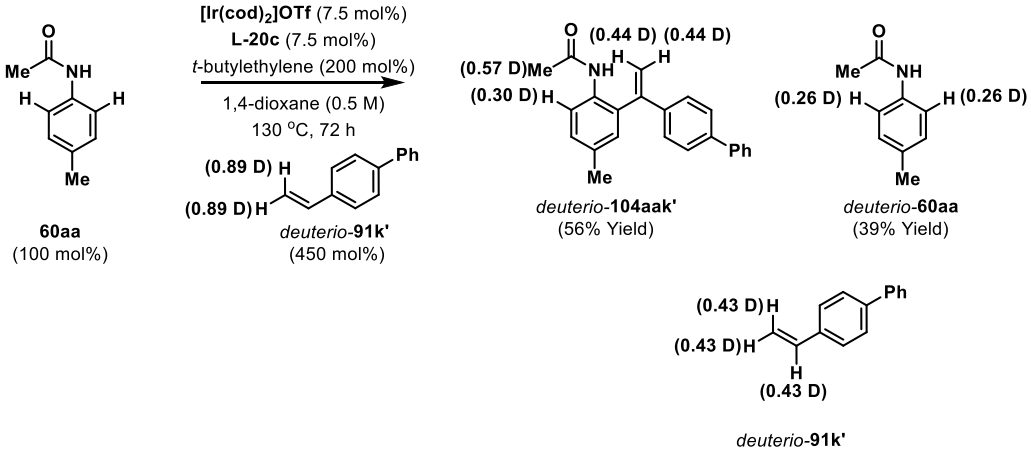
7.7.5 – Deuterium Labelling Experiments

[4-(vinyl-*β*,*β*-*d*$_2$)-1,1'-biphenyl] *(deuterio*-**91k'**)



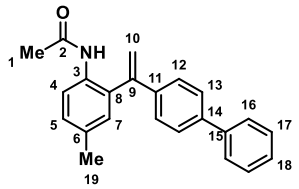
To a suspension of methyl-d_3-triphenylphosphonium iodide (2.69 g, 6.60 mmol) and biphenyl-4-carboxaldehyde (1.00 g, 5.50 mmol) in anhydrous THF (25 mL) was added portion-wise NaH (581 mg, 24.2 mmol, 60% in mineral oil) at 0 ˚C. The reaction was slowly warmed to ambient temperature and stirred for 16 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by FCC (hexane/EtOAc 0–10%) to provide the title compound (1.00 g, quantitative yield, 89% deuteration) as a colourless solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 – 7.56 (4H, m), 7.56 – 7.41 (4H, m), 7.42 – 7.31 (1H, m), 6.78 (1H, br. s); ^{2}H NMR (CH_2Cl_2, 77 MHz): δ 5.81 (1D, br. s), 5.27 (1D, s); m.p. 121–123 ˚C (hexane/CH_2Cl_2) (Lit.[301] 122–125 °C, *no recrystallisation solvent specified*). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[301]

Deuterium labelling experiment of 60aa



An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with substrate **60aa** (21.3 mg, 0.143 mmol), [Ir(cod)$_2$]OTf (7.5 mol%) and **L-20c** (7.5 mol%). The tube was fitted with a rubber septum and purged with nitrogen. *Deuterio*-**91k'** (0.644 mmol) and *t*-butylethylene (200 mol%) in anhydrous 1,4-dioxane (0.5 M concentration with respect to substrate) was added and the tube was fitted with a Young's tap. The reaction mixture was then heated to 130 °C for 72 h, before being cooled to ambient temperature and concentrated *in vacuo*. Purification of the residues by FCC (toluene/EtOAc 0–10%) afforded the *deuterio*-products.

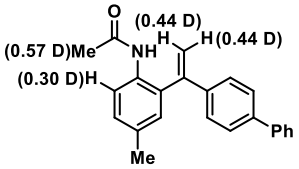
***N*-(2-(1-([1,1'-Biphenyl]-4-yl)vinyl)-4-methylphenyl)acetamide (104aak')**



For comparison, the non-deuterated product was synthesised by **General Procedure U**. The reaction was carried out with Ir(cod)$_2$]OTf (7.5 mol%), **L-20c** (7.5 mol%) and 1,4-dioxane (0.5 M with respect to substrate) and was run for 96 h. The crude material was purified by FCC (toluene/EtOAc 0−10%) to afford the title compound (23.1 mg, 49%) as colourless cubes. ν_{max}/cm^{-1}: 3283 (m), 3029 (m), 2923 (s), 1656 (s), 1513 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.50 – 7.45 (4H, m, C**13**-H, C**16**-H), 7.45 (2H, dd *J* = 7.5, 7.5 Hz, C**17**-H), 7.42 – 7.33 (3H, m, C**12**-H, C**18**-H), 7.20 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 7.10 (1H, d, *J* = 2.0 Hz, C**7**-H), 6.95 (1H, s, N-H), 5.91 (1H, s, C**10**-H$_2$), 5.37 (1H, s, C**10**-H$_2$), 2.35 (3H, s, C**19**-H$_3$), 1.81 (3H, s, C**1**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2 (C**2**), 146.1 (C**9**), 141.3 (C**14**), 140.4 (C**15**), 138.5 (C**11**), 134.2 (C**6**), 132.8 (C**3**), 132.1 (C**8**), 130.8 (C**7**), 129.5 (C**5**), 129.0 (C**17**), 127.7 (C**18**), 127.5 (C**13**), 127.1 (C**12**, C**16)**, 122.2 (C**4**), 117.0 (C**10**), 24.4 (C**1**), 21.0 (C**19**); HRMS: (ESI$^+$) calculated for $C_{23}H_{22}NO$ 328.1696. Found [M+H]$^+$ 328.1689; m.p. 152−154 °C ($CDCl_3$).

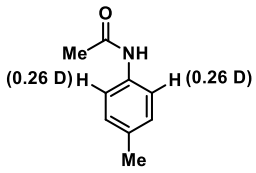
The data for the deuterated products is presented below:

*deuterio-**104aak'***



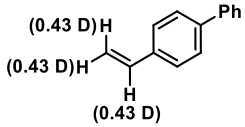
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (0.7H, d, *J* = 8.5 Hz), 7.62 – 7.53 (4H, m), 7.49 – 7.33 (5H, m), 7.24 – 7.16 (1H, m), 7.10 (1H, d, *J* = 2.0 Hz), 6.95 (1H, s), 5.91 (0.56H, d, *J* = 6.0 Hz), 5.37 (0.56H, d, *J* = 6.0 Hz), 2.36 (3H, s), 1.82 (2.43H, s); ^{2}H NMR (77 MHz, $CHCl_3$): δ 8.07 (0.3D, s), 5.94 (0.44D, s), 5.40 (0.44D, s), 1.81 (0.57D, d, *J* = 2.5 Hz). *Deuterium incorporation was calculated by integration of both ^{1}H NMR and ^{2}H NMR signals.*

*deuterio-**60aa***



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (1.48H, dd, *J* = 8.5, 6.0 Hz), 7.22 – 7.16 (1H, m), 7.16 – 7.06 (2H, m), 2.31 (3H, s), 2.15 (3H, s); ^{2}H NMR (77 MHz, $CHCl_3$): δ 7.43 (0.52D, s). *Deuterium incorporation was calculated by integration of both ^{1}H NMR and ^{2}H NMR signals.*

*deuterio-**91k'***



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.31 (9H, m), 6.86 – 6.74 (0.57H, m), 5.86 – 5.76 (0.57H, m), 5.35 – 5.24 (0.57H, m); ^{2}H NMR (77 MHz, $CHCl_3$): δ 6.83 (0.43D, s), 5.86 (0.43D, s), 5.34 (0.43D, s). *Deuterium incorporation was calculated by integration of both ^{1}H NMR and ^{2}H NMR signals.*

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