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
then undergoes a $\beta$-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 carbo-palladation 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
(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.
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 2.5** Regioselectivity observed during arylation insertion process

**Scheme 2.6** Rigby’s example of 5-*exo* and 6-*endo*, reagent controlled intramolecular Heck reaction
Following the initial 6-exo-trig cyclisation (93 → 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 → 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 → 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
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 Mérail, where R = 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 → 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.
A ring-closing metathesis (RCM) reaction of 113 and 116 in the presence of catalytic amounts of the Hoveyda-Grubbs second generation catalyst \[119\] 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 (Pd(OAc)$_2$ (10 mol\%), PPh$_3$ (20 mol\%), K$_2$CO$_3$ (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 $^1$H 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\% Pd(OAc)$_2$/2 mol\% PPh$_3$ providing 109 in 84 \% yield. Microwave irradiation \[20\] was briefly investigated as an alternative to standard conductive
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 isomers 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 [Pd(OAc)2/3(PPh3)] the identity of the palladium(0) species is the anionic complex [Pd(OAc)(PPh3)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](image-url)
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product(s)a (%) yield, ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Pd(PPh₃)₄] (10 mol%), K₂CO₃, DMF, 110 °C</td>
<td>109 (72)</td>
</tr>
<tr>
<td>2</td>
<td>Pd/C 10% w/w (10 mol%), Et₃N, MeCN, 50 °C</td>
<td>108 (85)</td>
</tr>
<tr>
<td>3</td>
<td>Herrmann-Beller cat. 130 (10 mol%), K₂CO₃, DMF, 110 °C</td>
<td>109 (69)</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), Et₃N, DMF, 110 °C</td>
<td>109 (69)</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), proton sponge 131, DMF, 110 °C</td>
<td>109 (34)</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), Ag₂CO₃, DMF, 110 °C</td>
<td>109 (24), 108 (35), 129 (6)</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), K₂CO₃, n-Bu₄NHSO₄, DMF-H₂O (9:1), 110 °C</td>
<td>109 (83)</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), K₂CO₃, PhMe, 110 °C</td>
<td>109/110 (59, 85:15)J91</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)₂ (10 mol%), P(o-tol)₃ (20 mol%), Et₃N, DMF, 110 °C</td>
<td>109 (10), 108 (75)</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)₂ (10 mol%), PMe₃ (1M soln in THF, 20 mol%), K₂CO₃, DMF, 110 °C</td>
<td>109 (56)</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)₂ (10 mol%), dppp 134 (20 mol%), K₂CO₃, DMF, 60 °C</td>
<td>109 (88)</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)₂ (10 mol%), K₂CO₃, DMF, 110 °C</td>
<td>109/110 (72, 88:12)J91</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)₂ (10 mol%), (R)-BINAP 132 (20 mol%), K₂CO₃, DMF, 110 °C</td>
<td>109/110 (91, 88:12)J91, 0% ee</td>
</tr>
<tr>
<td>14</td>
<td>[Pd(dba)₂] (10 mol%), (R)-BINAP 132 (23 mol%), PMP, 133, DMF, 110 °C</td>
<td>109 (41), 16% ee</td>
</tr>
</tbody>
</table>

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 Ag₂CO₃ 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-Bu₄NHSO₄, DMF/H₂O 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 J-coupling constant value of 1.5 Hz (see Fig. 2.2). Applying electron-rich phosphine ligands, P(o-tol)₃ [44] and PMe₃ (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 PPh₃ 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).
The chloro-Heck precursor 137 was prepared using commercially available 2-chlorobenzene sulfonyl chloride 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 aryl diazonium 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].
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 AlCl₃ 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](image-url)
crude sulfonyl chloride 147 (one isomer detected in the $^1$H 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 aryl diazonium salt 140 (Scheme 2.21), that the desired phenol 157 could be accessed from 140 via a Sandmeyer-type reaction.

![Scheme 2.19](image_url)

**Scheme 2.19** Attempts to alkylate sulfonamide 150

![Scheme 2.20](image_url)

**Scheme 2.20** Attempts to access 153

![Scheme 2.21](image_url)

**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
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 dihydro-pyrrole 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>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product(s)a (% yield, ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)2 (10 mol%), PPh3 (20 mol%), K2CO3, DMF, 110 °C</td>
<td>109 (15), 157 (55)</td>
</tr>
<tr>
<td>2</td>
<td>[Pd(PPh3)4] (10 mol%), Et3N, THF, 110 °C</td>
<td>109 (14), 139 (50)</td>
</tr>
<tr>
<td>3</td>
<td>[Pd(dba)2] (5 mol%), (R)-BINAP 132 (11 mol%), PMP 133, DMF, 110 °C</td>
<td>109 (93), 17% ee</td>
</tr>
</tbody>
</table>

a Isolated yields after purification by column chromatography
b Ratio determined by 1H NMR spectroscopy
formation of \textit{109} in a 80:20 ratio. The formation of pyrrole \textit{158} (37 \%) was still a complication. Recrystallisation of the mixture of regioisomers from cyclohexane gave predominantly \textit{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 \textit{109}.

It was then felt that changing the alkenyl substituent on the dihydropyrrole ring might be instructive. Based on this, sulfonamides \textit{164} and \textit{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 \textit{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 \textit{164}.

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

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

---

\textbf{Table 2.3} Intramolecular Heck reaction of \textit{140}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product(s)\textsuperscript{a} (% yield; ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Pd(dba)\textsubscript{2}] (10 mol%), K\textsubscript{2}CO\textsubscript{3}, MeCN, rt</td>
<td>\textit{109} (18), \textit{158} (49), \textit{163} (18)</td>
</tr>
<tr>
<td>2</td>
<td>[Pd(PPh\textsubscript{3})\textsubscript{4}] (10 mol%), K\textsubscript{2}CO\textsubscript{3}, MeCN, rt</td>
<td>\textit{109} (27), \textit{158} (27), \textit{163} (3)</td>
</tr>
<tr>
<td>3</td>
<td>[Pd(dba)\textsubscript{2}] (10 mol%), NaOAc, CH\textsubscript{2}Cl\textsubscript{2}, rt</td>
<td>\textit{109} (28), \textit{158} (10)</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)\textsubscript{2} (10 mol%), MeOH, 50 °C</td>
<td>\textit{109}/\textit{110} (26, 20:80)\textsuperscript{b}, \textit{158} (37)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yields after purification by column chromatography
\textsuperscript{b} Ratio determined by \textsuperscript{1}H NMR spectroscopy
Fig. 2.2 $^1$H NMR spectra of regioisomers 109 (top) and 110 (bottom)
Direct access to electrophiles was realised via allylic bromination (Wohl-Ziegler reaction) of commercially available olefins with N-bromosuccinimide (NBS) in refluxing chloroform [30, 63, 64] (Scheme 2.26). These alkylation agents were used without further purification and under our standard sulfonamide-alkylation conditions, using N-allyl sulfonamides and (electron-rich), diallyl compounds were obtained in moderate to high yields.

In terms of relating this sequence to that depicted in Scheme 2.12 (where R = Me), a higher loading (5 mol%) of ruthenium catalyst in refluxing CH$_2$Cl$_2$ was required to obtain the desired Heck precursors in high yields.

**Scheme 2.24** Retrosynthetic analysis of compounds 164/165

**Scheme 2.25** Methylenation of ketones 170/174

Direct access to electrophiles 166/167 was realised via allylic bromination (Wohl-Ziegler reaction) of commercially available olefins 177/178 with N-bromosuccinimide (NBS) 183 in refluxing chloroform [30, 63, 64] (Scheme 2.26). These alkylation agents were used without further purification and under our standard sulfonamide-alkylation conditions, using N-allyl sulfonamides 112 and (electron-rich) 115, diallyl compounds 117/179/175/180 were obtained in moderate to high yields.

In terms of relating this sequence to that depicted in Scheme 2.12 (where R = Me), a higher loading (5 mol%) of ruthenium catalyst 119 in refluxing CH$_2$Cl$_2$ was required to obtain the desired Heck precursors 164/181/165/182 in high yields.

**Scheme 2.26** Preparation of sulfonamides 164/181/165/182
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 $^1$H NMR analysis by the presence of characteristic doublets in the alkene region. Interestingly, the aromatic proton, HA, was found to be shielded by the adjacent phenyl ring and is observed in the $^1$H 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 $^1$H NMR spectra for the tertiary carbon (labelled HA) were seen at 3.28 ppm for both 188 and 190.

![Scheme 2.27 Intramolecular Heck reaction of 164/181](image)

![Fig. 2.3 X-ray crystal structure of 184](image)
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 2.28** Intramolecular Heck reaction of \(165/182\)

**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 \(R = \text{methyl and where } R = t\)-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](image-url)
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
would appear that for a reaction performed at elevated temperatures, DFT can only partly address the origin of selectivity.

The $^1$H 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 $^1$H 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. 2.6 Chemical shifts for Heck precursors 198, 108, 165, 164 and 233

Fig. 2.7 TMS-substituted Heck precursor 199
References

References

64. Djerassi C (1948) Chem Rev 43:271
Selectivity in the Synthesis of Cyclic Sulfonamides
Application in the Synthesis of Natural Products
Geoghegan, K.
2014, XIII, 151 p. 257 illus., 24 illus. in color., Hardcover
ISBN: 978-3-319-10337-2