

Chapter 2

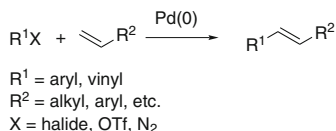
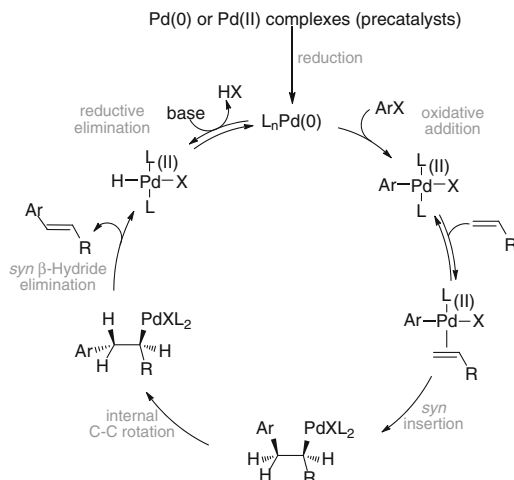
Regioselectivity in the Heck (Mizoroki-Heck) Reaction

2.1 General Introduction

The alkenylation, or arylation of olefinic compounds in the presence of catalytic amounts of Pd(0) to give substituted olefins is referred to as the Heck (Mizoroki-Heck) reaction [1, 2]. This is a powerful tool used for the construction of carbon-carbon bonds, that often might otherwise be difficult to assemble [3–8]. Complex molecular structures [9–12], including those bearing asymmetric stereogenic centres [13] can be rapidly prepared and in addition, the reaction conditions used for this process can tolerate a wide range of functional groups. The active palladium catalyst can be generated in situ from air-stable precatalysts (e.g. Pd(OAc)₂), and reactions are usually carried out at elevated temperatures, in the presence of base (bulky amines or inorganic salts) and monodentate or bidentate phosphine ligands. One significant limitation of the reaction is that substrates cannot contain a β-hydrogen. However, recent reports suggest conditions that can circumvent this constraint, albeit for a limited range of substrates (Scheme 2.1) [14, 15].

The precise mechanism of the Heck reaction is not fully understood, with the exact mechanistic pathways depending on reaction conditions and substrates employed [16–20]. However, Scheme 2.2 shows a simplified sequence of events for the catalytic cycle of the Heck reaction. This cycle begins by the formation of a homogenous palladium(0) complex as the catalytically active species (generated in situ by the reduction of Pd(II) salts (e.g. Pd(OAc)₂), or by employing a Pd(0)-precatalyst (e.g. Pd(PPh₃)₄).

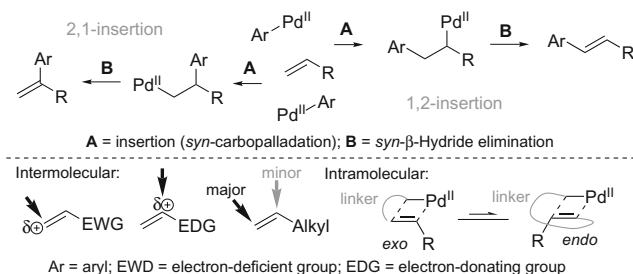
The first step of the catalytic cycle is insertion of Pd(0) into the ArX bond, a step referred to as oxidative addition. The rate of oxidative addition of aryl halides depends on the nature of X: ArI > ArBr ≫ ArCl. Alkene association can then occur via dissociation of a ligand (L), followed by *syn*-insertion (also referred to as carbopalladation) which leads to a σ-alkyl-palladium(II) halide. The nature of alkene substitution, or regioselectivity, is dictated by this step. An internal C–C bond rotation brings an sp³-bonded β-hydrogen *syn* to the palladium atom, which

**Scheme 2.1** Arylation/alkenylation of substituted olefins**Scheme 2.2** A general representation of the catalytic cycle for a homogenous Pd(0) species in the Mizoroki-Heck reaction

then undergoes a β -hydride elimination reaction. This process can be reversible, which may lead to alkene isomerisation of the initially formed Heck products. Alkene dissociation, followed by base induced reductive elimination regenerates the active palladium(0) complex.

The carbopalladation step, which governs the regiochemical outcome of the newly formed carbon-carbon bond, is of interest. By design, stereogenic C–C bonds can be accessed with ease. Also the selectivity observed (stereo- and regio-selectivity) can shed light on the mechanism of the overall process. In a typical cross-coupling reaction of an aryl halide and an alkene (Scheme 2.3), it is thought that the carbopalladation event (insertion reaction, step A) is irreversible, and therefore the regiochemical outcome is dictated by this step.

There are several factors that affect the regioselective outcome of the Heck reaction. The electronic features of the alkene play a significant role. Typically, carbon-carbon bond formation occurs preferentially at the most electron-deficient carbon (indicated by arrow in Scheme 2.3) [1, 21, 22]. Steric effects will dominate with alkenes where bond polarisation is not as dramatic, for example aliphatic alkenes, leading to a mixture of regioisomeric products. For intramolecular examples, ring-size of the newly formed cycle is an additional factor in the regiochemical outcome of the reaction. The nature of the reaction conditions and



Scheme 2.3 Regioselectivity in the inter- and intramolecular Heck reaction

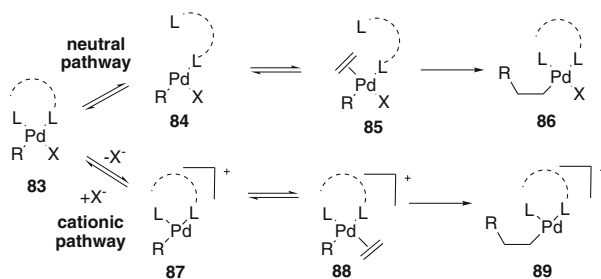
(*pseudo*) halide of the Heck precursor being employed also seem to be important, since these influence the identity, in terms of ligands and charge on the palladium atom of the active catalyst and thereby can affect the regiochemical outcome of the reaction.

2.2 Intermolecular Heck Reaction

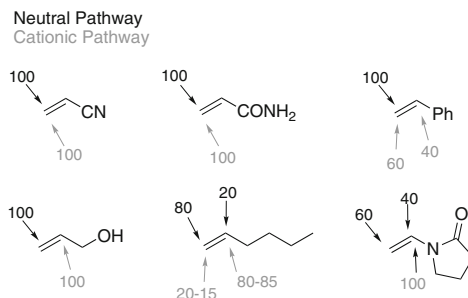
In a report by Cabri et al. two reaction pathways are proposed for the alkene coordination-insertion event (Scheme 2.4) [21].

In the neutral pathway olefin association to intermediate **83** can proceed via dissociation of one neutral ligand, generating neutral complex **84**. This pathway can be accessed by evoking halides such as I, Br and Cl, in the presence of phosphine ligands. In contrast, a cationic pathway involves dissociation of an anionic ligand (counterion) to give the cationic complex **87**. The use of triflates and halide scavengers (e.g. Ag and Tl salts when X is a halide) are thought to lead to this pathway. By accessing either pathway, differences in regioselectivity can be observed depending on the alkene substituent (Scheme 2.5).

These observations provide experimental evidence that the regiochemistry is related to the coordination-carbopalladation event.



Scheme 2.4 The alkene coordination-insertion process



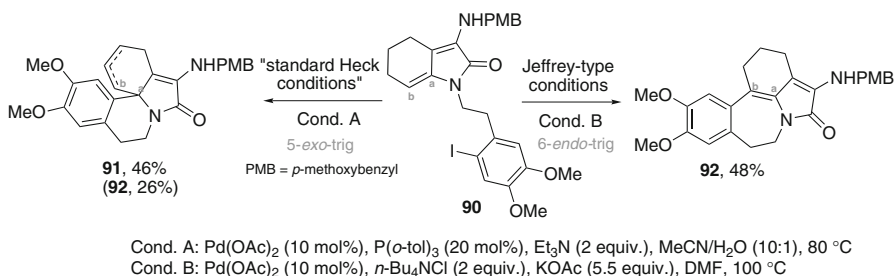
Scheme 2.5 Regioselectivity observed during arylation insertion process

2.3 Intramolecular Heck Reaction

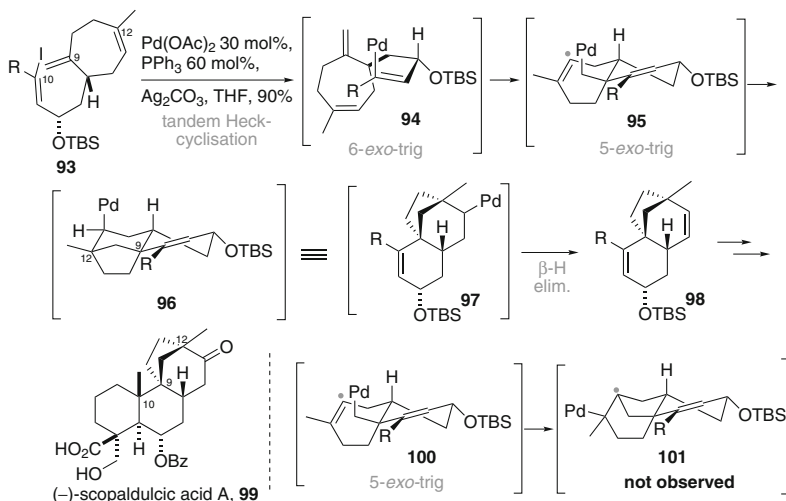
The intramolecular Heck reaction is an efficient method for the construction of cyclic compounds containing an *endo*- or *exo*-cyclic double bond. A feature of this reaction is that sterically hindered tertiary [23] and quaternary [24] carbon stereocentres can be assembled. However, unlike the intermolecular Heck reaction, there are no general methods for turning over the regioselectivity in intramolecular reactions. While there are a few literature examples [25, 26] that probe this idea, the examples used are substrate specific and are not very general for synthetic applications.

Generally, regioselectivity is governed by ring-size of the newly formed cycle (see Scheme 2.3) [4–7, 20, 27]. In one example, Rigby et al. showed that for a particular class of compound (**90**), they could obtain *exo*-adduct **91** as the major product under standard Heck conditions, and then reversed regioselectivity to obtain compound **92** solely, when Jeffrey-type conditions were employed ('ligand-free' conditions) (Scheme 2.6) [25].

A classic example of the intramolecular Heck reaction in action is Overman's synthesis of (–)-scopadulcic acid, whereby a tandem double Heck cyclisation (6-*exo*-trig followed by a 5-*exo*-trig) rapidly accesses the carbon skeleton found in the natural product **99** (Scheme 2.7) [28].



Scheme 2.6 Rigby's example of 5-*exo* and 6-*endo*, reagent controlled intramolecular Heck reaction



Scheme 2.7 Overman's example of an intramolecular tandem Heck reaction

Following the initial 6-*exo*-trig cyclisation (**93** $\rightarrow$ **94**), a subsequent cyclisation onto the trisubstituted alkene yields **96**. However, this alkene is unbiased in terms of ring-size and insertion to either carbon of the alkene would proceed via a 5-*exo*-trig cyclisation. Carbopalladation at the least substituted carbon (labelled with a grey dot in **95**) would also proceed via an 5-*exo*-trig cyclisation, leading to intermediate **100**.

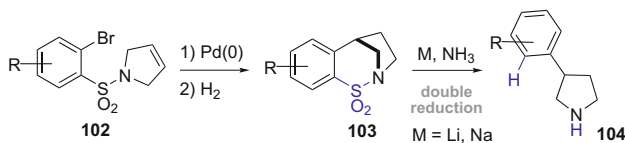
To date, what is lacking are examples where substrates are unbiased in terms of the ring-size of the new cycle formed (i.e. **95** $\rightarrow$ **96** or **101**). If substrates of this type could be designed, more information about the alkene-insertion event could be obtained.

2.4 Regioselectivity in the Intramolecular Heck Reaction of Sulfonamides

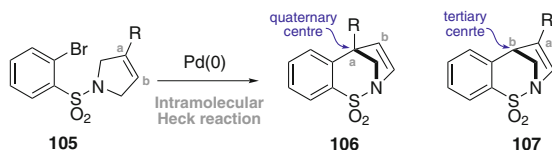
For several years, the Evans group have been interested in utilising a novel double reduction reaction of cyclic sulfonamides (of type **103**) in the preparation of substituted nitrogen-containing heterocycles (**104**) [29, 30]. An intramolecular Heck reaction of symmetrical alkenes of type **102**, followed by alkene hydrogenation, gave access to these substrates (**102** $\rightarrow$ **103**) (Scheme 2.8) [29].

Aryl-insertion (carbopalladation) to either alkenyl carbon atoms in **102** would proceed via a 6-*exo*-trig mode of cyclisation to provide, after hydrogenation, compound **103**.

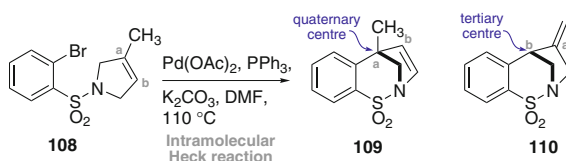
Replacing a hydrogen atom for an R-group on the alkene of **102** would generate an unsymmetrical alkene, e.g. **105**, where the carbon atoms are no longer chemically



Scheme 2.8 Evans' synthesis of aryl-substituted pyrrolidines



Scheme 2.9 Intramolecular Heck reaction of unsymmetrical sulfonamides

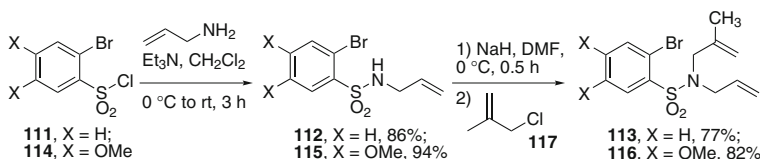


Scheme 2.10 Intramolecular Heck reaction of unsymmetrical sulfonamide **108**

equivalent (Scheme 2.9). Notably, the system is still unbiased in terms of ring-size; following an intramolecular Heck cyclisation of **105** could give **106** and/or its regioisomer **107**.

Preliminary results concerning this sequence, obtained by Erasmus student Nicolas Méral, where $\text{R} = \text{Me}$ (**108**), showed that in the Heck reaction there is a high preference for the formation of the more sterically hindered compound **109** (Scheme 2.10). Carbon-carbon bond formation occurred at the most substituted carbon of the system (position a) in excellent yield. Only trace amounts of material attributed to its regioisomer **110** could be detected (obtained after insertion at position b).

To try to understand the unusual regioselectivity observed and to further probe the scope of the reaction shown above, synthetic sequence **108** $\rightarrow$ **109** was repeated. Two series of dihydropyrrole Heck precursors were synthesised, within which the substituents on the aromatic moiety were varied (Scheme 2.11). Sulfonamides **112** and **115** were prepared in high yields using commercially available allylamine, the appropriate sulfonyl chloride **111**, or **114** (prepared from bromoveratrole **67**) [29] and triethylamine as a base. Subsequent *N*-alkylation of sulfonamides **112** and **115** with 3-chloro-2-methylpropene **117**, utilising NaH in DMF, furnished diallyl compounds **113** and **116** in 77 and 82 % isolated yields, respectively.

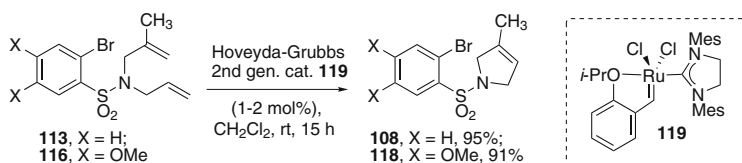


Scheme 2.11 Preparation of diallyl compounds **113/116**

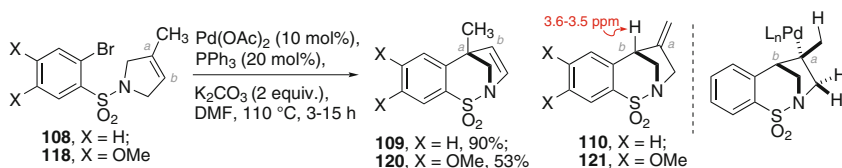
A ring-closing metathesis (RCM) reaction of **113** and **116** in the presence of catalytic amounts of the Hoveyda-Grubbs second generation catalyst [**31**] **119** in dichloromethane (0.05 M solution) at room temperature generated dihydropyrrole Heck precursors **108** (95 %) and **118** (91 %). No cross-metathesis products were isolated. This reaction is complete within a few hours with a catalyst loading of 10–15 mol%. However, catalyst loadings can be decreased to as low as 1–2 mol%, and, as a consequence, a longer reaction time is required (Scheme 2.12).

When Heck precursors **108** and **118** were submitted to standard Heck conditions ($\text{Pd}(\text{OAc})_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 equiv.), DMF, 110 °C) the formation of cyclic sulfonamides **109** and **120**, possessing a quaternary all-carbon centre were observed in 90 and 53 % yields respectively (Scheme 2.13). The protons of the newly formed alkene present in **109** and **120** were observed as two doublets at approximately 6.4 and 6.3 ppm in the proton NMR spectra. Trace amounts of material corresponding to the regioisomeric products **110** and **121** (*exo*-cyclic alkene observed) could be detected in the ^1H NMR spectra of the crude reaction mixture (<5 %).

The Heck reaction of **108** can be also be performed with a lower catalyst loading of 1 mol% $\text{Pd}(\text{OAc})_2$ /2 mol% PPh_3 providing **109** in 84 % yield. Microwave irradiation [20] was briefly investigated as an alternative to standard conductive



Scheme 2.12 Ring-closing metathesis of **113/116**



Scheme 2.13 Regioselectivity in the intramolecular Heck reaction of sulfonamides **108/118**

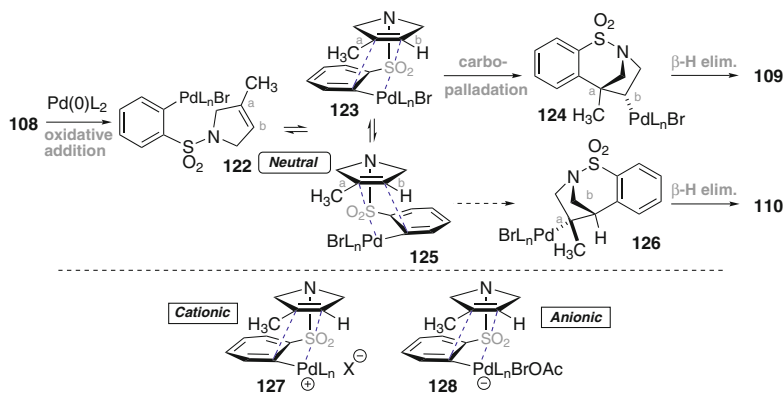
heating. Irradiation at 300 W at 125 °C for 25 min under otherwise identical reaction conditions gave an isolated yield of 62 and 68 % of **109** and **120** respectively.

Since both isomer **109/120** and **110/121** possess the same ring size and these reactions were carried out at elevated temperatures, the selectivity observed implies that there is an underlying preference for the formation of the quaternary isomer over the tertiary isomer.

Based on the generally accepted homogeneous pathway, which involves a coordinatively unsaturated palladium(0) species as the entity that undergoes oxidative addition with **108**, the formation of a neutral palladium(II) species (**122**) can be envisaged (Scheme 2.14).

Ligand dissociation, followed by alkene association could generate a complex of the type **123/125**. Carbopalladation (insertion step) may occur via conformer **123** or **125** to give intermediates **124** or **126**, respectively. Since carbopalladation is considered irreversible [18, 32], selectivity at this stage dictates the formation of **109**, which occurs following β -hydride elimination. Two alternatives to the neutral pathway have also been proposed. If X is a leaving group with weaker ligand donor properties, for example a triflate group, then a cationic reaction intermediate of type **127** is observed [21, 33]. This is of particular significance when employing bidentate ligands, chiefly exploited in the area of asymmetric synthesis [13]. Jutand and Amatore [16, 17] have proposed that under the conditions $[\text{Pd}(\text{OAc})_2/3(\text{PPh}_3)]$ the identity of the palladium(0) species is the anionic complex $[\text{Pd}(\text{OAc})(\text{PPh}_3)_2]^-$, which results in intermediates such as **128** undergoing carbopalladation. In addition to the homogeneous reaction intermediates, investigations into the high turnover numbers of some palladacycles (e.g. Herrmann-Beller palladacycle **130**) have suggested that nano-particulate colloidal palladium(0) may actually be the active catalyst [34, 35].

It is apparent that the choice of reaction conditions employed and the type of reaction substrate chosen influence the type of palladium(0) complex (**123/125**, **127** or **128**) that

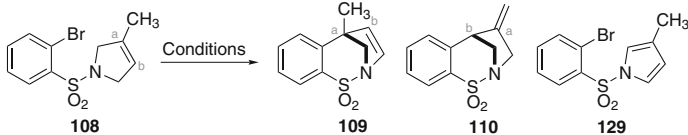
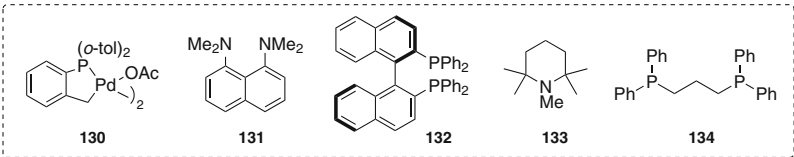


Scheme 2.14 Plausible reaction pathways for the regioselective carbopalladation

is undergoing carbopalladation (the regiochemical-establishing event). Based on this it was felt that the identity of the catalytically active palladium species participating in the initial oxidative addition step, and subsequent carbopalladation, might govern the regiochemical outcome of the reaction. Therefore, we initially aimed to uncover any effect the choice of reaction conditions would have on the regiochemical outcome of the cyclisation of **108** (Table 2.1).

As indicated in entry 1, when a palladium(0) source was used directly, there was no significant difference in the yield or regioselectivity to that observed in Scheme 2.10. A protocol by Danishefsky et al. [36] applying Pd/C as the catalyst gave only recovered starting material (entry 2). The use of palladacycle **130** also showed no dramatic difference in the regiochemical outcome (entry 3). A feature of catalyst **130** is extremely low loadings are often effective at higher temperatures (130 °C and above), and in fact result in a faster reaction [37–40]. However, in our hands, poor conversions were encountered for lower loadings of **130** (1–0.01 mol% at 130 °C). Replacement of K₂CO₃ with homogeneous amine bases (Et₃N and proton sponge **131**) proved detrimental to the isolated yields of **109** (entries 4 and 5).

Table 2.1 Intramolecular Heck reaction of **108**

		
		
Entry	Conditions	Product(s) ^a (% yield, ratio)
1	[Pd(PPh ₃) ₄] (10 mol%), K ₂ CO ₃ , DMF, 110 °C	109 (72)
2	Pd/C 10% w/w (10 mol%), Et ₃ N, MeCN, 80 °C	108 (85)
3	Herrmann-Beller cat. 130 (10 mol%), K ₂ CO ₃ , DMF, 110 °C	109 (69)
4	Pd(OAc) ₂ (10 mol%), PPh ₃ (20 mol%), Et ₃ N, DMF, 110 °C	109 (69)
5	Pd(OAc) ₂ (10 mol%), PPh ₃ (20 mol%), proton sponge 131 , DMF, 110 °C	109 (34)
6	Pd(OAc) ₂ (10 mol%), PPh ₃ (20 mol%), Ag ₂ CO ₃ , DMF, 110 °C	109 (24), 108 (35), 129 (6)
7	Pd(OAc) ₂ (10 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ , <i>n</i> -Bu ₄ NHSO ₄ , DMF-H ₂ O (9:1), 110 °C	109 (83)
8	Pd(OAc) ₂ (10 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ , PhMe, 110 °C	109/110 (59, 85:15) ^[b]
9	Pd(OAc) ₂ (10 mol%), P(<i>o</i> -tol) ₃ (20 mol%), Et ₃ N, DMF, 110 °C	109 (10), 108 (75)
10	Pd(OAc) ₂ (10 mol%), PMe ₃ (1M soln in THF, 20 mol%), K ₂ CO ₃ , DMF, 110 °C	109 (56)
11	Pd(OAc) ₂ (10 mol%), dppp 134 (20 mol%), K ₂ CO ₃ , DMF, 60 °C	109 (88)
12	Pd(OAc) ₂ (10 mol%), K ₂ CO ₃ , DMF, 110 °C	109/110 (72; 88:12) ^[b]
13	Pd(OAc) ₂ (10 mol%), (<i>R</i>)-BINAP 132 (20 mol%), K ₂ CO ₃ , DMF, 110 °C	109/110 (91, 88:12) ^[b] , 0% ee
14	[Pd(dba) ₂] (10 mol%), (<i>R</i>)-BINAP 132 (23 mol%), PMP 133 , DMF, 110 °C ^c	109 (41), 16% ee

^a Isolated yields after purification by column chromatography

^b Ratio determined by ¹H NMR spectroscopy

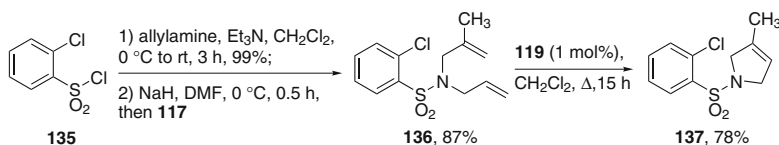
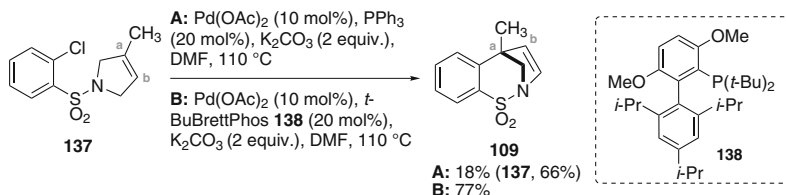
^c Reaction was conducted following three freeze-pump-thaw cycles

However, again regioisomer **110** was not detected in the reaction mixture. Thallium and silver salts [41] are often used as halide scavengers in these types of Heck processes generating cationic intermediates of the type **127**. As indicated in entry 6, the inclusion of Ag_2CO_3 led to an inefficient Heck process from which **109** was isolated in a low yield (24 %). The remaining mass balance was attributed to recovered starting material (35 %) and the isolation of pyrrole **129** (6 %), which is probably the product of a silver(I) mediated oxidation [42] of the dihydropyrrole ring.

Conditions employed successfully to influence regioselectivity in intramolecular Heck reactions reported by Genêt et al. [43] and Evans et al. [26] ($n\text{-Bu}_4\text{NHSO}_4$, DMF/ H_2O mixture) afforded no change in regiochemistry, yielding only compound **109** in 83 % yield (entry 7). Heck-type processes are usually performed in polar solvents, and under some reaction conditions, these solvents have been shown to stabilise the catalytically active intermediate [20]. Replacing DMF with toluene (chosen for its low dielectric constant) gave a chromatographically inseparable mixture of **109** and its regioisomer **110** in 59 % yield, in a 85:15 ratio (entry 8). Compound **109** was separated from **110** by recrystallisation. Characteristic shifts for the *exo*-cyclic methylene unit in **110** were observed as two doublets at 5.21 and 4.96 ppm, each with a 2J -coupling constant value of 1.5 Hz (see Fig. 2.2). Applying electron-rich phosphine ligands, $\text{P}(o\text{-tol})_3$ [44] and PMe_3 (entries 9 and 10), gave low to moderate yields for the formation of **109**. Bidentate phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) **134** gave only **109** in 88 % isolated yield (entry 11).

This survey of reaction conditions suggests that either there is an underlying preference for the formation of the quaternary isomer **109** (possibly via conformer **123** rather than **125**), or, that irrespective of the conditions employed, the same type of palladium species is responsible for the formation of **109** in each case. In relation to the latter, it has been suggested [34, 35] that for some examples the active catalyst is in fact nanoparticulate palladium(0) clusters, as opposed to the discrete, homogenous phosphine-bound monomeric species. Possible support for this argument was uncovered when ligand-free conditions (entry 12) gave a mixture of **109** and **110** in 72 % isolated yield in a ratio of 88:12. Asymmetric bidentate phosphine ligand (*R*)-BINAP **132** was studied since any enantioselectivity detected would be indicative of a step where the ligand is directly involved in the induction of asymmetry (i.e. directly bound to the metal centre). Replacing PPh_3 with (*R*)-**132** gave a racemic mixture of **109** and **110** in 91 % isolated yield in a ratio of 88:12 (entry 13). However, the use of conditions developed by Overman et al. [45], yielded compound **109** (41 %) with a low enantiomeric excess (ee) of 16 % (entry 10), suggesting that a phosphine-bound arylpalladium(II) species is involved, at least in some part, in a process that converts **108**–**109**. The enantiomers of **109** were resolved by high-performance liquid chromatography (HPLC).

After an extensive study of a range of reaction conditions to convert bromide **108**, the less reactive chloride **137** was synthesised in order to investigate how the rate of oxidative addition might impact on the overall reaction (Scheme 2.14).

**Scheme 2.15** Synthesis of dihydropyrrole **137****Scheme 2.16** Cyclisation of aryl chloride **137**

The chloro-Heck precursor **137** was prepared using commercially available 2-chlorobenzene sulfonamide as shown previously in Scheme 2.15.

Under identical conditions that furnished **109** from bromide **108** in 90 % yield (conditions **A** in Scheme 2.16), the use of chloride **137** gave **138** in a low 18 % yield. While it is appreciated that aryl chlorides are slow to undergo oxidative addition, it was reasoned that the electron-withdrawing effect of the *ortho*-sulfonamide functional group in **137** would assist with this process. Nevertheless, the use of electron-rich phosphine ligand *t*-BuBrettPhos **139** [46] gave **138** in 77 % yield (conditions **B**).

The reaction of halides **108/137** under a range of conditions gave exclusively, or in high selectivity, the quaternary regioisomer, even in examples with conditions thought to evoke a cationic pathway of type **127** (entries 5 and 6). It is well appreciated that the use of leaving groups triflates and nitrogen (diazonium salts) evoke a cationic palladium(0) species in the catalytic cycle of the Heck reaction. With this in mind, the Heck precursors **108/137** were modified to incorporate *pseudo*-halides (triflate and nitrogen groups, **139** and **140**). These labile leaving groups should not coordinate the intermediate arylpalladium(II) species (Fig. 2.1).

Aryl- and vinyl-triflates are routinely used as precursors for asymmetric Heck reactions. One classic example is the asymmetric construction of *cis*-decalin rings of type **142** by Shibasaki et al. in their synthesis of (+)-vernolepin [47]. The palladium catalysed arylation of olefins using arenediazonium salts is frequently referred to as the Matsuda-Heck reaction. Attractive features of this reaction are that aryldiazonium salts have a high reactivity at room temperature, and they do not require phosphine ligands to stabilise the active palladium species. This reaction has been employed in an intermolecular sense as the key step in Correia's racemic synthesis of the antidepressant paroxetine (Scheme 2.17) [48, 49].

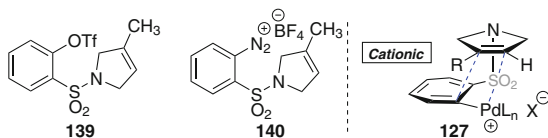
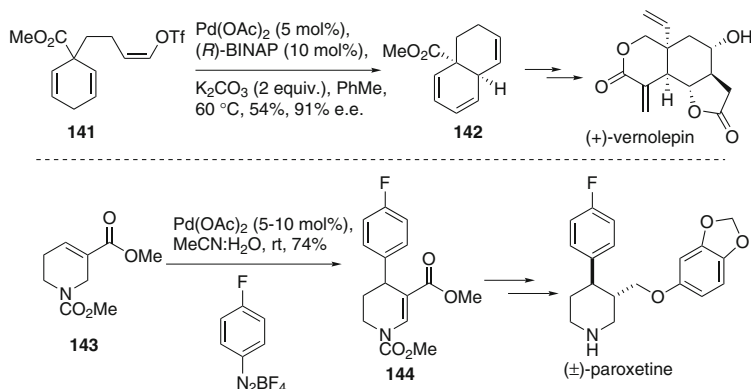


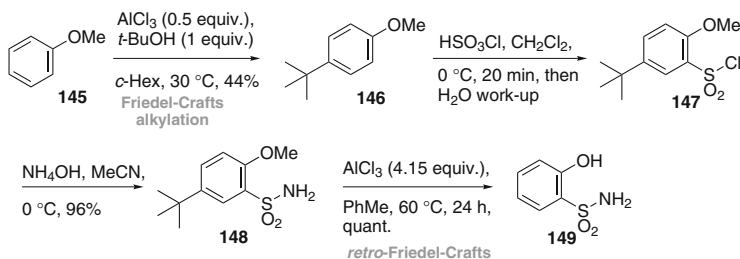
Fig. 2.1 Aryl triflate **139** and aryl diazonium salt **140**



Scheme 2.17 Examples of aryltriflates and aryldiazonium salts in total synthesis

Our first target, linked to the goal of probing how a cationic arylpalladium(II) species would participate in the intramolecular Heck reaction, was to synthesise the aryltriflate **139**. Our initial attempt towards this compound, was to use a Friedel-Crafts alkylation followed by a *retro*-Friedel-Crafts strategy [50] to access the required phenol functional group, is outlined in Scheme 2.18. This strategy allows us to perform electrophilic aromatic substitution at the *ortho*-positions by first blocking the *para*-position.

The reaction of anisole with *t*-butanol in the presence of Lewis acid AlCl_3 afforded the 1,4-disubstituted benzene **146** in a moderate 44 % isolated yield. Treatment of this material with chlorosulfonic acid, after water work-up, gave the

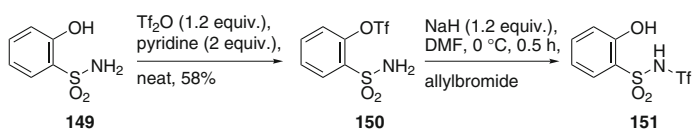


Scheme 2.18 Synthesis of 2-hydroxybenzene sulfonamide **149**

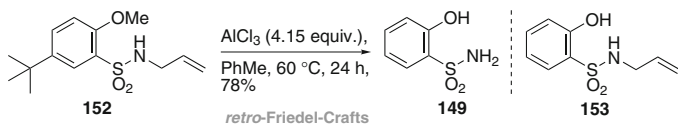
crude sulfonyl chloride **147** (one isomer detected in the ^1H NMR spectra), which was treated with excess ammonium hydroxide in MeCN to furnish sulfonamide **148** in an excellent 96 % isolated yield. A *retro*-Friedel-Crafts reaction, with AlCl_3 in refluxing toluene, cleaved both the *t*-butyl blocking group and the methyl ether, to afford 2-hydroxybenzene sulfonamide **149** [50] in quantitative yield. Conversion of phenol **149** to triflate **150** went smoothly (58 %). However, attempts to alkylate the nitrogen atom in compound **150** gave **151** as the sole product, resulting from migration of the triflate group (Scheme 2.19).

It was hoped that by pre-installing the allyl group (**152**) we could isolate the desired *N*-allyl sulfonamide **153** after the *retro* Friedel-Crafts reaction. However, only **149** was isolated resulting from cleavage of both alkyl groups and the nitrogen allyl group (Scheme 2.20).

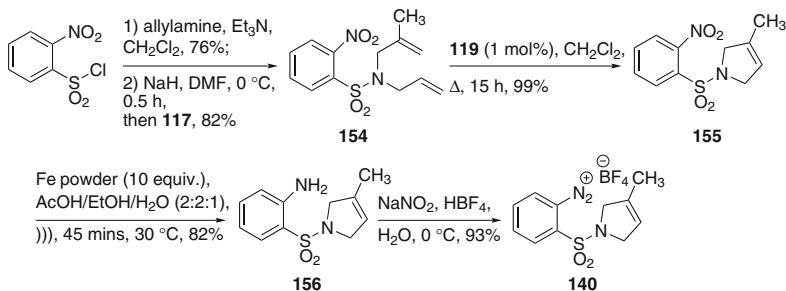
This route was then abandoned when it was realised, during our preparation of aryldiazonium salt **140** (Scheme 2.21), that the desired phenol **157** could be accessed from **140** via a Sandmeyer-type reaction.



Scheme 2.19 Attempts to alkylate sulfonamide **150**



Scheme 2.20 Attempts to access **153**



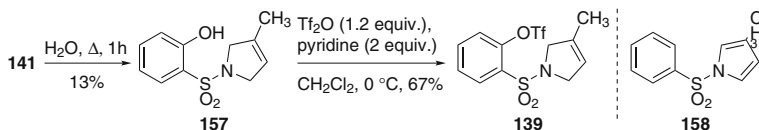
Scheme 2.21 Synthesis of tetrafluoroborate salt **140**

Commercially available 2-nitrobenzenesulfonyl chloride was converted into dihydropyrrole **155** over 3 steps using the standard chemistry we have developed to access these types of compounds. A chemoselective reduction of the nitro group was effected using Fe-AcOH in an ethanol/water mixture which gave **156** in 82 % isolated yield [51–53]. Diazonium-ion formation was achieved under typical conditions [48], obtaining salt **140**, after precipitation from cold ether/acetone, as a brown fluffy solid in 93 % yield. This material now serves two purposes for our studies; it can be used to access the requisite phenol for the preparation of aryltriflate **139**, and it can itself be used as a substrate in a Matsuda-Heck reaction.

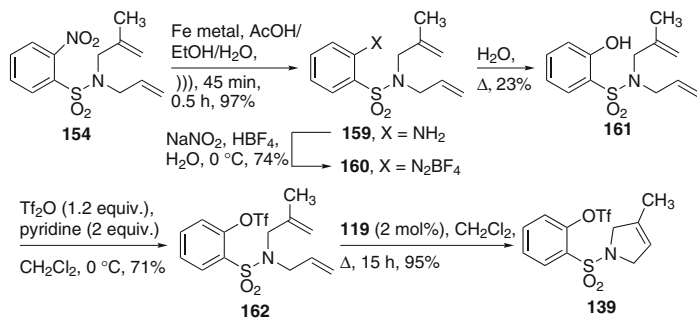
Heating **140** in water (either at pH 4 or 7) generated phenol **157** in poor yields of 10–20 %. *N*-sulfonylpyrrole **158** was always formed as a side product, along with coloured material that could not be characterised. Attempts to obtain higher yields for the hydrolysis of **140** to access the phenol were unsuccessful. Following a literature procedure [54], the use of Cu(II) salts gave only pyrrole **158** [55]. However, with sufficient material in hand, the synthesis of aryltriflate **139** was realised using triflic anhydride (Tf₂O) in neat pyridine in 67 % from phenol **157** (Scheme 2.22).

Unsatisfied with the poor yield obtained for the formation of phenol **157**, and to avoid the competing pyrrole formation reaction, it was reasoned that the unwanted oxidation, presumably favoured by aromaticity, would be avoided if the acyclic diazonium salt **140** was used instead (Scheme 2.23).

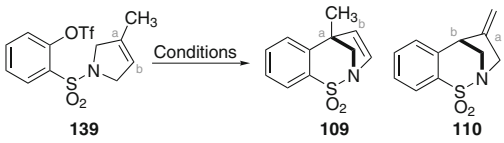
Nitro reduction of **154** cleanly gave aniline **159** in an excellent 97 % isolated yield, which was then converted to the diazonium salt **160** (74 %). Hydrolysis of **160** gave phenol **161** in low yields of 20–25 %. Nevertheless, the reaction was reproducible and thus provided sufficient material for our synthetic purposes.



Scheme 2.22 Synthesis of aryltriflate **139**



Scheme 2.23 Alternative route to **139**

Table 2.2 Intramolecular Heck reaction of aryltriflate **139**


Entry	Conditions	Product(s) ^a (% yield; ratio)
1	Pd(OAc) ₂ (10 mol%), PPh ₃ (20 mol%), K ₂ CO ₃ , DMF, 110 °C	109 (15), 157 (55)
2	[Pd(PPh ₃) ₄] (10 mol%), Et ₃ N, THF, 110 °C	109 (14), 139 (50)
3	[Pd(dba) ₂] (5 mol%), (<i>R</i>)-BINAP 132 (11 mol%), PMP 133 , DMF, 110 °C	109 (93), 17% ee

^a Isolated yields after purification by column chromatography^b Ratio determined by ¹H NMR spectroscopy

Phenol **161** was converted into triflate **162** (71 %) and a ring-closing metathesis reaction provided **139** in 95 %.

Cyclisation of **139** under our standard Heck conditions (Table 2.2, entry 1) provided quaternary regioisomer **109** in a low 15 % yield. However, phenol **157** was isolated as the major product (55 % yield).

We reasoned that this was due to the presence of water in the reaction conditions, a process presumably facilitated by the *ortho* electron-withdrawing sulfonyl moiety. A literature procedure for the cross-coupling of enoltriflates [56] gave poor conversion for the reaction, affording **109** and starting material **139** in 14 % and 50 % isolated yield respectively (in entry 2). In contrast, conditions developed by Overman et al. [23, 45]. (palladium(0)-BINAP) gave compound **109** in an excellent 94 % isolated yield, albeit with a low e.e. Interestingly, this result (entry 3) is almost identical in terms of yield and enantioselectivity observed with bromide **108** in Table 2.1, entry 14. In conclusion, unexpectedly employing triflate **139** in the Heck reaction in order to evoke a cationic reaction pathway (Scheme 2.14) did not alter the regiochemical outcome observed in Scheme 2.13.

Correia et al. recently reported the first example of a series of intramolecular Matsuda-Heck reactions [57]. With this report in mind, the Heck reaction was attempted on tetrafluoroborate **140**. Thus, treatment of tetrafluoroborate salt **140** with a palladium(0) source ([Pd(dba)₂] or [Pd(PPh₃)₄]) in the presence of K₂CO₃ in acetonitrile at room temperature led to the isolation of **109** in low yields, in a process which was accompanied by the formation of pyrrole **158**, and dihydropyrrole **163** [55] as side products (Table 2.3, entries 1 and 2).

Switching the reaction conditions to sodium acetate in dichloromethane [58] led to reduced pyrrole formation, albeit compound **109** was isolated in a low 28 % yield (entry 3). No material attributable to regioisomer **110** was detected in entries 1–3. However, an interesting result was observed in entry 4 when base-free ligand-free conditions [59] were applied; a chromatographically inseparable mixture of **109** and **110** was isolated in 26 % yield. Analysis of the ¹H NMR spectra showed that for the first time we observed the formation of regioisomer **110** preferentially over the

Table 2.3 Intramolecular Heck reaction of **140**

Entry	Conditions	Product(s) ^a (% yield; ratio)
1	[Pd(dba) ₂] (10 mol%), K ₂ CO ₃ , MeCN, rt	109 (18), 158 (49), 163 (18)
2	[Pd(PPh ₃) ₄] (10 mol%), K ₂ CO ₃ , MeCN, rt	109 (27), 158 (27), 163 (3)
3	[Pd(dba) ₂] (10 mol%), NaOAc, CH ₂ Cl ₂ , rt	109 (28), 158 (10)
4	Pd(OAc) ₂ (10 mol%), MeOH, 50 °C	109/110 (26, 20:80) ^[b] , 158 (37)

^a Isolated yields after purification by column chromatography^b Ratio determined by ¹H NMR spectroscopy

formation of **109** in a 80:20 ratio. The formation of pyrrole **158** (37 %) was still a complication. Recrystallisation of the mixture of regioisomers from cyclohexane gave predominantly **110**, which allowed unambiguous assignment (see Fig. 2.2) and confirmation of the minor side-product encountered in Table 2.1 (entries **12** and **13**).

In summary, studies conducted towards altering the regiochemical outcome of the Heck reaction through condition screening and changing the aryl-leaving group indicated a high preference for the formation of the quaternary isomer **109**.

It was then felt that changing the alkenyl substituent on the dihydropyrrole ring might be instructive. Based on this, sulfonamides **164** and **165** were considered for their steric and electronic effect on the alkene (Scheme 2.24).

It was previously highlighted (Scheme 2.5) that the Heck arylation of styrenes generally occurs regioselectively at the least substituted carbon (labelled with a grey dot in compound **164**). While arylation of alkyl-substituted olefins produce a mixture of regioisomers, where sterics are thought to dictate regioselectivity, it seemed appropriate to investigate compound **164**.

Retrosynthetically, these compounds can be accessed by alkylating the common starting material in our sulfonamide synthesis (**112**) with electrophiles of the type **166/167**. These alkylating reagents are not commercially available. Thus α -bromo ketones **169** and **173** were prepared, using a literature procedure [60] (Scheme 2.25).

Alkylation of **112** with the appropriate electrophile, **169/173**, provided ketones **170** (65 %) and **174** (79 %). Analysis of the carbon NMR spectra data showed signals at 193 ppm (for compound **170**) and at 209 ppm (for compound **174**), characteristic for the ketone functional group. Conversion of the carbonyl functional group into a methylene unit was then attempted. Reaction of **170** under standard Wittig conditions, or with the highly reactive Tebbe reagent **176** [61, 62] was successful. However, synthetically useful quantities of **171** were not easily obtained. Interestingly, under the same set of conditions no reaction was observed for the *t*-butyl compound **174**, possibly due to the steric hinderance of the *t*-butyl group.

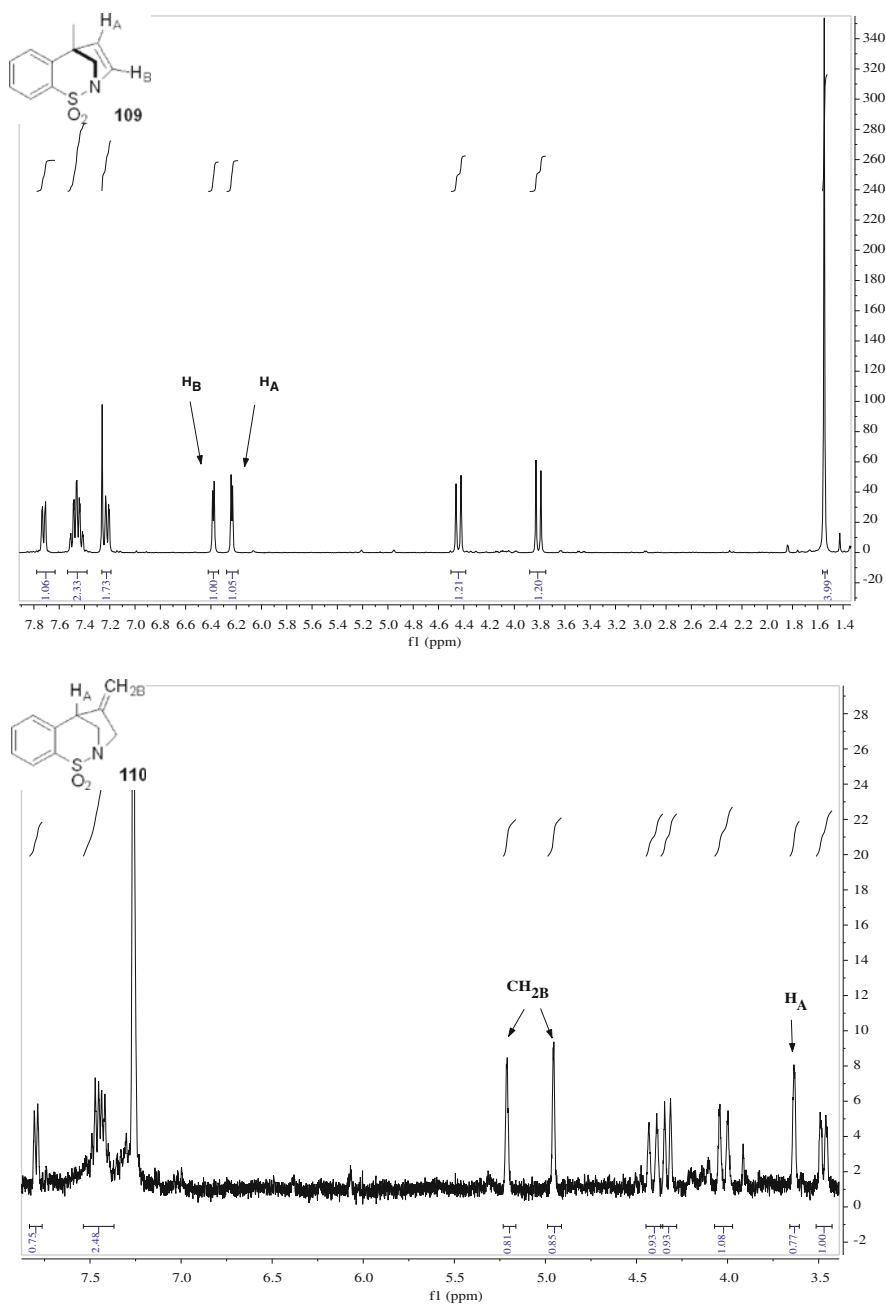
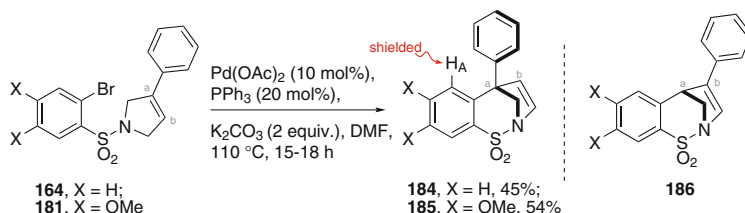


Fig. 2.2 ^1H NMR spectra of regioisomers **109** (top) and **110** (bottom)



Scheme 2.27 Intramolecular Heck reaction of **164/181**

Firstly, the intramolecular Heck reactions of styrene-derivatives **164/181** were studied under our standard Heck conditions (Scheme 2.27).

The Heck reaction of both compounds **164** and **181** provided quaternary isomers **184** (45 %) and **185** (54 %), respectively, with traces of starting material also detected in the proton spectrum of the crude reaction mixture. None of the regioisomeric product **186** was isolated. Formation of the alkene was confirmed by ^1H NMR analysis by the presence of characteristic doublets in the alkene region. Interestingly, the aromatic proton, H_A , was found to be shielded by the adjacent phenyl ring and is observed in the ^1H NMR spectra as a singlet at 6.65 ppm for compound **184**, and at 6.11 ppm for compound **185**. The origin of this effect can be seen in the X-ray crystal structure of **184** (Fig. 2.3).

Next, the Heck reaction of **165** and **182** was considered and in both cases material for the tertiary regioisomers **188** and **190** was detected in the proton NMR spectra, along with quaternary isomers **187** and **189**. Fortunately, these regioisomers proved separable by column chromatography, allowing access to material for characterisation purposes (Scheme 2.28).

Pyrrole **191** formation, accompanied by halogen-proton exchange, was also observed during the cyclisation of **165**. Diagnostic shifts in the ^1H NMR spectra for the tertiary carbon (labelled H_A) were seen at 3.28 ppm for both **188** and **190**.

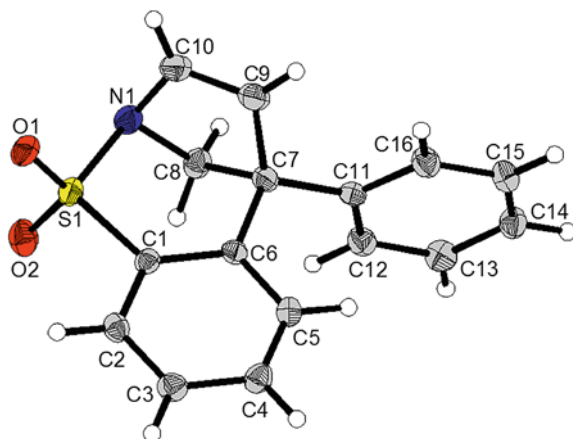
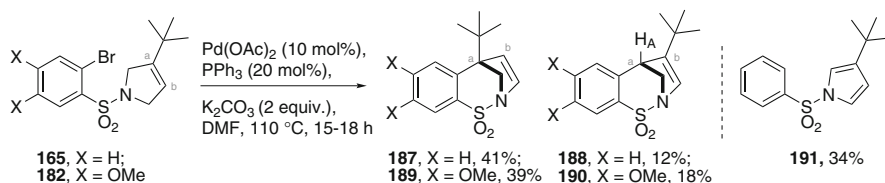


Fig. 2.3 X-ray crystal structure of **184**



Scheme 2.28 Intramolecular Heck reaction of **165/182**

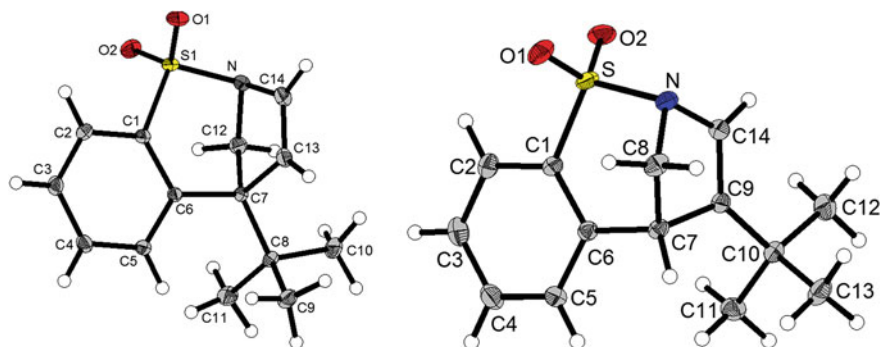


Fig. 2.4 X-ray crystal structures of **187** (left) and **188** (right)

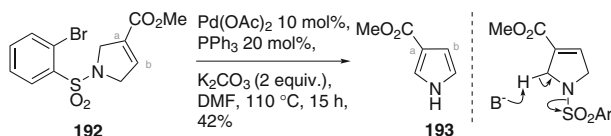
Structural confirmation of the regioisomers formed was achieved by X-ray crystallography (Fig. 2.4).

It should be noted that, following several attempts, the outcome observed from the Heck reaction of **165/182** is reproducible in terms of the ratio of products obtained.

Having obtained a sample of methyl ester **192** (previously prepared in the Evans group) its Heck cyclisation was attempted (Scheme 2.29).

Unfortunately, in this case no products for the Heck cyclisation were detected. Instead pyrrole **193**, most likely resulting from a base-catalysed sulfinate elimination reaction followed by isomerisation [65], was isolated as the sole product (43 %).

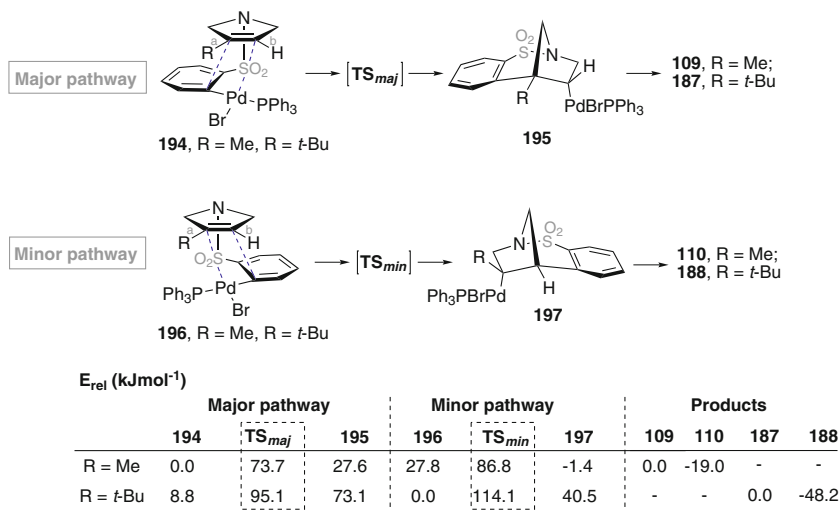
The investigation into the use of alternative alkenyl substituents in order to alter the regioselectivity demonstrated, yet again, an underlying preference for the



Scheme 2.29 Formation of pyrrole **193**

formation of the quaternary isomer, observed either as the sole product (**109/184/185**), or as the major isomer (**187/189**).

Mechanistic details of Heck reactions have been successfully interrogated computationally using density functional theory (DFT) methods [66]. Based on these precedents, we felt that a similar study might provide a basis for the regioselectivity that is experimentally observed. DFT studies were performed using the classic neutral Heck reaction pathway for the methyl and *t*-butyl substituents. These calculations were performed by our collaborators, Prof. Isabel Rozas (Trinity College Dublin, Ireland) and Prof. Ibon Alkorta (Instituto de Quimica Medica (IQM-CSIC), Spain). Calculations were performed on the likely chemical species involved in the regiochemistry setting event. Following a step-wise procedure, starting with simple computational methods up to the highest level readily considered, the Heck reaction of **108** and **165** ($R = \text{Me}$ and *t*-Bu) was studied. Results were obtained using a B3LYP DFT function with the 6-31G* basis set for all the atoms, except for palladium, which used the pseudopotential LANL2DZ(d), and bromine that is described by LANL2DZ. This consideration enabled the characterisation of the possible complexes involved in the regiochemical setting sequence. Scheme 2.30 describes possible intermediates in the major pathway (based on experimental results) and in the corresponding minor pathway. Both conformations of the square planar alkene-complex were investigated where $R = \text{methyl}$ and where $R = t\text{-butyl}$. Since regioselectivity is governed by the alkene-insertion event (carbopalladation), only the possible intermediates after the oxidative addition step were only considered.



Scheme 2.30 DFT calculations performed for the regiochemistry-establishing sequence in which $R = \text{Me}$ or *t*-Bu

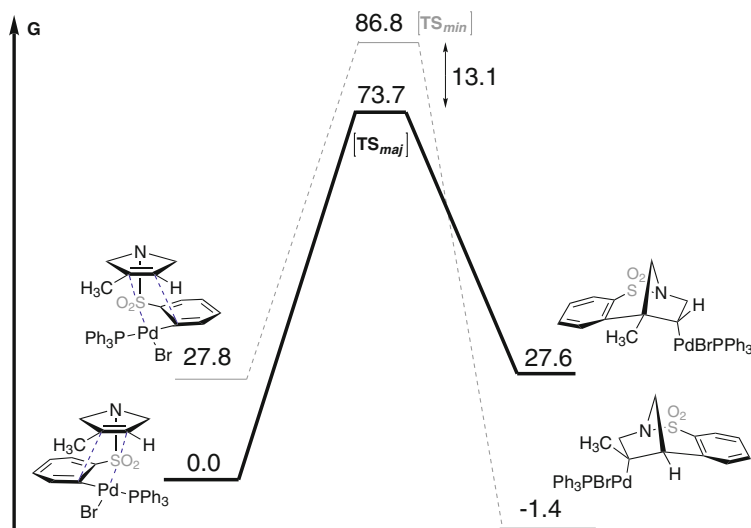


Fig. 2.5 Possible reaction pathways for the intramolecular Heck reaction of **108**, with free energies in kJmol^{-1}

A comparison of the possible final Heck products **109/187** and **110/188**, for both Me and *t*-Bu substituents, found that the experimentally observed *minor* product, the tertiary regioisomer, was more stable by 19 and 48.1 kJmol^{-1} for R = Me and *t*-Bu, respectively (Scheme 2.30). Next, the relative energies associated with the square planar carbopalladated intermediates **194** versus **196** (again for both R = Me and *t*-Bu) were calculated and were found to vary on the identity of the R-substituent.

The energies associated with the transition states in the pathway towards the carbopalladated intermediates **195** and **197** were considered for both the major pathway (based on experimental results) and the minor pathway. For both substituents (R = Me and *t*-Bu), the transition state associated with the major pathway (TS_{maj}) was found to be the most stable. The energy difference between the pathways (13.1 and 19 kJmol^{-1} for R = Me and *t*-Bu, respectively) was lower than expected, considering the overriding preference for the formation of the quaternary isomer (Fig. 2.5).

From these results it can be concluded that the key step in the formation of the major-pathway product depends mostly on the stability of the TS, despite the stability of the final products (which favours formation of products through the minor pathway).

In summary, this DFT study provides corroborative evidence for the experimental study and indicates that the reason for the counter-intuitive regiochemical outcome is kinetic. Product selection occurs because the transition state associated with formation of the quaternary centre is lower in energy. However, based on the relatively low difference in energies between the competing transition states, it

		δ_{H}	δ_{C}
	198	5.7 ppm	125 ppm
	108	5.4 ppm	119 ppm 135 ppm
	165	5.3 ppm	115 ppm 148 ppm
	164	6.0 ppm	118 ppm 132 ppm
	233	5.4 ppm	114 ppm 142 ppm

(synthesis discussed in Chapter 3)

Fig. 2.6 Chemical shifts for Heck precursors **198**, **108**, **165**, **164** and **233**

would appear that for a reaction performed at elevated temperatures, DFT can only partly address the origin of selectivity.

The ^1H and ^{13}C NMR chemical shifts of the methine functional group and the alkenyl carbon of the participating Heck precursors have been summarised in Fig. 2.6. All protons contain a similar chemical shift except for the styrene derivative, whose proton is slightly deshielded by the adjacent phenyl ring, appearing at 6.0 ppm in the ^1H NMR spectrum. The same trend is observed in the carbon chemical shifts. In comparison, the substituted alkenyl carbon (in bold) for all compounds have a higher chemical shift in the carbon spectrum, downfield from the neighbouring C–H which is not undergoing C–C bond formation, suggesting that the alkenyl carbon is more electropositive than the methine group.

An interesting substrate to attempt our intramolecular Heck cyclisation would be the trimethylsilyl-derivative **199** (Fig. 2.7), where the TMS-substituent should have a stronger influence on the electronics of the alkene, and consequently might have a different outcome in our intramolecular Heck reaction.

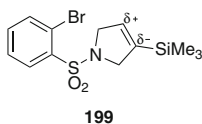


Fig. 2.7 TMS-substituted Heck precursor **199**

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Selectivity in the Synthesis of Cyclic Sulfonamides

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