Neighbouring-Group Effects in Heck Reactions

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The Heck reaction is a widely used carbon–carbon bond forming process in organic synthesis. A prominent variant that has found widespread application in targeted complex-molecule synthesis is the asymmetric intramolecular Heck reaction. This methodology has outshone another powerful facet of Heck chemistry that has been prospering in recent years, namely heteroatom-directed Heck reactions. Initially designed to achieve high regiocontrol in intermolecular reactions, this technique has recently been successfully applied to highly diastereoselective and even enantioselective substrate-directed inter- as well as intramolecular Heck reactions. This microreview delineates, for the first time, the evolution of this chemistry from regio- to diastereo- and, finally, enantioselective transformations. Flexible syntheses of stereodefined, multi-arylated alkenes, the diastereoselective construction of tertiary and quaternary carbon centres, as well as combining substrate- with catalyst-control in an enantioselective transformation are covered.

Introduction

Among the transition-metal-catalysed transformations that had conquered organic and organometallic chemistry by the end of the last century,[1] the (Mizoroki–)Heck reaction had been a Sleeping Beauty for more than a decade since its initial appearance in the literature.[2] As a carbon–carbon bond forming process, this arylation/vinylation of an alkene inherently holds exciting synthetic potential if regio- and stereoselectivity are controllable elements in this reaction. However, both regio- (α or β) and diastereoselectivity (*E* or *Z*) were found to be notoriously difficult to control in *inter*molecular Heck reactions[3] of **A** and **B** (Figure 1), which is clearly detrimental to synthetic applications. Conversely, an *intra*molecular reaction[4] allows control of the regiochemistry, which is usually determined by the length of the tether in the cyclisation precursor **C** (Figure 1). Depending on the mode of the ring closure (*endo* or *exo*), there is occasionally a lack of stereocontrol in the newly formed exocyclic alkene moiety.

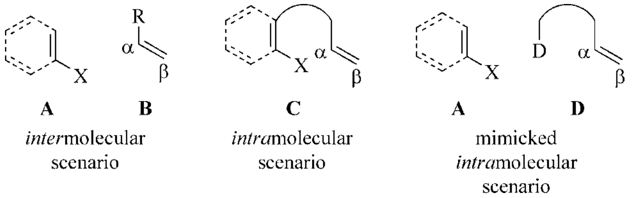

Figure 1. Three different scenarios for Heck reactions (X = I or OTf; R = alkyl, aryl, or heteroatom; D = NR_2, PPh_2, or OH)

Additionally, this variant is endowed with an important advantage: whereas intermolecular Heck reactions are limited to mono- and disubstituted alkenes, the substrate scope of intramolecular Heck reactions also includes tri- and

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Martin Oestreich was born in Pforzheim (Germany), in 1971. He studied chemistry at the Heinrich-Heine-Universität in Düsseldorf, UMIST in Manchester (UK), and the Philipps-Universität in Marburg. After an internship at Hoffmann-La Roche in Basel (Switzerland), he returned to Marburg where he obtained his diploma under the direction of Paul Knochel in 1996. He completed his doctoral degree with Dieter Hoppe at the Westfälische Wilhelms-Universität in Münster in 1999. After two postdoctoral years with Larry E. Overman at the University of California at Irvine (USA) he moved to the Albert-Ludwigs-Universität in Freiburg and initiated an independent research programme under the mentorship of Reinhard Brückner. He was awarded a Kekulé fellowship (1997–1999) by the Fonds der Chemischen Industrie and an Emmy Noether postdoctoral fellowship (1999–2001) as well as an Emmy Noether "Junior Research Group" (2001–2005) by the Deutsche Forschungsgemeinschaft. His major research interests involve the synthesis and chemistry of organosilicon compounds with silicon-centred chirality and transition metal catalysis.

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tetrasubstituted double bonds. Carbon–carbon bond formation at these highly substituted alkenes establishes an entry into the construction of sterically congested tertiary and quaternary all-carbon centres.

The state of hibernation did not end until Shibasaki and Overman simultaneously disclosed the enantioselective formation of tertiary and quaternary stereogenic carbons by means of catalytic asymmetric intramolecular Heck reactions;[5] the need for the construction of such stereocentres in the course of total synthesis inspired this development. Today, it still is the most prominent, if not indispensable, tool for this pivotal synthetic challenge[6] as reflected by the numerous beautiful applications in the synthesis of structurally intriguing natural products.[7]

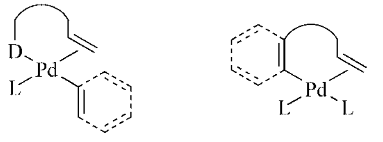
Shortly after the advent of asymmetric Heck cyclisations, Hayashi reported the first enantioselective intermolecular Heck reaction of 2,3-dihydrofuran.[8] This substrate was carefully selected since the high α-regioselectivity of its arylation is steered electronically and there is no issue of diastereoselectivity (*E* or *Z*). Interestingly, this asymmetric Heck reaction is restricted to a single substrate and there have been hardly any synthetic applications so far. Instead, this reaction has served as a sharpening stone for the development of novel chiral ligands in asymmetric catalysis.[9]

These Heck reactions have been extensively reviewed, with particular focus on synthetic[4,6,7] as well as mechanistic aspects,[3,10] and are therefore beyond the scope of this microreview. With regard to synthetic usefulness, the intramolecular Heck reaction has undoubtedly outshone many other efforts in the wide-ranging area of Heck chemistry. One of these unappreciated areas, which has recently been going through a second childhood, was introduced by Hallberg several years ago.[11] In order to control the regioselectivity of an intermolecular Heck reaction, Hallberg designed an alternative to intramolecular Heck processes by installation of a suitable donor D in the alkene fragment **B** (**B** ⇒ **D**, Figure 1), which is capable of coordinating the palladium catalyst. This allows for intramolecular delivery of the aryl/vinyl fragment **A**, thereby mimicking an intramolecular Heck reaction, a scenario that has been coined by Hallberg as a "chelation-controlled" Heck reaction.[11] This microreview will summarise the evolution of this concept from achieving the initial objective of controlling regioselectivity to recent diastereoselective and even enantioselective "chelation-controlled" Heck reactions.

Concept of "Chelation Control"

Controlling regio- and stereoselectivity with the aid of attractive interactions between substrate and reagent/catalyst is a continuing challenge in organic synthesis. Although the literature is interspersed with wonderful examples, including the contributions by Hallberg, the generality of the concept itself was realized and summarised by Evans only a decade ago.[12] The targeted development of such *substrate-directable chemical reactions* has flourished recently.

For achieving high regioselectivity in an intermolecular Heck reaction, Hallberg modified an alkene **B**, considered as the substrate, by the introduction of a donor group D (**B** ⇒ **D**, Figure 1). The donor D coordinates to an aryl/vinylpalladium intermediate, considered as the reagent, to provide the alkene-palladium complex **E** (Figure 2). Delivery of the aryl/vinyl group onto the alkene moiety will now proceed intramolecularly, thus reshaping a bimolecular into a unimolecular process. An intermediate such as **E** nicely reproduces the scenario of an intramolecular reaction **F** (Figure 2). These donor groups have been illustratively described by Breit as *reagent*- or *catalyst-directing groups*.[13]



E
chelation-controlled
*inter*molecular
Heck reaction

F
*intra*molecular
Heck reaction

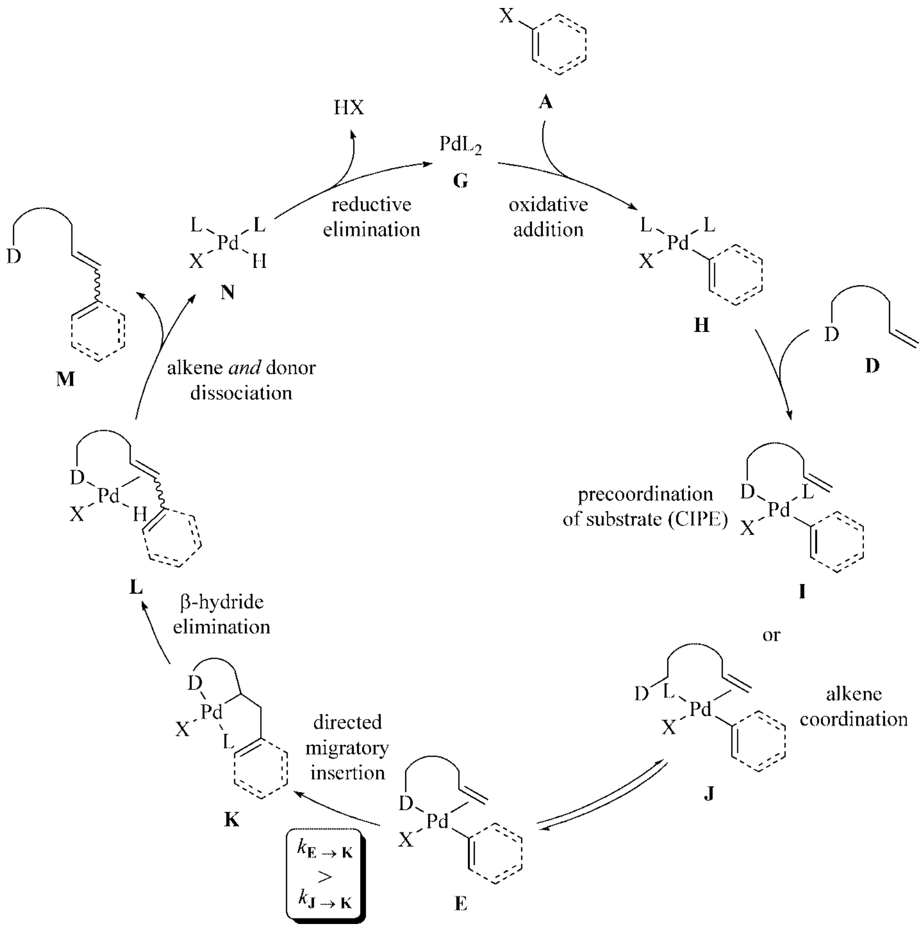
Figure 2. Concept of "chelation control" (L = neutral or anionic ligand)

Although chelation is the essential feature in these Heck reactions, it must be noted that the descriptive term "chelation control" is somewhat unfortunate. As already mentioned, the intermolecular, substrate-controlled Heck reaction is a (pseudo-)unimolecular process, as is the corresponding intramolecular reaction, whereas chelation control is associated with bimolecular transformations, as in addition of nucleophiles to carbonyl compounds. In this context, chelation and non-chelation control have been discussed in an excellent review by Reetz.[14] Therefore, these Heck reactions are part of the family of substrate-directed reactions, and such directing influences will sometimes be referred to as neighbouring-group effects.

Catalytic Cycle and Mechanistic Considerations

The textbook mechanism of the Heck reaction is still widely accepted even though detailed mechanistic investigations have led to a more refined understanding in recent years.[3] However, many of these mechanistic subtleties[10] only apply to specific reaction conditions. In particular, palladium precatalysts, ligands and additives have a profound influence on the reaction mechanism.[10] Scheme 1 shows a general catalytic cycle, which is adjusted to the presentation of the principles needed in substrate-directed Heck reactions.

The catalytic cycle begins with the oxidative addition of a palladium(0) catalyst **G** into the C(sp^2)–X bond of **A**. The resulting σ-arylpalladium(II) complex **H** is usually more Lewis acidic (or electrophilic) than **G**. Intermediate **H** will initially coordinate to one of the two Lewis basic sites available in substrate **D**. Precoordination of **H** to the donor group D in **D**, followed by alkene coordination, is only favoured (**H** → **I** → **E**) if the tether creates an ideal vicinity of both Lewis basic moieties. This desired order of coordination events is called the complex-induced proximity effect



Scheme 1. Catalytic cycle for a substrate-directed Heck reaction; depending on the nature of X and L, these ligands are interchangeable in the complexes

(CIPE),[15] in which the donor D provides a temporary residence site prior to subsequent processes. Conversely, if the tethered donor in **I** is unable to deliver the palladium centre to the alkene, the chelate **E** will not be formed. Hence, **I** might dissociate and directly coordinate to the alkene fragment (**H** → **J**). The unwanted intermediate **J** will proceed in the catalytic cycle without any substrate direction as in a standard bimolecular intermolecular Heck reaction.

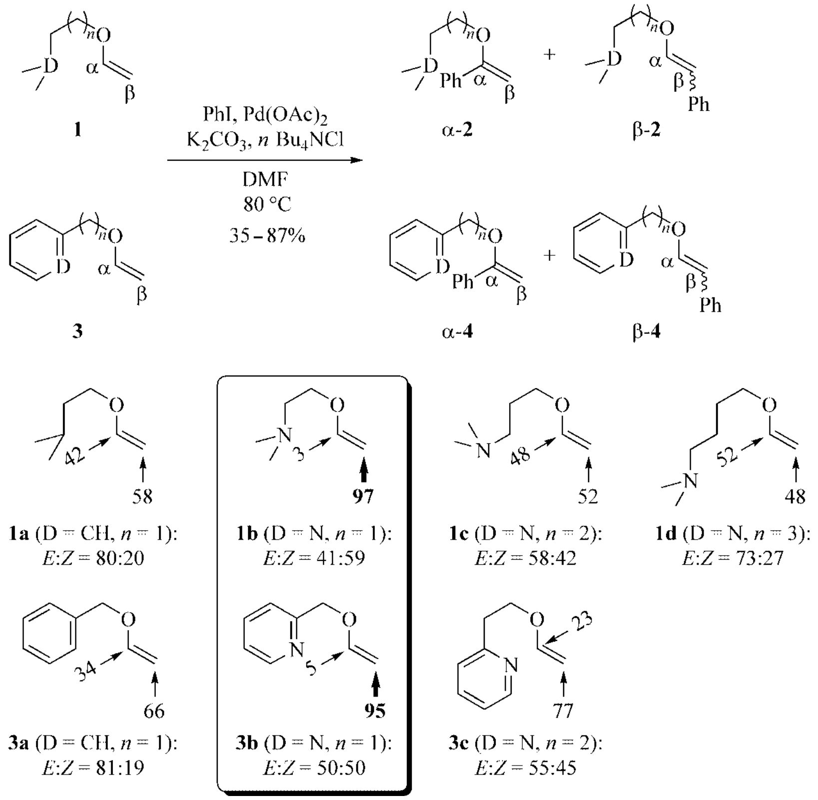
Both σ-arylpalladium(II) complexes **J** and **E** might undergo the migratory insertion, which will occur at different reaction rates k, with $k_{\mathbf{E}\rightarrow\mathbf{K}}$ being substantially larger than $k_{\mathbf{J}\rightarrow\mathbf{K}}$. An enhanced reaction rate is often a reliable indicator of the presence of a substrate-directing effect.[12] Given an optimal array of ligands at palladium in **E**, the alkene insertion will afford σ-alkylpalladium(II) intermediate **K** highly regioselectively. After the carbon–carbon bond formation, **K** readily undergoes β-hydride elimination (**K** → **L**), often without control of the double-bond geometry, to release the product **M** (**L** → **N**). Importantly, both the alkene and the donor have to dissociate from the palladium(II) centre in order to avoid product inhibition. Therefore, choosing a suitable donor group must be well-balanced for reversible binding. Reductive elimination of the hydridopalladium(II) species **N** completes the catalytic cycle (**N** → **G**).

Apart from enhanced reaction rates and control of regioselectivity, the presence of a reagent-directing donor offers another advantage of eminent synthetic potential. These intermolecular Heck reactions are applicable to trisubstituted alkenes, which otherwise would react sluggishly.

Heteroatom-Directed Heck Reactions: Neighbouring-Group Effects

Intermolecular Heck Reactions: Controlling Regioselectivity

In his seminal investigations, Hallberg nicely delineated the essential demands for achieving excellent regiocontrol in an intermolecular Heck reaction.[11a,11b] A series of vinyl ethers **1** and **3** was arylated under so-called Jeffery conditions (**1** → **2** and **3** → **4**, Scheme 2). Substrates **1a** ($n = 1$) and **3a** ($n = 1$), devoid of a coordinating group (D = CH), were chosen as reference systems since their arylation provides a mixture of regioisomers. This poor regioselectivity improved dramatically with the installation of an sp^3-[16a] or sp^2-hybridised[16b] nitrogen, as in **1b** (D = N, $n = 1$) or as part of a pyridyl moiety in **3b** (D = N, $n = 1$).[16] Both substrates displayed a pronounced preference for β- rather than α-arylation. However, the mere presence of such a co-

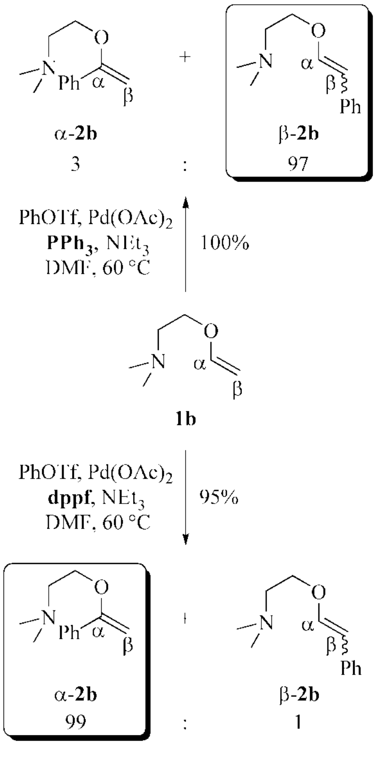


Scheme 2. Amino-directed intermolecular Heck reaction of vinyl ethers; arrows in bold indicate preferential regioselectivity

ordinating amino functionality is not sufficient; Heck reactions of **1c** (D = N, *n* = 2), **1d** (D = N, *n* = 3) and **3c** (D = N, *n* = 2), with stepwise elongated tethers, furnished the disubstituted alkenes **2c/2d** and **4c** in α-/β-selectivities comparable to those of **2a** and **4a** lacking the donor (D = CH). This comparative investigation[11b] verified the assumption that a catalyst-directing amino group located in an ideal vicinity to the carbon–carbon double bond in **1** and **3** is the controlling element for the regiochemistry.

A separate experiment provided further evidence:[11b] the directing effect of the tertiary amine in **1b** is almost completely compensated (α:β = 3:97 vs. α:β = 33:67) when performing the Heck reaction in the presence of an external (strong) donor such as pyridine (1.0 equiv.).

In the course of this systematic study, Hallberg discovered a remarkable peculiarity in the arylation of the standard workhorse **1b**[17] (Scheme 3).[11b] As for the previously described Jeffery conditions (**1b** → β-**2b**, Scheme 2), high regioselectivities were also obtained with the usual Heck protocol for cationic reaction conditions (**1b** → β-**2b**, Scheme 3). Interestingly, however, replacing the monodentate PPh_3 by a bidentate phosphane such as dppf resulted in a complete reversal of the regioselectivity (**1b** → α-**2b**, Scheme 3)! Careful analysis of this puzzling observation led to an interdependence of the bite angle (P–Pd–P) of the bidentate phosphane ligand and the regioselectivity (Figure 3): whereas the β-selectivity remained untouched in the



Scheme 3. Mono- vs. bidentate phosphane: a regiochemical switch

presence of dppm, all other bidentate phosphanes screened favoured the formation of the α-product. Though only a bite angle of approximately 90°, as in dppp and dppf, ensures optimal α-selectivity, slightly different angles, as in dppe (<90°) or dppb (>90°), reduced the selectivity due to the diminished stability of the diphosphanepalladium chelates.

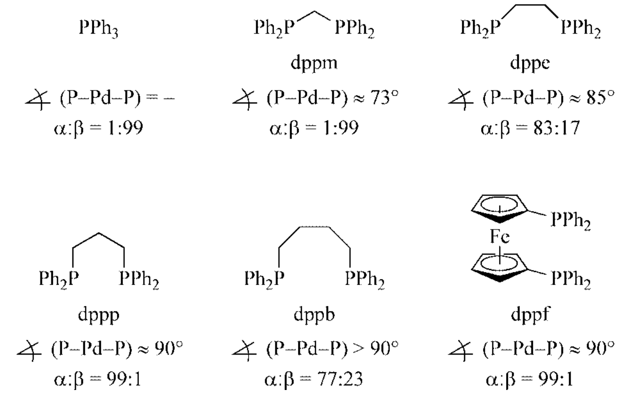
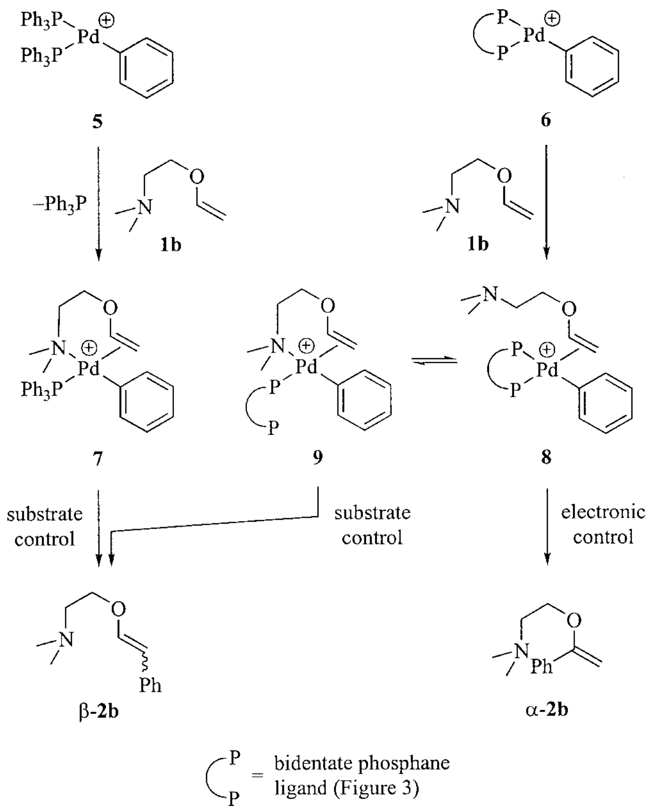


Figure 3. Influence of the bite angle

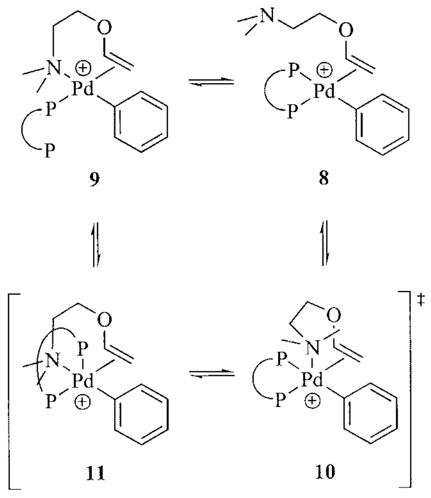
A mechanistic rationale is depicted in Scheme 4. With a monodentate phosphane ligand present, oxidative addition of a palladium(0) precatalyst to the aryl triflate generates the cationic σ-arylpalladium(II) intermediate **5**; the triflate counterion is considered a particularly weak ligand and, therefore, is not coordinated to the electrophilic palladium centre. Following a reaction sequence of precoordination of the amino group and the alkene (**H** → **E**, Scheme 1), the tetracoordinate alkenepalladium complex **7** is formed (**5** → **7**, Scheme 4). Directed migratory insertion and subsequent steps liberate the β-regioisomer β-**2b**.

A different scenario applies with palladium complexed by a bidentate (chelating) phosphane. The carbon–carbon double bond of **1b** is coordinated by the cationic palladium reagent (**6** → **8**, Scheme 4; alternative precoordination of the tertiary amine by **6** is omitted for the sake of clarity). Without the amine donor coordinated by the palladium catalyst, the regioselectivity of the alkene insertion is controlled by electronic (and steric) factors as in a usual intermolecular Heck reaction favouring regioisomer α-**2b**.[11] The palladium complex **8** is in equilibrium with another tetracoordinate complex **9**, in which one of the phosphanyl groups of the bidentate diphosphane is substituted by the intramolecularly available amino group. Depending on the bite angle of the diphosphane, and hence the stability of the P–Pd–P chelate, this displacement is a more- or less-facile process (bite angle ≠ 90°) shifting the equilibrium to the left-hand side (Scheme 4).

Current understanding suggests that the equilibrium of the square-planar complexes **8** and **9** might proceed via the pentacoordinate complex **10** by axial association of the tertiary amine. This hypothetical intermediate, in turn, equilibrates with **11** by pseudorotational processes (Scheme 5); this is supported by literature precedent.[18] It should be noted that migratory insertion involving pentacoordinate palladium complexes such as **10** or **11** appears rather unlikely.[19]



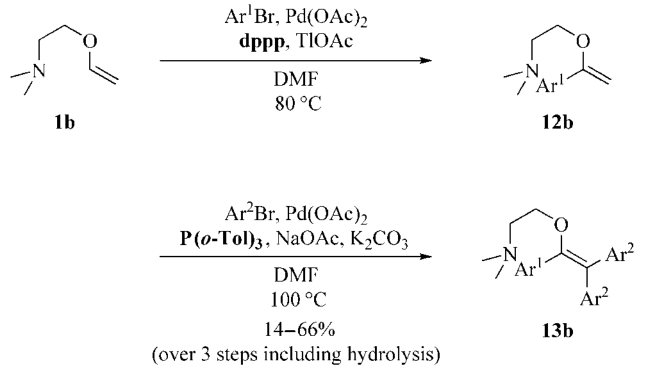
Scheme 4. Mechanistic rationale for inverted regioselectivity



Scheme 5. Substitution at a square-planar palladium complex

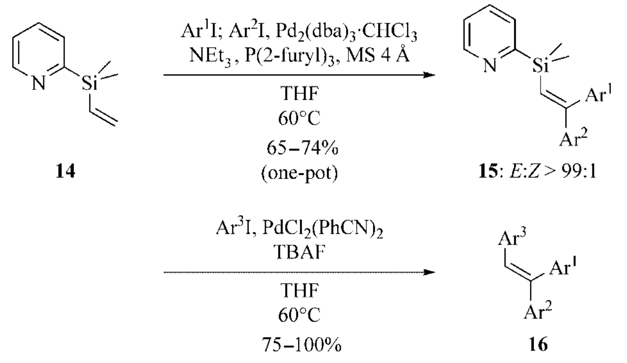
This regiochemical switch has recently found a noteworthy synthetic application.[20] Hallberg has employed the simple platform **1b** for the practical, two-step synthesis of triarylated vinyl ethers **13b** (Scheme 6), which furnish β,β-diarylated acetophenone derivatives upon hydrolysis. In the first step, the regiochemical controller is switched “off” by the bidentate diphosphane dppp, which ensures high α-regioselectivity (**1b** → **12b**). Replacing dppp by monodentate

P(o-tol)$_3$ switches the regiocontroller "on" and allows for selective twofold β-arylation. It proved advantageous to perform α-arylation prior to β-arylation; highly regioselective α,β- (38–70%) as well as β,β-diarylations (36–65% without hydrolysis) work equally well.[20] This reaction sequence is an impressive example of the benefits of a removable directing group enabling the threefold arylation of a carbon–carbon double bond; these are known to be extremely sluggish in the absence of a donor.



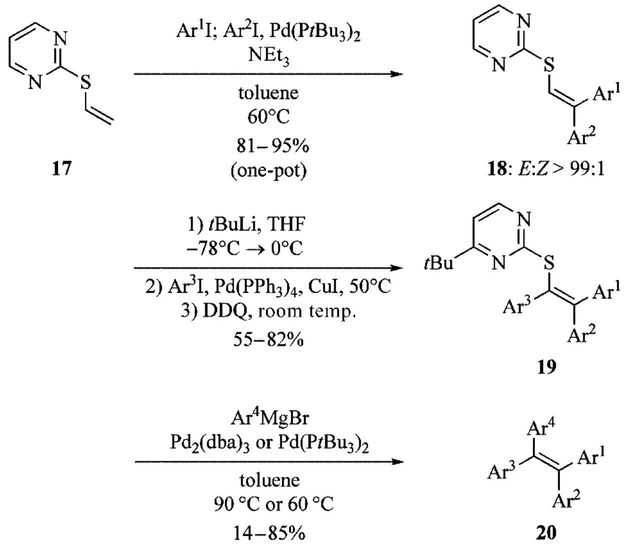
Scheme 6. Sequential directed Heck arylations reported by Hallberg; Ar^1 and Ar^2 = versatile (functionalised) aryl groups

During the quest for such useful platforms, Yoshida has independently developed the two versatile starting materials **14** (Scheme 7)[21] and **17** (Scheme 8).[22] Both the 2-pyridyl and the 2-pyrimidyl group are excellent catalyst-directing groups but, more importantly, Yoshida has elegantly connected these groups to the carbon–carbon double bond by employing synthetically useful tethers. The silicon tether of the vinylsilane **14** is a simple place holder for hydrogen (protodesilylation) or a useful functional group for subsequent Hiyama cross-coupling reactions.[21,23] Similarly, the thioether moiety in **17** is easily cross-coupled with Grignard reagents under palladium catalysis.[22]



Scheme 7. Multisubstituted alkenes by directed Heck arylations reported by Yoshida, Ar^1, Ar^2 and Ar^3 = versatile (functionalised) aryl and heteroaryl groups

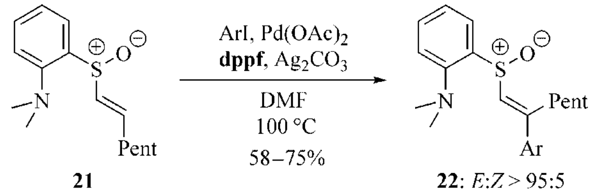
A typical reaction sequence is depicted in Scheme 7.[21] Compound **14** is subjected to a one-pot, double Heck arylation with two different aryl iodides, which are added successively (**14** → **15**); the β,β-diaryl vinylsilanes **15** are formed with high regio- and diastereoselectivity. Notably, cleavage of the carbon–silicon bond, commonly observed in Heck reactions of vinylsilanes, is not detected. A third aryl group is introduced by Hiyama cross-coupling of the integrated silicon group.[23] This extremely flexible methodology offers an approach to the straightforward preparation of a library of triarylated alkenes **16** with defined double-bond geometry!



Scheme 8. Multisubstituted alkenes by directed Heck arylations reported by Yoshida; Ar^1, Ar^2 and Ar^3 = versatile (functionalised) aryl and heteroaryl groups

Using platform **17**, Yoshida even accomplished a stereoselective route to tetraarylated alkenes **20** (Scheme 8).[22] Again, the initial step is a one-pot double Heck arylation that furnishes the β,β-diaryl vinyl thioether **18** with high diastereoselectivity (**17** → **18**). Cleverly, the pyrimidyl moiety is employed in a directed α-lithiation of **18** to form a five-membered chelate. A second equivalent of tBuLi is consumed by the pyrimidyl group, which is prone to nucleophilic attack; this flaw is ironed out by final reoxidation using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). The intermediate vinyllithium is cross-coupled with a third aryl iodide under copper and palladium catalysis (**18** → **19**). Finally, the fourth aryl substituent is introduced by the above-mentioned palladium-catalysed cross-coupling of the vinyl sulfide moiety and a Grignard reagent (**19** → **20**). This constitutes a modular and diastereoselective synthesis of this difficult-to-obtain class of tetraarylalkenes.

Carretero has designed a sulfoxide tether bearing a 2-anilido group as the catalyst-directing donor.[24] The otherwise capricious arylation of α,β-unsaturated sulfoxides is facilitated by the coordinating amino group, and carbon–carbon bond formation occurs selectively in the β-position (**21** → **22**, Scheme 9). Nota bene: The observation by Hallberg that mono-/bidentate phosphanes influence the reaction rate and regioselectivity (Scheme 3)[11b] is not transferable to the work of Carretero.

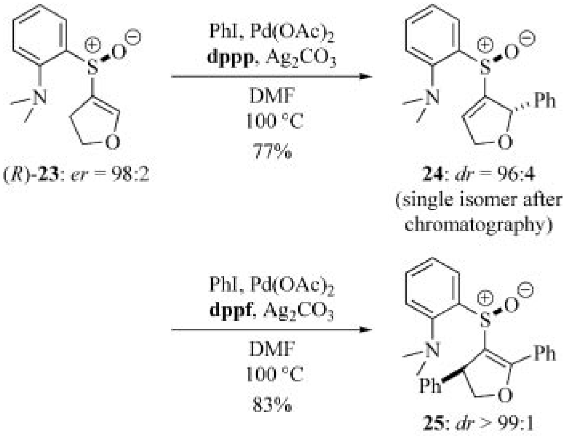


Scheme 9. Amino-directed Heck reaction reported by Carretero using a sulfoxide tether; Ar = versatile (functionalised) aryl groups

Apart from this targeted design of several catalyst-directing groups for intermolecular Heck reactions,[11,17,20–24] a few other substrate-controlled Heck reactions have been reported in the literature. Cacchi, for example, suspected a hydroxy-directing effect in the vinylation of allylic alcohols,[25a] which was applied by Kang to the arylation of allylic diols.[25b] *O*-[26a] as well as *N*-allylated[26b] carbamates also display neighbouring-group effects.

Intermolecular Heck Reactions: Controlling Diastereoselectivity

The first to realize that these neighbouring-group effects in Heck reactions are potential handles for controlling diastereoselectivity was Carretero.[27] Exploitation of the inherent chirality of the sulfoxide tether as a stereochemical controller led to the enantioenriched 2,3-dihydrofuran derivative (*R*)-**23**, which is decorated with an asymmetrically substituted sulfoxide tying together the furan backbone and the coordinating 2-anilido group (Scheme 10).[27a]



Scheme 10. Sequential, diastereoselective, amino-directed Heck reaction reported by Carretero

Indeed, intermolecular Heck arylation of (*R*)-**23** yields **24** with excellent diastereoselectivity. The substrate control was unambiguously secured by Heck reaction of the requisite precursor devoid of the *N*,*N*-dimethylamino donor; arylation under identical reaction conditions clearly favoured the opposite diastereomer (not shown, *dr* = 23:77).

The high stereoselectivity is conceivable by means of the two diastereomeric alkenepalladium complexes **26** and **27**.[27a,27c] With substrate-control operating, the carbon–carbon double bond is attacked from the *si*-face (**26**, Figure 4); steric control in turn would result in *re*-face attack (**27**, Figure 4). As already discussed, the migratory insertion is believed to involve tetra- rather than pentacoordinate alkenepalladium complexes. The complexes depicted in Figure 4 are only to be understood as a simplified presentation since the ligand L is in reality a bidentate diphosphane. Therefore, formation of **26** might follow the pathways delineated in Scheme 5. However, other reaction pathways cannot be ruled out at this stage. One might hypothesize that coordination of the amino group is only preorganizing the palladium-substrate complex; displacement of the catalyst-directing group by the alkene itself leaves the chelating diphosphane untouched.

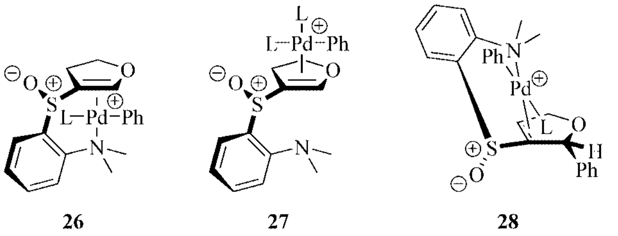
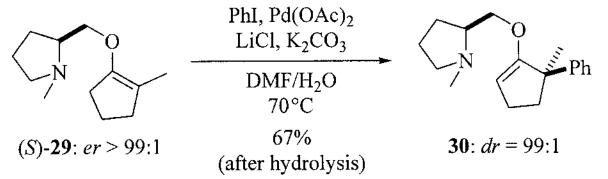


Figure 4. Mechanistic rationale for single and double Heck arylation

Carretero nicely extended this chemistry by subjecting **24** to a second Heck arylation, which shows perfect diastereoselectivity (**24** → **25**, Scheme 10).[27] The complex **28** proposed by the authors is a reasonable explanation for the observed top-face attack (Figure 4). Later, the same methodology was applied to the related cyclopentene derivative.[27b]

Hallberg had already substantiated experimentally in his early work[11a] that, if the nitrogen of the platform **1b** is incorporated into a six-membered cycle, the regiocontrol is still very high. Amazingly, the modified proline-derived system (*S*)-**29** has only been reported very recently (Scheme 11).[28] The intermolecular arylation of its tetrasubstituted (!) alkene generates a stereogenic quaternary carbon centre with fantastic diastereoselectivity [(*S*)-**29** → **30**]. This result is rationalised by the intermediacy of **31** (Figure 5).



Scheme 11. Sequential, diastereoselective, amino-directed Heck reaction reported by Hallberg

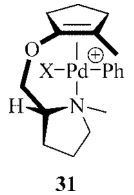

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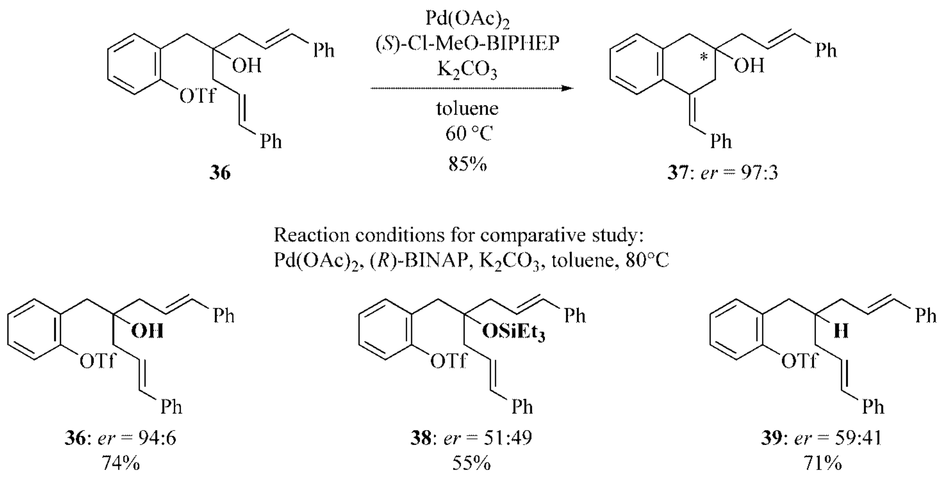
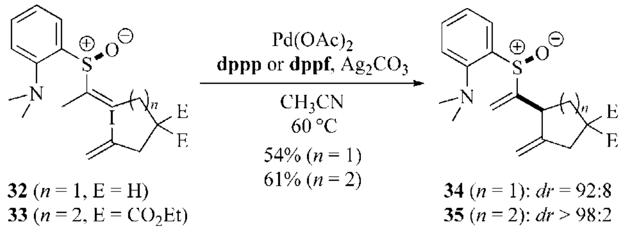
Figure 5. Proposed alkenepalladium complex



Scheme 13. Hydroxy-directed, desymmetrizing Heck cyclisation reported by Oestreich

Intramolecular Heck Reactions: Controlling Diastereoselectivity

Application of Carretero's auxiliary to an intramolecular Heck reaction has also been crowned with success.[29] Vinyl iodides **32** (*n* = 1) and **33** (*n* = 2) cyclise in moderate yield yet with good to excellent diastereoselectivity (**32** → **34** and **33** → **35**, Scheme 12). The origin of this diastereoselectivity still remains unclear, although control experiments have identified unequivocally the catalyst-directing group as the decisive feature in these ring closures. As in the intermolecular variant, the diastereoselectivity decreases substantially (*dr* = 54:46).



Scheme 12. Amino-directed, diastereoselective Heck cyclisation reported by Carretero

Intramolecular Heck Reactions: Controlling Enantioselectivity

A recent discovery by Oestreich indicates that a catalyst-directing group in an achiral (!) substrate is controlling the level of enantioselectivity in a catalytic asymmetric intramolecular Heck reaction with external chiral induction.[30] The desymmetrizing Heck cyclization[5a,6b–6d] of acyclic **36** provides the six-membered ring **37** in very good yield and enantiomeric ratio under optimised reaction conditions (**36** → **37**, Scheme 13).

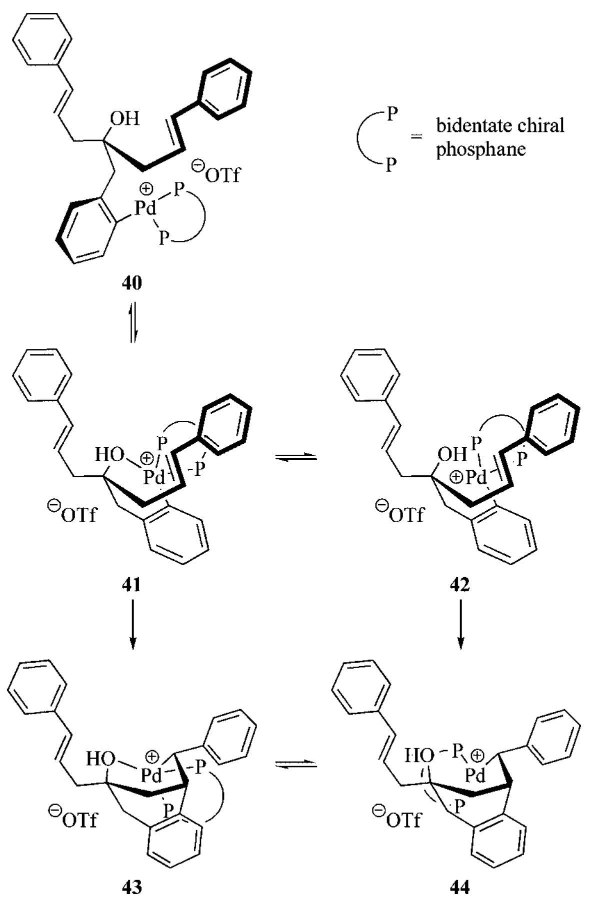
Further investigations disclosed that the tertiary hydroxy group[25] in **36** is the enantiocontrolling element in this enantioselective Heck ring closure. Cyclisation of the *O*-silylated precursor **38** as well as the deoxygenated substrate **39** required higher reaction temperatures (80 °C instead of 60 °C) and generated the corresponding products in almost racemic form (*er* = 51:49 for **38** and *er* = 59:41 for **39**). In an important experiment, the influence of the internal hydroxy group was restrained by the addition of an external tertiary alcohol such as *t*BuOH (1.0 equiv.); the enantiomeric ratio eroded from *er* = 94:6 to *er* = 77:23.

Based on these experimental observations, Oestreich has proposed a mechanism,[30] in which the cationic arylpalladium species **40** is reversibly coordinated by the tertiary hydroxy group,[25] forming a six-membered ring (**40** and **41**, Scheme 14). The fate of key intermediate **41** is in question since direct migratory alkene insertion involving pentacoordinate palladium is not to be expected.[31] As for many of the other alkenepalladium complexes presented in this microreview, the understanding of this process is very vague (**41** → **43**). However, a modified scenario might be likely: coordination of the hydroxy group in **41** generates a highly ordered transition state which allows for efficient differentiation of the formerly enantiotopic branches of **36**. Thus, a dissociative (**41** → **42** → **44**) migratory insertion seems more plausible than an associative (**41** → **43** → **44**) one. The high enantioselectivity observed for **36** could stem from the ideal vicinity of the hydroxy group and the palladium centre. In addition, the corresponding precursor for a five-membered ring cyclises with poor enantioselectivity.

An interesting experimental and theoretical study by Moberg has revealed weak hydrogen bonding [O–H···Pd^0] as a stabilizing factor in palladium-catalysed allylic alkylations.[32] Thus, it might not be the oxygen of the hydroxy group interacting with the palladium(0) [or palladium(II)] centre (**41**, Scheme 14).

Summary

Starting from the systematic work by Hallberg,[11b] heteroatom-directed Heck reactions have been elaborated into a many-facetted area in synthetic organic chemistry. Several removable catalyst-directing groups have been developed



Scheme 14. Proposed mechanism for hydroxy-directed asymmetric Heck reaction

for the regioselective intermolecular arylation of alkenes.[11,20,21,24] Apart from achieving excellent regiocontrol, the major advantage might be that tri- and tetrasubstituted carbon–carbon double bonds are now introduced to intermolecular Heck chemistry. The enormous synthetic potential has been demonstrated by Hallberg and Yoshida with a modular approach to tri- and tetrasubstituted alkenes with a defined configuration.[20,21]

A further significant advancement has been accomplished by Carretero, who reported the first diastereoselective substrate-controlled Heck reaction with the aid of a catalyst-directing group.[27,29] The same concept has been successfully applied by Hallberg to the first construction of chiral quaternary carbons using an intermolecular Heck reaction.[28]

It is known from a publication by Cacchi that an unprotected hydroxy group interferes with the palladium centre in a Heck reaction.[25a] Oestreich has shown that such an interaction is the enantiocontrolling element in a catalytic asymmetric Heck cyclisation of an achiral precursor.[30] This first evident example of a substrate-controlled enantioselective reaction illustrates that enantioselection is sometimes discriminated not only by the chiral reagent but also by a suitably located donor.

This microreview might sharpen the view for similar neighbouring-group effects, which might have been overlooked in the past, and stimulate further investigations in this area of Heck chemistry.

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