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Regioselectivity in the Intramolecular Heck Reaction of a Series of Cyclic Sulfonamides: An Experimental and Computational Study

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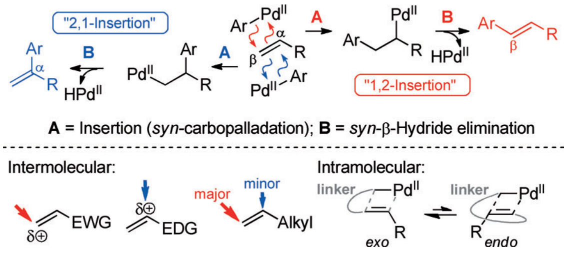
Abstract: Regioselectivity in the intramolecular Heck reaction of a series of *N*-sulfonyl-2,5-dihydro-3-substituted pyrroles was studied. These substrates are unbiased in terms of the formed ring size of the new heterocycle. Results indicate that high levels of regioselectivity are observed under a range of conditions, and that there is an underlying propensity for carbon–carbon bond formation at the most hindered end of the alkene. For two examples (3-Me and 3-*t*Bu), DFT calculations were performed and indicate that in both cases, the modelled transition state for carbopalladation is energetically lower for the experimentally preferred isomer.

Keywords: catalysis · cyclization · density functional calculations · Heck reaction · palladium · regioselectivity

Introduction

The Heck (Mizoroki–Heck) reaction represents a general method for the construction of carbon–carbon bonds and is widely used in both its inter- and intramolecular guises.[1] Various aspects of the reaction arguably contribute to this popularity, including functional group tolerance, its use in the construction of complex molecules, and its ability (particularly in its intramolecular form) to form bonds and structural motifs that would be difficult to achieve by alternative means. An example is its capacity to form what would be considered sterically demanding tertiary and quaternary centres. Impressive asymmetric examples of this reaction have also been reported.[2] Recently, one significant limitation of the reaction, that the halide- or pseudo-halide-substituted carbon atom needed to be sp^2 hybridised or lack a β-hydrogen atom, has been circumvented; albeit only for a limited range of substrates at this stage.[3]

The location, or regiochemistry, of the newly formed carbon–carbon bond is of great interest, in part because this selectivity sheds light on the mechanisms involved in the overall alkenylation process. Because the Cossée–Arlman-type alkene-insertion reaction (step A, Scheme 1) is considered to be irreversible, the formation of the substituted alkene is dictated by this process. Evidence has indicated that the regioselective outcome of the Heck reaction depends on several critical features. The electronic features of the alkene play a significant role and, typically, carbon–carbon bond formation takes place exclusively or preferentially at the most electron-poor carbon atom (indicated by an arrow in Scheme 1).[1,4,5] For situations in which alkene polarisation is less dramatic, for example, in compounds with an alkyl substituent, steric effects are said to dominate and the major site of carbon–carbon bond formation is at the less-substituted or less-sterically encumbered alkenyl carbon atom. It should be noted that this widely held consideration implies that the aromatic portion of the intermediate complex possesses greater steric burden than the palladium fragment.[1a]



Scheme 1. Regioselectivity in the inter- and intramolecular Heck reaction. Ar = aryl; EWG = electron-withdrawing group (e.g., CO_2R, Ar); EDG = electron-donating group (e.g., OR).

The nature of the reaction conditions employed are also important because these dictate the identity, in terms of the ancillary ligands and charge on palladium, of the entity undergoing insertion. For example, if the reaction is performed in a way that favours an electron-deficient, cationic, aryl–palladium(II) species, as opposed to an electron-rich, neu-

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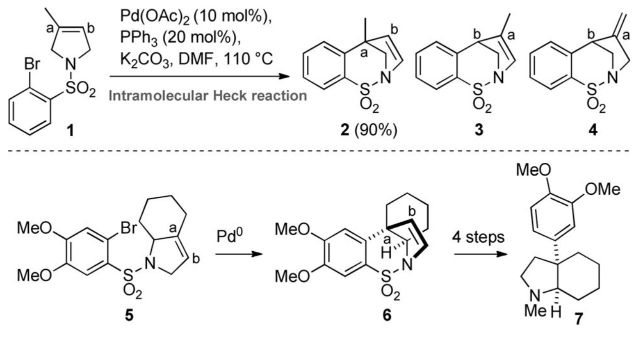
tral, aryl–palladium(II) species (either with an aryl/vinyl triflate, or with certain additives/solvents), then a dramatic reversal in the regiochemistry of the resulting product (indicated by arrows in Scheme 1) can be observed.[4,6] Coordination between the metal and a Lewis basic group on the substrate has also been used to provide regioselectivity during intermolecular Heck reactions.[7]

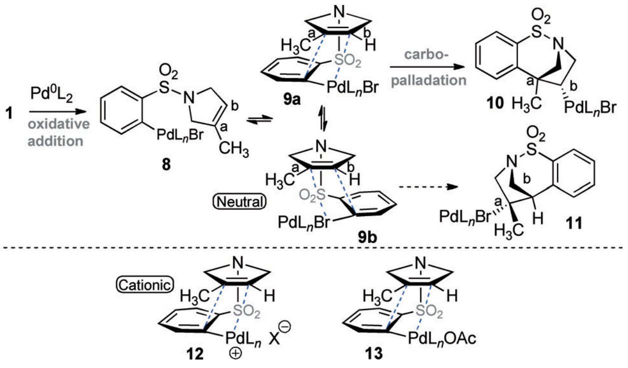
In relation to the regiochemical outcome of intramolecular Heck reactions, the rules discussed above are not completely applicable because the presence of a tether linking the reactive entities plays a dominant role. Numerous examples demonstrate how the size of the newly formed cyclic fragment and conformational effects associated with the tether can override any electronic bias the alkene may possess.[8] An explanation for this behavioural divergence is linked to the ideal eclipsed orientation between the alkene and the carbon–palladium(II) bond required for synchronous carbopalladation, which, although there are exceptions, most favourably occurs following alkene insertion by an *exo* mode of action (Scheme 1). Thus, in terms of the intramolecular Heck reaction, one may state that it is the *exo* mode and the size of the newly formed ring that is of most importance when considering the regiochemistry that is observed.

To date, what is lacking in relation to the intramolecular Heck reaction are examples in which carbon–carbon bond formation at either end of an unsymmetrically substituted alkene would lead to identically sized, newly formed rings.[9] If substrates of this type could be designed, then insights into the alkene-insertion event could be uncovered. For several years,[10] we have been interested in the intramolecular Heck reaction of cyclic *N*-sulfonyl compounds and we have recently uncovered a highly regioselective process.[11] Treatment of **1** with a palladium(0) pre-catalyst gave the adduct **2**, resulting from selective bond formation at position a, in excellent isolated yield (Scheme 2). No regioisomeric material attributable to the isomer **3** or its alkene isomer **4**, which would both result from carbon–carbon bond formation at position b, was observed. This is notable because the selectivity observed in this case is not governed by the size of the ring that is formed. Subsequently, this same type of regioselectivity was successfully employed in the conversion of **5** into **6** to introduce the aromatic portion of the octahydroindole alkaloid mesembrane (**7**). Based on the fact that these intramolecular Heck reactions were performed at elevated temperatures, the high level of regioselectivity that was detected appears to be indicative of an underlying reactivity preference for this type of intramolecular process.



Scheme 2. Regioselectivity in the intramolecular Heck reaction of sulfonamides.

Although much has been written concerning the mechanism of the Heck reaction, it is fair to say that the precise mechanism, or mechanisms, by which the Heck reaction proceeds are still not completely understood.[1,2] Based on the accepted pathway, which involves a coordinatively unsaturated palladium(0) species (that may be stabilised by associated ligands) as the entity that undergoes oxidative addition with **1**, the formation of a neutral palladium(II) species that resembles **8** can be envisaged (Scheme 3). Alkene association, probably accompanied by the loss of one 2-electron ligand, leads to a square-planar, or distorted square-planar, alkene–palladium(II) complex of the type **9**. Subsequent carbopalladation may occur *via* conformer **9a** or **9b** to generate product **10** or **11**, respectively. Because this carbopalladation event is irreversible,[1e,g] selectivity at this stage governs the formation of product **2** following the β-hydride elimination of **10**. Alternatives to this neutral pathway have also been well-discussed. If a leaving group (X) with weaker ligand donor properties, such as the triflate group, is employed, then a cationic reaction intermediate becomes possible; for example, intermediate **12** is of particular significance when bidentate asymmetric ligands are used. Jutland and Amatore[1g,12] have proposed that under $Pd(OAc)_2/PPh_3$ conditions, the palladium(0) source that participates in the initial oxidative addition is $[Pd(PPh_3)_2OAc]^-$, which results in intermediates such as **13** undergoing carbopalladation. In addition to the homogeneous reaction intermediates, investigations into the impressive turnover numbers achieved by some palladacycle catalysts (e.g., **32**) led to the suggestion that these species serve as a reservoir of the real catalyst, nanoparticulate colloidal palladium(0), and that this ligand-free material serves as an effective catalyst.[13]



Scheme 3. Plausible reaction pathways for the regioselective carbopalladation of **1**.

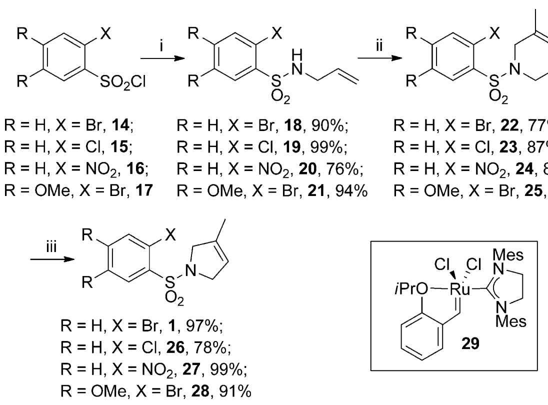
Thus, current evidence suggests that it is very likely that more than one distinct reaction pathway exists for the Heck reaction, depending on the type of reaction conditions employed and the type of reaction substrate. Based on this, we felt that selection of the type of intermediate undergoing carbopalladation during the regiochemistry-establishing event, that is, **9**, **12** or **13** (Scheme 3), might enable us to challenge the regiochemical preference uncovered in the previous work.[11]

Herein, we report studies aimed at understanding and probing this regioselective reaction. Specifically, we aimed to uncover any effect that the choice of reaction conditions has on this process, and to establish whether the identities of the palladium catalyst or pre-catalyst, the ligand (bidentate, σ-donor capacity, etc.), the solvent, the base or the halide/pseudo-halide have any role. We also sought to study any effect that the variation of the alkenyl substituent has on the reaction, and designed alternative Heck-reaction substrates that offered different polarisation of the alkenyl group and possessed different steric considerations.

Results and Discussion

Commercially available 2-bromobenzene sulfonyl chloride (**14**), 2-chlorobenzene sulfonyl chloride (**15**), 2-nitrobenzene sulfonyl chloride (**16**) and then 2-bromo-3,4-dimethoxybenzene sulfonyl chloride (**17**; prepared from 2-bromo-3,4-dimethoxybenzene)[10a] were converted into their respective allylamine adducts **18**–**21**. Subsequent alkylation with 3-chloro-2-methylpropene, followed by ring-closing metathesis (RCM) in the presence of **29**,[14] efficiently generated the *N*-sulfonyldihydropyrrole derivatives **1** and **26**–**28** (Scheme 4). The nitro derivative **27** was prepared to provide access to the corresponding triflate (see Scheme 5). The ring-closing metathesis took place at room temperature, but optimal yields were obtained when the solution was heated at reflux.

With the materials **1**, **26** and **28** in hand, a systematic survey of reaction parameters was undertaken (Table 1). As indicated in Table 1, entry 1, when a palladium(0) source was used directly, no significant difference in the yield or regioselectivity to that previously reported (Scheme 2)[11] was encountered. The use of the palladacycle **32**[15] also showed no dramatic difference in the regiochemical outcome (Table 1, entry 2). A feature of catalyst **32** is that the use of extremely low loadings are often effective at temperatures of 130 °C and above, and that in fact these lower catalyst loadings result in faster reactions, a finding that can be attributed to diminished rates of active-catalyst decomposition pathways.[13] However, we found that unsatisfactory conversions were encountered at lower loadings of **32** (1 to 0.01 mol% at 130 °C) and the recovery of starting material **1** was the major outcome. Replacement of K_2CO_3 with homogeneous amine bases proved detrimental to the isolated yields of **2** (Table 1, Entries 3 and 4), but as before, no material resulting from a regioisomeric intramolecular Heck reaction was detected. As the inclusion of thallium and silver salts[16] has been advocated for their ability to alter the outcome of Heck-type processes (possibly due to the removal of the halide from the coordination sphere of the palladium(II) intermediate; that is, cationic intermediates of the type **12**), the use of Ag_2CO_3 was investigated (Table 1, entry 5). In this case an inefficient Heck process occurred from which **2** was isolated in low yield (24 %), and the remaining mass balance was attributed to **1** (35 %) and traces of *N*-sulfonylpyrrole **31** (6 %), which is presumably present as a result of redox chemistry caused by the silver species.

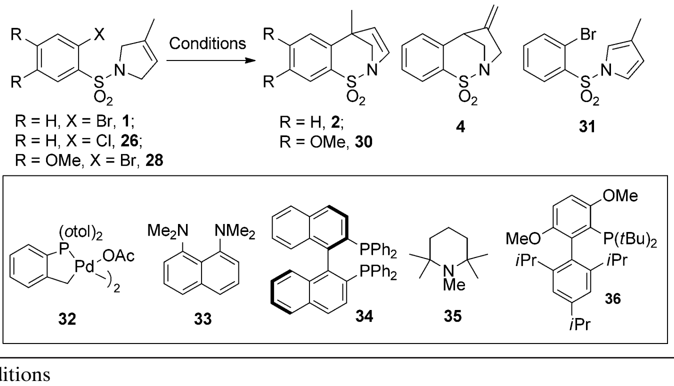


Scheme 4. Preparation of dihydropyrroles **1** and **26**–**28**. Conditions: i) allylamine, Et_3N, CH_2Cl_2, 0 °C to RT; ii) a) NaH, DMF, 0 °C; b) 3-chloro-2-methylpropene, 0 °C to RT; iii) Hoveyda–Grubbs 2nd-generation catalyst **29** (1–2 mol %), CH_2Cl_2, 40 °C.

Similarly, the inclusion of the ammonium salt $n\mathrm{Bu}_4\mathrm{NHSO}_4$ with a dimethylformamide (DMF)/H_2O mixture[17] used as the solvent has been proposed to facilitate the formation of cationic organopalladium(II) intermediates, and in the past we have used these reaction conditions to improve the regioselectivity of a different intramolecular Heck reaction.[18] However, as indicated in Table 1, entry 6, no change in regioselectivity was observed under these reaction conditions and the adduct **2** was isolated in 83 % yield.

Heck-type processes are typically performed in polar solvents and, under some reaction conditions, this may be linked to the formation and stabilisation of the catalytically active palladium(0) species.[1,19] Therefore, because we felt that the identity of the catalytically active Pd species that participates in the initial oxidative addition and subsequent carbopalladation event would be key in terms of governing the regiochemical outcome of the process, we investigated toluene because of its low dielectric constant (Table 1, entry 7). In this instance, a moderate yield of **2** was obtained with a small amount of an impurity that proved chromatographically inseparable with **2**. Analysis of proton and carbon NMR spectra suggested that this impurity was compound **4**, which was formed from exocyclic β-hydride elimination of the reaction intermediate, and that the ratio between **2** and **4** was 85:15. Compound **4** was separated from **2** by recrystallisation. In the next experiment (Table 1, entry 8) the chelating ligand 1,3-bis(diphenylphosphino)propane (dppp) was investigated. In this case, 88 % of **2** was isolated and no isomeric material could be detected.

Table 1. Intramolecular Heck reactions of **1**, **26** and **28**.



	Substrate	Conditions	Products[a] (yield [%]; ratio)
1	**1**	$[Pd(PPh_3)_4]$ (10 mol %), K_2CO_3, DMF, 110 °C	**2** (72)
2	**1**	Herrmann–Beller cat. **32** (10 mol %), K_2CO_3, DMF, 110 °C	**2** (69)
3	**1**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N, DMF, 110 °C	**2** (69)
4	**1**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), proton sponge **33**, DMF, 110 °C	**2** (34)
5	**1**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3, DMF, 110 °C	**2** (24), **1** (35), **31** (6)
6	**1**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3, nBu$_4$NHSO$_4$, DMF/H_2O (9:1), 110 °C	**2** (83)
7	**1**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3, PhMe, 110 °C	**2**/**4** (59; 85:15)[b]
8	**1**	$Pd(OAc)_2$ (10 mol %), dppp (20 mol %), K_2CO_3, DMF, 110 °C	**2** (88)
9	**1**	$Pd(OAc)_2$ (10 mol %), K_2CO_3, DMF, 110 °C	**2**/**4** (72; 88:12)[b]
10	**1**	$Pd(OAc)_2$ (10 mol %), *R*-BINAP **34** (20 mol %), K_2CO_3, DMF, 110 °C	**2**/**4** (91; 88:12),[b] 0 % *ee*
11	**1**	$[Pd(dba)_2]$ (10 mol %), *R*-BINAP **34** (23 mol %), PMP **35**, DMF, 110 °C[c]	**2** (41), 16 % *ee*
12	**26**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3, DMF, 110 °C	**2** (18), **26** (66)
13	**26**	$Pd(OAc)_2$ (10 mol %), *t*BuBrettPhos **36** (31 mol %), K_2CO_3, DMF, 110 °C	**2** (77)
14	**28**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3, DMF, 110 °C	**30** (53)

[a] Isolated yields after purification by flash column chromatography. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Reaction was conducted following three freeze–pump–thaw cycles. dppp = 1,3-bis(diphenylphosphino)propane.

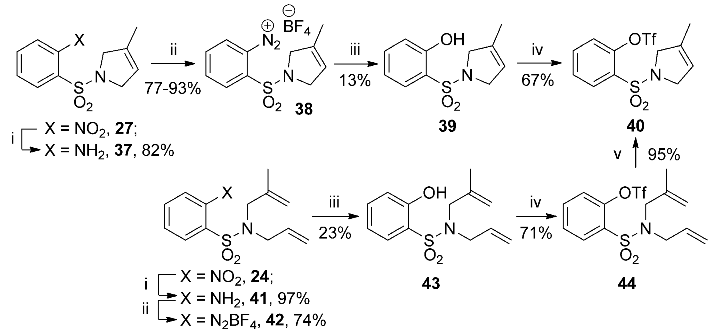
This survey of reaction conditions suggested that either there is an overriding propensity for compound **1** to react in a process that forms the most substituted carbon–carbon bond (i.e., via a transition state resembling **9a** rather than **9b**), or that irrespective of the different conditions, the same type of palladium species was responsible for the formation of the adduct **2** in each case. In relation to this latter possibility, it has been argued[1g,13] that in certain situations the actual catalyst for many Heck reactions could be nanoparticulate palladium(0) clusters as opposed to a discrete, homogeneous phosphine-bound monomeric palladium complex. Possible support for this situation was uncovered when ligand-free conditions were studied (Table 1, entry 9). In this instance, a mixture of **2** and **4** was isolated in 72 % combined yield in a ratio of 88:12.

To further investigate the reaction mechanism, an asymmetric phosphine ligand was used in the reaction because any product enantioselectivity would be indicative of a step in which the ligand was directly involved to induce asymmetry. Based on literature precedent, two alternative reactions were performed in which BINAP (**34**; 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) was used as a source of potential asymmetry. As indicated in Table 1, entry 10, when **34** was used in place of PPh_3, the efficient formation of **2** occurred but the resultant product was racemic. However, the use of conditions developed by Overman et al.[20] provided **2** in moderate yield (41 %) and approximately 16 % enantiomeric excess (Table 1, entry 11). No regioisomeric material (**3** or **4**) was isolated. This result suggests that an arylpalladium(II) intermediate, in which the phosphine is associated, is involved, at least in part, in a process that converts **1** into **2**.

Table 1, Entries 12 and 13 concern the use of the chloride **26**, with a view to investigating how altering the rate of oxidative addition might impact on the overall process. Under identical conditions to those that furnished **2** from bromide **1** in 90 % yield (Scheme 2), the use of chloride **26** gave only an 18 % yield of **2** (Table 1, entry 12). However, use of the electron-rich phosphine **36**,[21] which is known to enhance oxidative addition, gave **2** in 77 % yield (Table 1, entry 13). These two examples provide evidence that **2**, with its quaternary stereogenic centre, was formed following homogeneous catalysis with a ligand-bound palladium species. Next the dimethoxy-substituted aryl bromide **28** was studied, which was found to give **30** in a moderate yield of 53 % (Table 1, entry 14). In the past,[10a,d] we observed lower yields when this more electron-rich bromide was employed in this type of reaction.

The reactions involving halides under the range of conditions discussed above all led exclusively, or in high selectivity, to the quaternary regioisomer, even in the presence of conditions that are thought to involve a cationic palladium(II) species of the type **12** (Table 1, Entries 6 and 7). Therefore, we next considered whether we could specifically perform the same type of intramolecular Heck reaction with substrates in which the entity released following palladium(0) oxidative addition would not coordinate to the intermediate arylpalladium(II) species.

By using the nitro-substituted sulfonamide **27**, the synthesis of diazonium salt **38** and triflate **40** was addressed (Scheme 5).[22] Chemoselective reduction of **27** with iron/acetic acid[23]gave the corresponding aniline **37** in high yield, and subsequent diazonium-ion formation was achieved under typical conditions.[24,25] This enabled the isolation of **38** in moderate to good yield in two steps following recrystallisation of the initially formed precipitate from acetone/diethyl ether. Heating **38** in water (at either pH 7 or 4)[25] generated the desired phenol **39**; however, yields were routinely poor. *N*-Sulfonylpyrrole **45** was always formed as a side product, as was additional coloured material that could not be characterised. The use of Cu^{II} salts[26] led to the exclusive formation of **45**.



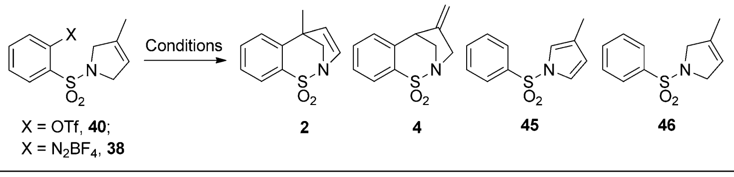
Scheme 5. Preparation of diazonium salt **38** and triflate **40**. Conditions: i) Fe^0, AcOH/EtOH/H_2O (2:2:1), RT; ii) $NaNO_2$, HBF_4, H_2O, 0 °C; iii) H_2O, 100 °C; iv) Tf_2O, pyridine, CH_2Cl_2, 0 °C; v) Hoveyda–Grubbs 2nd-generation catalyst **29** (2 mol %), CH_2Cl_2, 40 °C. Tf = triflyl.

Because competitive oxidation of the dihydropyrrole was clearly an issue, we aimed to perform the diazonium-ion–phenol conversion on the acyclic diazonium salt **42**. Compound **42** was readily prepared in good yield from a two-step conversion of **24**. Although heating **42** in water also gave phenol **43** in low yields, the 20–25 % observed was higher than for the corresponding conversion of **38** into **39** and was reproducible and thus enabled sufficient material to be accumulated. Phenol **43** was converted into triflate **44** prior to ring-closing metathesis, which then smoothly gave **40** in good yield over two steps (Scheme 5).

The treatment of **40** with our favoured intramolecular Heck-reaction conditions (Pd(OAc)$_2$, PPh_3, K_2CO_3, DMF, 110 °C) provided **2**; however, the main product proved to be phenol **39** (Table 2, entry 1). We reasoned that **39** was formed due to the presence of water under the basic reaction conditions, a process presumably facilitated by the *ortho* electron-withdrawing sulfonyl moiety. Therefore, a literature method for the intramolecular Heck reaction of an enoltriflate was investigated.[27] Although this solved the issue of triflate hydrolysis, conversion proved to be low and **2** was only isolated in 14 % yield (Table 2, entry 2). In both cases, the formation of **3** or **4** was not detected. In contrast, the use of the palladium(0)–BINAP conditions developed by Overman et al.[20,28] gave **2** in excellent yield, albeit with only low enantiomeric excess (Table 2, entry 3). Interestingly, the outcome of this process closely mirrored, in terms of both yield and enantiomeric excess, the behaviour of bromide **1** under identical reaction conditions (Table 1, entry 11).

Based on a recent report that describes the first intramolecular Matsuda–Heck reaction,[24] diazonium ion **38** was considered. Several often-reported protocols for the reaction of diazonium salts with alkenes were investigated (Table 2).[16] The use of [Pd(dba)$_2$] to catalyse a reaction mixture that included pyrrole **45** (49 %) and dihydropyrrole **46** (18 %) resulted in the isolation of a low yield of **2** (18 %); Table 2, entry 4). In the presence of a phosphine, the formation of a slightly higher yield of **2** (27 %) was observed; however, this was again accompanied by the formation of **45** and **46** (Table 2, entry 5). The use of NaOAc in dichloromethane[29] reduced the quantity of the pyrrole by-product obtained, but overall conversion remained poor

Table 2. Applications of triflate **40** and diazonium salt **38** in the intramolecular Heck reaction.



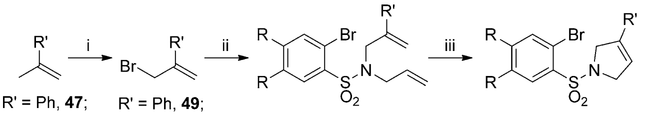
	Substrate	Conditions	Products[a] (yield [%]; ratio)
1	**40**	Pd(OAc)$_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3, DMF, 110 °C	**2** (15), **39** (55)
2	**40**	[Pd(PPh$_3$)$_4$] (10 mol %), Et_3N, THF, 100 °C	**2** (14), **40** (50)
3	**40**	[Pd(dba)$_2$] (5 mol %), *R*-BINAP **34** (11 mol %), PMP **35**, DMF, 110 °C	**2** (93), 17 % *ee*
4	**38**	[Pd(dba)$_2$] (10 mol %), K_2CO_3, MeCN, RT	**2** (18), **45** (49), **46** (18)
5	**38**	[Pd(PPh$_3$)$_4$] (10 mol %), K_2CO_3, MeCN, RT	**2** (27), **45** (27), **46** (3)
6	**38**	[Pd(dba)$_2$] (4 mol %), NaOAc, CH_2Cl_2, RT	**2** (83)
7	**38**	Pd(OAc)$_2$ (10 mol %), MeOH, 50 °C	**2**/**4** (26; 20:80),[b] **45** (37)

[a] Isolated yields after purification by flash column chromatography. [b] A mixture of **2** and **4** was isolated and the ratio was determined by ^{1}H NMR spectroscopy. dba = dibenzylideneacetone.

(Table 2, entry 6). These reactions were conducted at room temperature, demonstrating the facile oxidative addition of diazonium salts in comparison with their halide/pseudohalide counterparts. In all cases (Table 2, Entries 4–6), the only intramolecular Heck reaction product, **2**, contained the quaternary carbon centre. However, by using a ligand-free, base-free colloidal palladium procedure (Table 2, entry 7),[24,30] an interesting observation was made: although conversion was poor and the generation of pyrrole **45** was again a complication, a 26 % yield of the intramolecular Heck reaction products was isolated following column chromatography. Inspection of the proton NMR spectrum indicated that for the first time, formation of the regioisomeric Heck adduct **4**, which does not contain a quaternary centre, was favoured (**4**/**2**, 80:20; Table 2, entry 7). Recrystallisation of the mixture of regioisomers from cyclohexane provided predominantly **4**, which enabled unambiguous assignment and confirmation of the minor byproduct encountered in Table 1, Entries 7 and 9.

In summary, the use of either molecular nitrogen or triflate as a leaving group in the Heck process proved less efficient than the corresponding bromide due to poor conversion and the formation of side products. Results indicate that from reactions in which the carbopalladation is likely to occur via a cationic organopalladium(II) intermediate species (e.g., **12**), regiosiomer **2** was routinely observed. The only exception to this was found in when a preformed, colloidal palladium(0) mixture preferentially formed the regioisomer **4** (Table 2, entry 7).

At this point, after screening a range of conditions and different aryl leaving groups there was a clear preference for the formation of the more sterically congested adduct **2** over **3** (or **4**). Therefore, it was felt that an investigation of alternative alkenyl substituents might be instructive. 3-Phenyl-, 3-*tert*-butyl- and 3-methyl-ester-substituted unsaturated bromides **49**–**51** were targeted based on their different electronic and steric properties. As indicated in Scheme 6, compounds **49** and **50** were prepared by allylic bromination of **47** and **48** using *N*-bromosuccinimide (NBS),[31] whereas **51** is commercially available. Alkylation of these compounds with **18** gave the RCM precursors **52**–**54**, and subsequent RCM with catalyst **29** provided the corresponding dihydropyrrole derivatives **57**–**59** in reasonable to good yields, even for the sterically hindered *tert*-butyl-substituted example **53** and the electron-poor and Lewis basic α,β-unsaturated ester **54**. The methoxy-substituted analogues **60** and **61** were efficiently prepared in a similar fashion.



R' = Ph, **47**;
R' = *t*Bu, **48**

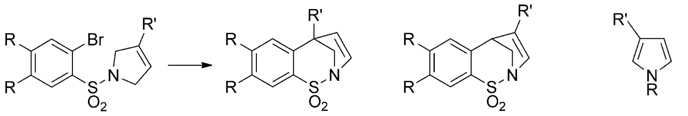
R' = Ph, **49**;
R' = *t*Bu, **50**;
R' = CO_2Me, **51**

R = H, R' = Ph, **52**, 69%;
R = H, R' = *t*Bu, **53**, 90%;
R = H, R' = CO_2Me, **54**, 92%;
R = OMe, R' = Ph, **55**, 76%;
R = OMe, R' = *t*Bu, **56**, 89%

R = H, R' = Ph, **57**, 92%;
R = H, R' = *t*Bu, **58**, 87%;
R = H, R' = CO_2Me, **59**, 60%;
R = OMe, R' = Ph, **60**, 95%;
R = OMe, R' = *t*Bu, **61**, 77%

Scheme 6. Ring-closing metathesis for the synthesis of substituted sulphonamides **57**–**61**. Conditions: i) NBS, $CHCl_3$, sealed tube, 65 °C; ii) **18** (or **21**), NaH, DMF, 0 °C to RT; iii) Hoveyda–Grubbs 2nd generation catalyst **29** (2 mol %), CH_2Cl_2, 40 °C. NBS = *N*-Bromosuccinimide.

Table 3. Study of alternative alkenyl substituents in the intramolecular Heck reaction.[a]



R = H, R' = Ph, **57**;
R = H, R' = *t*Bu, **58**;
R = H, R' = CO_2Me, **59**;
R = OMe, R' = Ph, **60**;
R = OMe, R' = *t*Bu, **61**

R = H, R' = Ph, **62**;
R = H, R' = *t*Bu, **63**;
R = H, R' = CO_2Me, **64**;
R = OMe, R' = Ph, **65**;
R = OMe, R' = *t*Bu, **66**

R = H, R' = Ph, **67**;
R = H, R' = *t*Bu, **68**;
R = H, R' = CO_2Me, **69**;
R = OMe, R' = Ph, **70**;
R = OMe, R' = *t*Bu, **71**

R = $PhSO_2$, R' = *t*Bu, **72**;
R = H, R' = CO_2Me, **73**

	Substrate	R	R′	Products[b] (yield [%])
1	**57**	H	Ph	**62** (45)
2	**58**	H	*t*Bu	**63** (41), **68** (12), **72** (34)
3	**59**	H	CO_2Me	**73** (42)
4	**60**	OMe	Ph	**65** (54)
5	**61**	OMe	*t*Bu	**66** (39), **71** (18)

[a] Conditions: $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3, DMF, 110 °C. [b] Isolated yields after purification by flash column chromatography.

Each Heck-precursor compound was then submitted to the reaction conditions involving $Pd(OAc)_2/PPh_3$ with K_2CO_3 in DMF (Table 3). In the case of styrene **57**, compound **62** was isolated in 45 % yield and its structure was determined by X-ray crystallography (Table 3, entry 1).[32] Only traces of starting material **57** were isolated following this reaction, and no material consistent with a regioisomeric Heck adduct **67** was detected. Next, the reaction of **58** was investigated, and in this case, isolable and characterisable amounts of the regiosiomeric adduct **68** were obtained alongside the major product **63** (Table 3, entry 2). After separation of the isomers by column chromatography, **63** was isolated in 41 % yield and **68** was isolated in 12 % yield. Proton NMR spectroscopy of the crude reaction mixture indicated that **63** and **68** were formed in a ratio of 4:1, and their structures were confirmed by X-ray crystallography (Figure 1).[32] In this process, the remaining mass balance was provided by pyrrole **72** (34 %).

As indicated in Table 3, entry 3, for the case of methyl ester **59**, no products resulting from an intramolecular Heck reaction (e.g., **64**) were detected; instead, pyrrole **73** was formed as the sole isolable product (42 %). It seems reasonable to speculate that this product resulted from a base-mediated sulfinate-elimination process, which was then followed by aromatisation of the product.[10b] Based on the success of the styrene and *tert*-butyl substituents, the corresponding dimethoxy-substituted Heck precursors **60** and **61** were considered. As indicated in Table 3, Entries 4 and 5, the corresponding quaternary regioisomer was either the sole (**65**; 54 %) or the major product (**66**; 39 %) in each

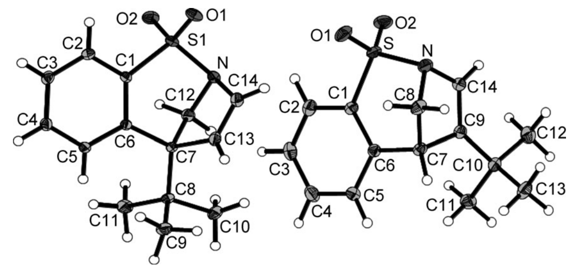
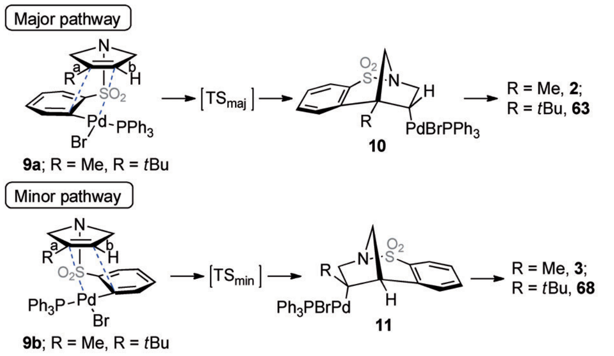


Figure 1. X-ray crystallographic structures of **63** and **68** (ellipsoids are shown at the 50 % probability level).



E_{rel}(kJmol^{-1}):

	Major pathway			Minor pathway			Products			
	9a	TS_{maj}	**10**	**9b**	TS_{min}	**11**	**2**	**3**	**63**	**68**
R = Me	0.0	73.7	27.6	27.8	86.8	-1.4	0.0	-19.0	-	-
R = *t*Bu	8.8	95.1	73.1	0.0	114.1	40.5	-	-	0.0	-48.2

Scheme 7. DFT calculations performed for the regiochemistry-establishing sequence in which R = Me or *t*Bu.

case. Although successful Heck reactions were only observed for the phenyl- and *tert*-butyl-substituted systems, the findings clearly demonstrate that in both instances bond formation at the more congested carbon atom is favoured, and leads to the quaternary benzo-fused bicyclic product.

Mechanistic details of Heck reactions have been successfully investigated computationally by using density functional theory (DFT) methods.[5,33] Based on these precedents, we felt that a similar study might provide a basis for the selective carbon–carbon bond formation that was observed experimentally in the processes described above. By following a stepwise procedure, from simple computational methods to the highest level that can be readily considered, key intermediates in the Heck reactions of **1** and **58** (R = Me and *t*Bu) were studied. Results were obtained by using the B97D functional,[34] which includes dispersion forces, with the 6-31G* basis set[35] for all the atoms except palladium and bromine, results for which were calculated by using the pseudopotential LANL2DZ(d) and LANL2DZ functionals, respectively.[36] In addition, a solvent continuum model (PCM) using the DMF parameter was used to model the reaction solvent.[37] All of the energetic values reported herein correspond to the free energy plus the solvation energy. This model enabled the characterisation of the possible complexes involved in the regiochemical-establishing sequence (Scheme 7).

Firstly, the final possible reaction products (without palladium) were compared for both Me and *t*Bu substituents. As expected in both cases, the tri-substituted alkenyl products **3** and **68**, formed by following the experimentally observed, minor pathway, were more stable by 19.0 and 48.2 kJ mol^{-1} for R = Me and *t*Bu, respectively. Next, the possible intermediates **10** and **11** and the transition states leading to their formation (TS_{maj} and TS_{min}, respectively) were considered for both the major pathway (based on experimental results) and the corresponding minor pathway. Both conformations of the square-planar alkene complex, in which R = Me or *t*Bu, were investigated. As shown, the relative energies for conformer **9a** versus **9b** depend on the identity of the R substituent.

The corresponding transition states in the pathway to the carbopalladated intermediates **10** and **11** were also computed and the associated energies were considered. For both substituents (R = Me and *t*Bu), the most stable transition state was found to be associated with the major pathway. However, the difference in relative energies between the major and minor transition states, 13.1 and 19.0 kJ mol^{-1} for R = Me and *t*Bu, respectively, was less dramatic than anticipated on the basis of the experimental results obtained (for R = Me in particular). As was the case for the initial alkene complexes **9a** and **9b**, the relative energies of the carbopalladated intermediates **10** and **11** were dependant on the identity of R.

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 the formation of products through the minor pathway) and the stability of the intermediate complexes (which are substituent dependent).

In summary, this DFT study provides corroborative evidence for the experimental study, suggesting that the regiochemical outcome is kinetically favoured and that product selection occurs because a lower-energy transition state is associated with the formation of the quaternary centre. 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, these DFT studies can only partly address the origin of the selectivity.

Conclusion

The preference for the formation of a quaternary centre over a tertiary centre following an intramolecular Heck reaction was studied for a series of differently substituted *N*-sulfonyldihydropyrroles. Results indicated that for the methyl-substituted substrate **1**, irrespective of a range of typical experimental protocols, a high selectivity for the formation of the quaternary regioisomeric adduct **2** was observed (see Table 1). Attempts to employ triflate as a leaving group (**40**) in the Heck reaction and thereby invoke a cationic reaction pathway did not alter the regiochemical outcome observed in the reactions of bromide **1** or chloride **26**. The use of the diazonium salt **38** proved to not be straightforward based on the propensity of **38** to form byproducts that result from dihydropyrrole oxidation and proton–nitrogen exchange. However, by using an in situ formed, colloidal palladium(0) catalyst, the alternate regiochemistry was observed preferentially, albeit in low overall yield. More work is required to understand and build upon this initial finding. Alternative substituents were investigated and it was found that the phenyl-substituted compounds **57** and **60** gave only the product of quaternary carbon–carbon bond formation. In the case of the *tert*-butyl-substituted precursors **58** and **61**, mixtures of products were detected. Separation of these mixtures led to the isolation and characterisation of products resulting from both regiochemical outcomes, in which the major product (ca. 3.5:1) was the quaternary isomer. The presence of different substituents (R = Me, Ph, *t*Bu), which have different steric and electronic effects, resulted in a preference for the formation of the more hindered, quaternary carbon–carbon bond.

DFT studies were performed to probe the experimentally observed results, and were calculated by using the classic neutral Heck reaction pathway for the methyl and *tert*-butyl-substituted compounds. Calculations were performed for the chemical species likely to be involved in the regiochemistry-establishing event. Although differences were noted for the methyl substituent versus the bulkier and more electron-donating *tert*-butyl substituent, the energy of the transition state leading to carbopalladation is lower in both cases for the experimentally preferred intermediate that leads to formation of the quaternary carbon centre.

Experimental Section

Representative procedure for the Heck reaction: A degassed solution of compound **58** (170 mg, 0.49 mmol, 1 equiv) in DMF (4 mL) was treated with $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol %), PPh_3 (26 mg, 0.098 mmol, 20 mol %) and K_2CO_3 (135 mg, 0.98 mmol, 2 equiv) under a N_2 atmosphere, and the solution was heated at 110 °C for 18 h. The reaction mixture was cooled and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was separated and further extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration was followed by solvent removal under reduced pressure to give the crude product. Purification by flash column chromatography (*c*-Hex/EtOAc, 15:1) provided product **63** (51 mg, 41 %) as a colourless solid, as well as co-products **68** (16 mg, 12 %) and pyrrole **72** (45 mg, 34 %).

*1-tert-Butyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide (**63**)*: $R_f = 0.4$ (*c*-Hex/EtOAc, 3:1); m.p. 164–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (dd, $J = 8.0$, 1.5 Hz, 1 H), 7.68 (dd, $J = 8.0$, 1.0 Hz, 1 H), 7.45 (td, $J = 8.0$, 1.0 Hz, 1 H), 7.38 (td, $J = 8.0$, 1.5 Hz, 1 H), 6.43 (d, $J = 4.0$ Hz, 1 H), 6.36 (d, $J = 4.0$ Hz, 1 H), 4.36 (d, $J = 12.0$ Hz, 1 H), 4.21 (d, $J = 12.0$ Hz, 1 H), 1.28 ppm (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.1$, 137.3, 134.9, 133.5, 130.8, 129.4, 128.6, 125.9, 63.6, 56.7, 32.8, 28.9 ppm; IR (NaCl, in CH_2Cl_2): $\tilde{\nu}_{max} =$ 3112, 2965, 2935, 1330, 1165 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_2S^+$: 264.1058 [M^+]; found: 264.1058.

*11-tert-Butyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene-8,8-dioxide (**68**)*: $R_f = 0.3$ (*c*-Hex/EtOAc, 3:1); m.p. 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$–7.71 (m, 1 H), 7.48–7.41 (m, 1 H), 7.39–7.33 (m, 1 H), 7.20 (d, $J = 8.0$ Hz, 1 H), 6.10 (s, 1 H), 4.42 (d, $J = 12.0$ Hz, 1 H), 4.16–4.07 (m, 1 H), 3.28 (d, $J = 4.0$ Hz, 1 H), 1.07 ppm (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.6$, 140.9, 135.6, 131.2, 129.7, 127.6, 127.1, 125.6, 64.8, 43.6, 33.2, 29.1 ppm; IR (NaCl, in CH_2Cl_2): $\tilde{\nu}_{max} = 3086$, 2967, 1642, 1336, 1156 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_2S^+$: 263.0980 [M^+]; found: 263.0988.

*3-tert-Butyl-N-benzenesulfonyl pyrrole (**72**)*: light-brown waxy solid; $R_f = 0.5$ (*c*-Hex/EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 7.5$ Hz, 2 H), 7.59 (t, $J = 7.5$ Hz, 1 H), 7.50 (t, $J = 8.0$ Hz, 2 H), 7.07 (s, 1 H), 6.89 (s, 1 H), 6.25 (s, 1 H), 1.18 ppm (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.8$, 139.5, 133.7, 129.4, 126.8, 121.1, 115.2, 112.9, 31.0, 27.0 ppm; IR (NaCl, in CH_2Cl_2): $\tilde{\nu}_{max} = 3139$, 3066, 1584, 1368, 1161 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_2S^+$: 263.0980 [M^+]; found: 263.0976.

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[1] For general reviews concerning the Heck reaction, see: a) R. F. Heck, *Org. React.* **1982**, *27*, 345–390; b) S. E. Gibson, R. Middleton, *Contemp. Org. Synth.* **1996**, *3*, 447–471; c) J. T. Link, *Org. React.* **2002**, *60*, 157–534; d) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680; e) J. P. Knowles, A. Whiting, *Org. Biomol. Chem.* **2007**, *5*, 31–44; f) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609–679; g) for a monograph, see: *The Mizoroki–Heck Reaction* (Ed.: M. Oestreich), Wiley, New York, **2009**.

[2] For reviews in the area of asymmetric Heck reactions, see: a) D. Mc Cartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122–5150; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945–2963.

[3] a) L. Firmansjah, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 11340–11341; b) K. S. Bloome, R. L. McMahen, E. J. Alexanian, *J. Am. Chem. Soc.* **2011**, *133*, 20146–20148.

[4] W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2–7.

[5] a) H. von Schenck, B. Akermark, M. Svensson, *J. Am. Chem. Soc.* **2003**, *125*, 3503–3508; b) R. J. Deeth, A. Smith, J. M. Brown, *J. Am. Chem. Soc.* **2004**, *126*, 7144–7151.

[6] a) J. Ruan, J. Xiao, *Acc. Chem. Res.* **2011**, *44*, 614–626; b) P. Wucher, L. Caporaso, P. Roesle, F. Ragone, L. Cavallo, S. Mecking, I. Göttker-Schnetmann, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 8955–8959; c) G. K. Datta, H. von Schenk, A. Hallberg, M. Larhad, *J. Org. Chem.* **2006**, *71*, 3896–3903.

[7] For an example, see: G. K. Datta, M. Larhed, *Org. Biomol. Chem.* **2008**, *6*, 674–676.

[8] For a selection of intramolecular examples in which the bias of electron-poor alkenes has been overcome, see: a) O. Kwon, D. S. Su, D. Meng, W. Deng, D. C. D'Amico, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 1978–1981; *Angew. Chem. Int. Ed.* **1998**, *37*, 1877–1880; b) B. M. Trost, H. C. Tsui, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 3534–3535; c) P. Diaz, F. Gendre, L. Stella, B. Charpentier, *Tetrahedron* **1998**, *54*, 4579–4590; d) J. W. Dankwardt, L. A. Flippin, *J. Org. Chem.* **1995**, *60*, 2312–2313; e) A. Ashimori, B. Bachand, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487.

[9] D. J. Kucera, S. J. O'Connor, L. E. Overman, *J. Org. Chem.* **1993**, *58*, 5304–5306.

[10] a) P. Evans, T. McCabe, B. S. Morgan, S. Reau, *Org. Lett.* **2005**, *7*, 43–46; b) P. Evans, *J. Org. Chem.* **2007**, *72*, 1830–1833; c) S. Kelleher, P. Y. Quesne, P. Evans, *Beilstein J. Org. Chem.* **2009**, *5*, No. 69; d) K. Geoghegan, S. Kelleher, P. Evans, *J. Org. Chem.* **2011**, *76*, 2187–2194.

[11] J. E. M. N. Klein, K. Geoghegan, N. Méral, P. Evans, *Chem. Commun.* **2010**, *46*, 937–939.

[12] a) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321; b) A. Jutand, *Pure Appl. Chem.* **2004**, *76*, 565–576; c) for a recent example, see: F. Proutiere, F. Schoenebeck, *Angew. Chem.* **2011**, *123*, 8342–8345; *Angew. Chem. Int. Ed.* **2011**, *50*, 8192–8195.

[13] a) M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559–1563; b) J. G. de Vries, *Dalton Trans.* **2006**, 421–429.

[14] For an example, see: T. Vorfalt, K. J. Wannowius, H. Plenio, *Angew. Chem.* **2010**, *122*, 5665–5668; *Angew. Chem. Int. Ed.* **2010**, *49*, 5533–5536, and references therein.

[15] a) M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Brossmer, *Angew. Chem.* **1995**, *107*, 1992–1993; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1848–1849; b) W. A. Herrmann, C. Brossmer, K. Öfele, C. P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989–1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848.

[16] A. Putey, L. Joucla, L. Picot, T. Besson, B. Joseph, *Tetrahedron* **2007**, *63*, 867–879.

[17] a) S. Lemaire-Audoire, M. Savignac, C. Dupuis, J. P. Genêt, *Tetrahedron Lett.* **1996**, *37*, 2003–2006; b) K. S. A. Vallin, M. Larhed, A. Hallberg, *J. Org. Chem.* **2001**, *66*, 4340–4343.

[18] J. E. M. N. Klein, H. Müller-Bunz, Y. Ortin, P. Evans, *Tetrahedron Lett.* **2008**, *49*, 7187–7190.

[19] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[20] A. Ashimori, B. Bachand, M. A. Calter, S. P. Govek, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499.

[21] L. M. Chapman, B. Adams, L. T. Kilman, A. Makriyannis, *Tetrahedron Lett.* **2010**, *51*, 1517–1522.

[22] For reviews concerning diazonium-ion Matsuda–Heck reactions, see: a) A. Roglans, A. Pla-Quintana, M. Moreno-Mañas, *Chem. Rev.* **2006**, *106*, 4622–4643; b) J. G. Taylor, A. V. Moro, C. R. D. Correia, *Eur. J. Org. Chem.* **2011**, 1403–1428; c) F. X. Felpin, L. Nassar-Hardy, F. Le Callonnec, E. Fouquet, *Tetrahedron* **2011**, *67*, 2815–2831.

[23] a) L. Wang, P. Li, Z. Wu, J. Yan, M. Wang, Y. Ding, *Synthesis* **2003**, 2001–2004; b) G. A. Heropoulos, S. Georgakopoulos, B. R. Steele, *Tetrahedron Lett.* **2005**, *46*, 2469–2473; c) Y. Liu, Y. Lu, M. Prashad, O. Repič, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 217–219.

[24] F. A. Siqueira, J. G. Taylor, C. R. D. Correia, *Tetrahedron Lett.* **2010**, *51*, 2102–2105.

[25] P. Hanson, J. R. Jones, A. B. Taylor, P. H. Walton, A. W. Timms, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1135–1150.

[26] T. Cohen, A. G. Dietz, Jr., J. R. Miser, *J. Org. Chem.* **1977**, *42*, 2053–2058.

[27] B. F. Sun, C. L. Wang, R. Ding, J. Y. Xu, G. Q. Lin, *Tetrahedron Lett.* **2011**, *52*, 2155–2158.

[28] T. Takemoto, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1993**, *115*, 8477–8478.

[29] K. Kikukawa, K. Nagira, F. Wada, T. Matsuda, *Tetrahedron* **1981**, *37*, 31–36.

[30] a) G. Mehta, S. Sengupta, *Tetrahedron Lett.* **1996**, *37*, 8625–8626; b) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Sferrazza, *Synlett* **2009**, 973–977.

[31] T. Ohmura, K. Masuda, I. Takase, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 16624–16625.

[32] CCDC-876850 (**62**), CCDC-876851 (**63**) and CCDC-876852 (**68**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Compound **62**: $C_{16}H_{13}NO_2S$; $M_r=283.33$; monoclinic; space group $P2_1$; unit cell parameters: $a=8.0994(2)$, $b=18.8070(3)$, $c=8.8124(2)$ Å; $\alpha=90°$; $V=1336.41(5)$ Å^3; $T=100(2)$ K; $Z=4$; 26989 reflections measured, 5602 unique reflections ($R_{int}=0.0336$); $R_1=0.0270$ and $wR_2=0.0726$ (all data). Compound **63**: $C_{14}H_{17}NO_2S$; $M_r=263.35$; monoclinic, $P2_1/n$; unit cell parameters: $a=11.6193(2)$, $b=9.0842(1)$, $c=12.0434(2)$ Å; $\alpha=90°$; $V=1231.04(3)$ Å^3; $T=100(2)$ K; $Z=4$; 29893 reflections collected, 4350 unique ($R_{int}=0.0295$); $R_1=0.0466$ and $wR_2=0.1057$ (all data). Compound **68**: $C_{14}H_{17}NO_2S$; $M_r=263.35$; monoclinic, $P2_1/n$; unit cell parameters: $a=10.8789(1)$, $b=7.5258(1)$, $c=16.5713(2)$ Å; $\alpha=90°$; $V=1339.61(3)$ Å^3; $T=100(2)$ K; $Z=4$; 41893 reflections collected, 4756 unique ($R_{int}=0.0266$); $R_1=0.0332$ and $wR_2=0.0914$ (all data).

[33] C. Bäcktorp, P. O. Norrby, *Dalton Trans.* **2011**, *40*, 11308–11314, and references therein.

[34] S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787–1799.

[35] a) P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213–222; b) P. C. Hariharan, J. A. Pople, *Mol. Phys.* **1974**, *27*, 209–214.

[36] a) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299–310; b) T. H. Dunning, Jr., P. J. Hay, *Modern Theoretical Chemistry, Vol 3* (Ed.: H. F. Schaefer III), Plenum, New York, **1976**.

[37] V. Barone, M. Cossi, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3210–3221.

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Heck Reaction

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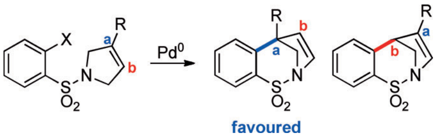
Regioselectivity in the Intramolecular Heck Reaction of a Series of Cyclic Sulfonamides: An Experimental and Computational Study



What the Heck: A series of cyclic sulfonamides (R = Me, Ph and *t*Bu; X = Br, Cl, Tf, N_2BF_4) were studied in the intramolecular Heck reaction. The outcome of this process was controlled by the presence of the substituent rather than the ring size of the heterocycle formed, and in all cases, formation of the quaternary product was observed (see scheme).