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REVIEW

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Enantioselective oxidative boron Heck reactions

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This review highlights the use of the oxidative boron Heck reaction in enantioselective Heck-type couplings. The enantioselective oxidative boron Heck reaction overcomes several limitations of the traditional Pd(0)-catalysed Heck coupling and has subsequently allowed for intermolecular couplings of challenging systems such as cyclic enones, acyclic alkenes, and even site selectively on remote alkenes.

1. Introduction

Intramolecular asymmetric Pd(0) Mizoroki–Heck couplings[1] were among the first catalytic enantioselective carbon–carbon bond forming reactions to be explored and have been successfully applied in natural product synthesis.[2] In contrast, efficient intermolecular enantioselective Pd(0)-catalysed Heck reactions have proven more elusive, with the exception of couplings with specific "benchmark" cyclic olefins such as dihydrofuran and dihydropyrrole. Recently, however, much progress has been made in the field of enantioselective Heck-type couplings[3,4] with the emergence of the Pd(II)-catalysed oxidative boron Heck variant (also called boron-Heck, or oxidative Heck) to overcome these limitations. The use of the oxidative Heck method has allowed for intermolecular couplings of more challenging systems, including desymmetrisation of quaternary centres, cyclic enones, acyclic alkenes and even site selectively on remote alkenes. This review will briefly outline the oxidative boron Heck reaction, followed by highlighting the major recent advances in enantioselective oxidative boron Heck couplings.

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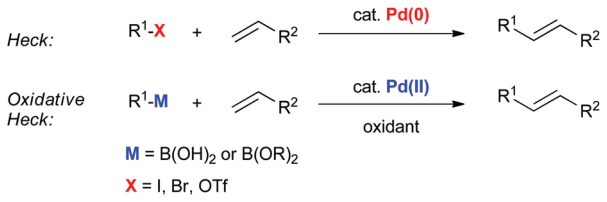
2. Oxidative boron Heck reaction

Oxidative boron Heck (hereafter shortened to oxidative Heck) reactions are catalysed by Pd(II) instead of Pd(0) and differ from the traditional Pd(0)-catalysed Mizoroki–Heck reactions during the first step in the catalytic cycle (Schemes 1 and 2).[5] The halide or triflate (R^1X) in the Mizoroki–Heck reaction is replaced by the corresponding organoboronic acid [$R^1B(OH)_2$] in the oxidative Heck reaction. Therefore, the first step in the catalytic cycle is the transmetallation between the organoboronic acid and Pd(II) catalyst (Scheme 2), instead of an oxidative addition of Pd(0) into a halide or triflate. As such, the oxidative Heck reaction often does not require high temperatures or bases. However, an oxidant [usually O_2, air, benzoquinone or $Cu(OAc)_2$] is required to re-oxidise Pd(0) to Pd(II) at the end of the catalytic cycle.

Oxidative Heck reactions are known to be efficient, mild (*e.g.* lower reaction temperatures, good functional group toler-



Scheme 1 Difference between the Mizoroki–Heck and oxidative Heck reactions.

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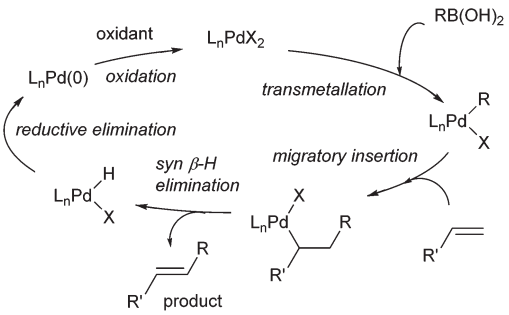
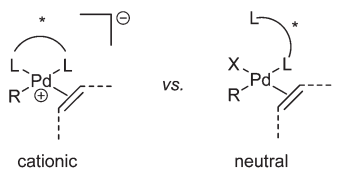


Scheme 2 Proposed general mechanism for the oxidative boron Heck reaction.

ance), tolerant of air and moisture and are capable of coupling challenging substrates such as highly substituted or cyclic olefins, many of which can be reluctant to undergo Pd(0)-catalysed Mizoroki–Heck couplings.[6] Another advantage of changing from Pd(0) to Pd(II) catalysis is that both N-based as well as P-based ligands can now be used (*vide infra*). Furthermore, the absence of a halogen–Pd intermediate in the reaction means it is likely to proceed *via* the cationic rather than neutral route, which is thought to be important for enantioselectivity (Scheme 3).[7]

The non-enantioselective and stoichiometric oxidative Heck coupling was first reported by Heck in 1975,[8] while the catalytic version was developed by Uemura in 1994.[9] However, it was not until the 2000's that the reaction was developed further, initially by Mori in 2001:[10] reporting the use of $Cu(OAc)_2$ as an oxidant, followed by the use of molecular oxygen as the oxidant by Jung in 2003.[11] The first ligand modulated reaction (using dimethyl-1,10-phenanthroline) was reported by Larhed in 2004.[12] Further investigations by Jung, Larhed and others led to the identification of bidentate N-ligands as optimal ligands, the discovery of base-free conditions, and air as the oxidant, which further improved the mildness and practicality of the reaction.[6,13]

The ability of the Pd(II)-oxidative Heck reaction to readily couple even cyclic substrates should be highlighted,[14] as cyclic enones are notoriously reluctant to undergo intermolecular Pd(0)-catalysed Mizoroki–Heck couplings and often produce the conjugate addition products instead.[15] This is usually attributed to the fact that cyclic systems such as **1** are stereochemically precluded from undergoing the final step in the traditional Pd(0) Heck cycle: the *syn*-β-H elimination.[15a,16] It should be noted that Pd(II)-catalysed reactions with enones

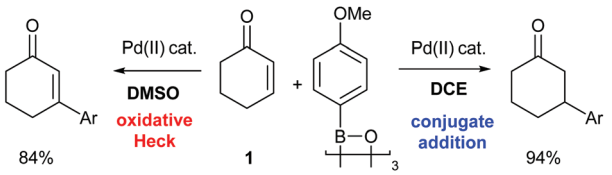


Scheme 3 Proposed cationic *vs.* neutral pathway.

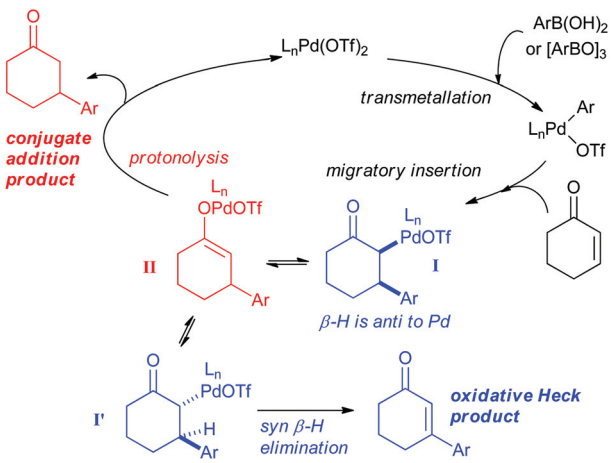
and boronic acids can, depending on the conditions, result in conjugate additions rather than Heck-type couplings,[17] and the two reactions can sometimes also be competing pathways. Within this context, controlled switching between the Pd(II)-catalysed oxidative Heck and conjugate addition reactions have recently been reported (Scheme 4).[18,19] A simple change of solvent from DCE ($ClCH_2CH_2Cl$) to DMSO switches the reaction from conjugate addition to oxidative Heck.

As shown in Scheme 5, the mechanism of the two reactions is thought to diverge after the transmetallation and migratory insertion steps. Intermediate **I** can either undergo epimerisation followed by *syn*-β-H elimination to produce the oxidative Heck product or protonolysis (possibly *via* Pd-enolate **II**) to produce the conjugate addition product. Conditions to promote the epimerisation of **I** to **I′**, and thereby allowing the *syn*-β-H elimination, are therefore required to favour the oxidative Heck reaction.

Although there are now opportunities to develop enantioselective Heck-type reactions on cyclic enone and related systems by adopting the oxidative Heck reaction protocol, sterically hindered alkene substrates are still a challenge[18] and conditions must be optimised to avoid the competitive conjugate addition reaction. Indeed, while there are several reports on Pd(II)-catalysed asymmetric conjugate addition reactions on cyclic enones (and related structures),[20] reports on the corresponding asymmetric oxidative Heck reaction have only begun



Scheme 4 Controlled switching between oxidative Heck and conjugate addition reactions.



Scheme 5 Proposed mechanisms for the Pd(II)-catalysed oxidative Heck and conjugate addition reactions.

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to emerge (*vide infra*). Nevertheless, the ability to couple even highly substituted alkenes and cyclic enones (both challenging substrates under traditional Pd(0) catalysis) under mild conditions using a wide variety of ligands means that the oxidative Heck reaction has great potential to progress the field of asymmetric Heck-type reactions, especially in the area of the more challenging intermolecular couplings.

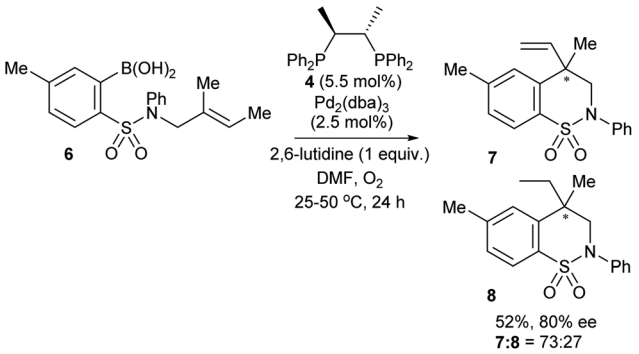
3. Enantioselective oxidative Heck reactions

3.1 Cyclic alkenes

The first reported attempt at enantioselective oxidative Heck coupling emerged in 2005 by Mikami and co-workers, who utilised the cyclic system **2**.[21] Following a screen of various chiral bidentate *N* as well as *P* ligands, the phosphine ligand (*S*,*S*)-chiraphos **4** was considered optimal, providing **5** with ees[22] of up to 49% (Scheme 6). It is worth noting that enantioselective Heck-type coupling is possible with substrate **2**, because the *syn*-β-H elimination occurs at the available position β′ instead of β, thus furnishing a chiral centre, and this also avoids any issues with having to epimerise at the β-position to form an available *syn*-β-H. Although this early work had a limited substrate scope (*e.g.* arylboronic acid **3a** only) and modest enantioselectivities, it was nevertheless pioneering, and paved the way for further studies in the area.

Since the main advantage of the oxidative Heck reaction is to enable asymmetric intermolecular Heck-type couplings, it is perhaps unsurprising that there appears to be only one report of an asymmetric intramolecular oxidative Heck reaction, again by Mikami and co-workers in 2007.[23] A chiral quaternary carbon is installed in 80% ee (**7**) *via* ring closure of a sulphonamide species **6** (Scheme 7). However, the reduced alkene product **8** is always present as a side product.

As previously mentioned, there are a few privileged alkene substrates in enantioselective Heck-type couplings and 2,3-dihydrofuran **9** is one such alkene which is often used as a standard benchmark substrate for enantioselective intermolecular Heck reactions. In 2007, Gelman and co-workers demonstrated that good enantioselectivities of **10** (up to 86% ee) could be achieved using oxidative Heck coupling

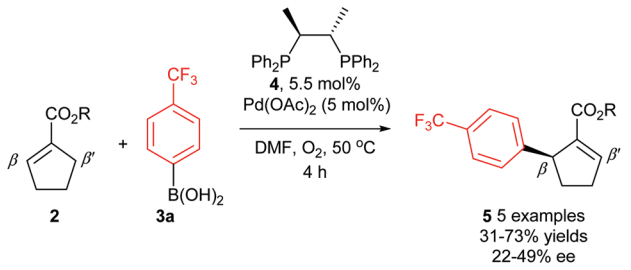


Scheme 7 Intramolecular enantioselective oxidative Heck coupling by Mikami.

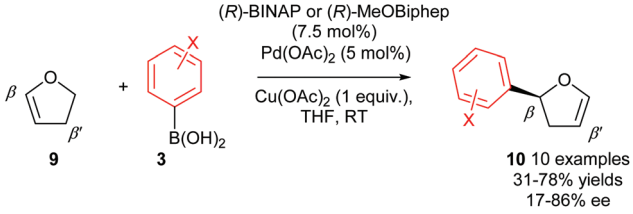
(Scheme 8).[7] Chiral bidentate phosphine ligands (*R*)-BINAP or (*R*)-MeOBiphep were found to be optimal and enantioselectivities were generally moderate to good for a range of arylboronic acid coupling partners **3** with the exception of *ortho* substituted aryls, which gave poor ees. Once again, the enantioselective Heck-type reaction is possible on 2,3-dihydrofuran **9** because the *syn*-β-H elimination step occurs at the β′-position, where a *syn*-H is available. Isomerisation of the resulting 3,4-dihydropyran intermediate subsequently provides the enol ether product **10**.

Although the abovementioned early examples utilised chiral phosphine ligands, subsequent reports on enantioselective oxidative Heck couplings have tended to move away from phosphines in favour of N-ligands. For example, the use of the chiral dimeric tridentate NHC–amidate–alkoxide palladium(II) complex **12** allowed Jung and co-workers to significantly improve the enantioselectivities as well as substrate scope of the oxidative Heck reactions on substrates **11** (*vs.* Mikami's original report in 2005, Scheme 6). Not only are the ees now consistently 81–88%, but various substituents on the arylboronic acid **3** are now tolerated (Scheme 9). However, the current drawback to using catalyst **12** is that the yields are generally moderate (44–62%), due to a significant amount of deborylation in a side reaction to produce phenolic side-products.

So far, the enantioselective oxidative Heck reactions described form a new stereogenic centre in cyclic alkenes where conformational rigidity and hence restricted rotation



Scheme 6 First example of enantioselective oxidative Heck reaction by Mikami.



Scheme 8 Enantioselective oxidative Heck couplings of 2,3-dihydrofuran by Gelman.

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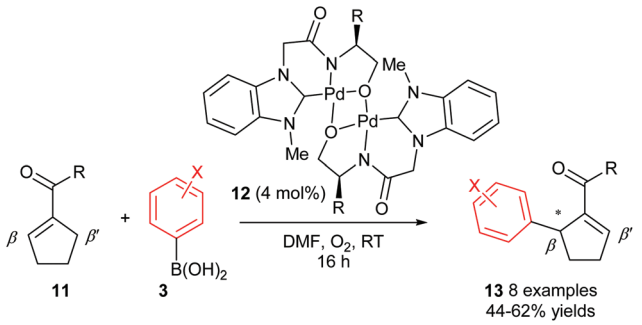
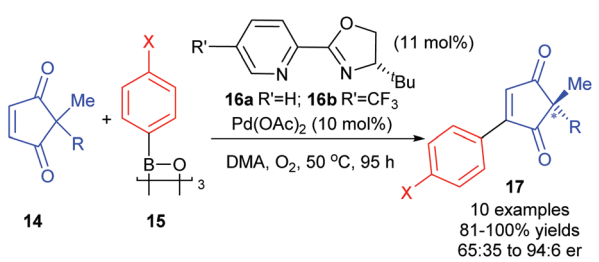


Scheme 9 Higher enantioselectivities achieved by Jung using catalyst **12**.

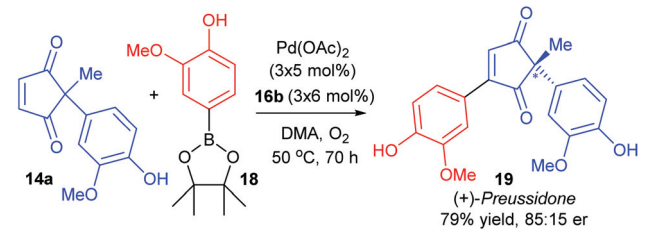
around the C–C bond steers the β-H elimination away from the newly formed C–C bond (β′ instead of β, Schemes 6–9). Instead of the formation of a migrated cross-coupled product, our group was interested in exploiting the oxidative Heck coupling *via* a different approach: a direct coupling to form a stereogenic all-carbon quaternary centre *via* desymmerisation (Scheme 10).[24] 2,2-Disubstituted cyclopentene-1,3-diones **14** were chosen as substrates as this core is found in several biologically active natural products and metabolites.[25] The use of chiral enantiopure PyOX ligands **16a**[26] and **16b**[27] allowed for the oxidative Heck coupling of **14** with a range of arylboroxines **15** (dehydrated form of arylboronic acids) to yield **17** in up to 94 : 6 er (Scheme 10). A current limitation is that the er is modest when R is not an aryl substituent (*e.g.* R═Bn in **14** with X═OMe in **15** gives only 65 : 35 er of corresponding product **17**). Nevertheless, the utility of the method was successfully demonstrated through the synthesis of (+)-preussidone **19** in one step from the enedione **14a**, without the need for any protecting groups on the hydroxyls (Scheme 11).

It should be noted that the solvent was switched from DMF for racemic studies to DMA (dimethylacetamide) for the enantioselective method, in order to avoid issues with competitive ligation from DMF.[28] The temperature of the reaction was also important: at RT, the conjugate addition reaction became competitive, so higher temperatures were necessary for oxidative Heck couplings onto enediones **14**.

In all of the examples highlighted in this section, the migratory insertion step is thought to be enantiodetermining, although mechanistic/modelling studies have yet to be carried out.



Scheme 10 Desymmertisation of all-carbon quaternary centres by Lee.



Scheme 11 Synthesis of (+)-preussidone using enantioselective oxidative Heck reaction.

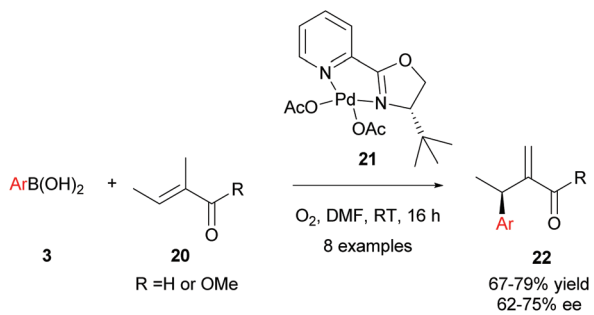
3.2 Acyclic alkenes

Intermolecular enantioselective Heck couplings of acyclic alkenes have traditionally been very challenging. For example, the first reported enantioselective intermolecular Heck coupling of a prochiral acyclic alkene by Uemura and co-workers occurred in a modest 17% ee under Pd(0) catalysis.[29] Therefore, Jung and co-workers' successful use of enantioselective Pd(II)-catalysed oxidative Heck reactions to achieve ees of up to 98% on challenging acyclic substrates are of substantial significance to the field.[30]

In Jung's initial proof-of-concept studies, a chiral N-bidentate ligand (PyOX) was adopted as P-based ligands proved to be inefficient due to side reactions, including homocoupling and phenol formation.[31] As shown in Scheme 12, **21** catalyses the oxidative Heck reaction of aryl boronic acids **3** and trisubstituted acyclic alkenes **20** at room temperature to furnish the migrated cross-coupled alkene **22** in moderate to good yields (67–79%) and enantioselectivities (62–75% ee). In contrast, the standard Pd(0)-catalysed Mizoroki–Heck reaction between iodobenzene and **20** using PPh_3 as the ligand proceeded in <5% yield, even at high temperatures (140 °C).

It should be noted that the pre-formed catalyst **21** provided much higher enantioselectivities compared to commonly used *in situ* formation of **21** *via* premixing $Pd(OAc)_2$ with PyOX ligand **16a** (Scheme 13). This observation was attributed to incomplete formation of **21** in the latter and/or relatively easy dissociation of the ligand **16a** under the reaction conditions.

As in Section 3.1, the migratory insertion step is proposed to be enantiodetermining. Fig. 1 shows the two plausible con-



Scheme 12 Jung's enantioselective oxidative Heck couplings on acyclic alkenes.

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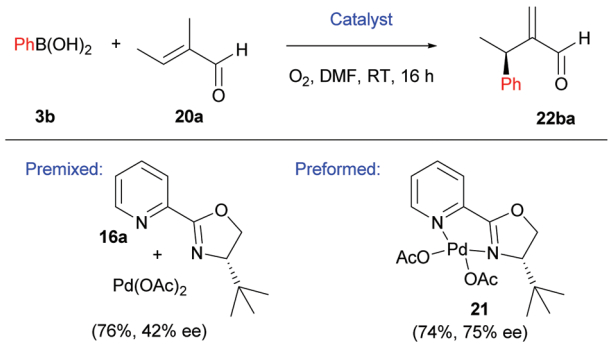


Scheme 13 Premixed *vs.* preformed catalysts.

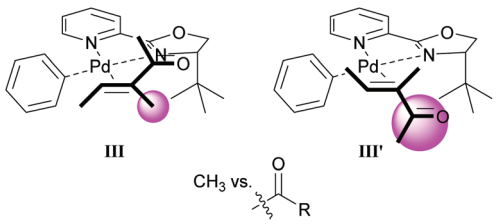
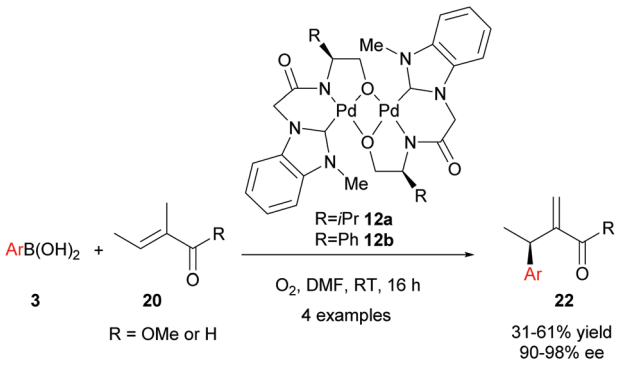


Fig. 1 Proposed conformations for the enantiodetermining step in the oxidative Heck reaction with catalyst **21**.

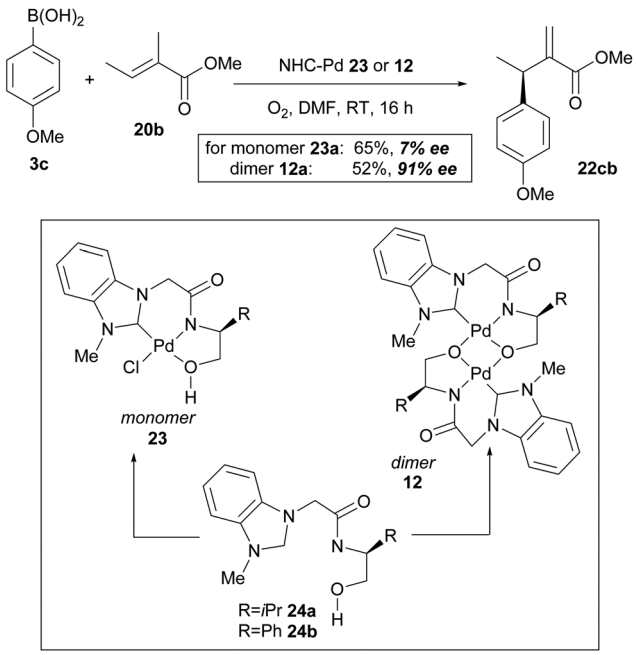
formations for the alkene-coordinated structures during the migratory insertion step. The reaction is thought to proceed through coordination **III** instead of **III′**, because there is more steric repulsion between the alkene substituents (Me in **III** and Ac in **III′**) and the *tert*-butyl group on the oxazoline ring in **III′** compared to **III**. The steric preference for conformation **III** thus leads to the observed enantioselectivity.

Following this proof-of-concept work, Jung and co-workers decided to develop a tighter chiral Pd(II)-ligand complex by utilising a strongly coordinating NHC ligand, as well as a tridentate, rather than bidentate, ligand. To this end, novel air and water-stable chiral palladium(II) complexes with a tridentate N-heterocyclic carbene (NHC) amidate alkoxide ligand **12** were developed in 2008. Complexes **12** successfully catalysed the oxidative Heck couplings of **20** and **3** with excellent enantioselectivities (90–98% ee, Scheme 14).[30] The high degree of asymmetric induction is proposed to stem from the tight binding of the tridentate ligands to Pd during the entire catalytic process. Although the yields of **22** were generally low to modest, the excellent enantioselectivities achieved using the oxidative Heck couplings (>90% ee) were unprecedented in intermolecular Heck-type reactions at the time.

In their subsequent full paper, Jung and co-workers disclosed that both monomer **23** and dimer **12** were originally investigated as catalysts for the coupling between boronic acid **3c** and alkene **20b**, with each providing drastically different results (7% ee and 91% ee of coupled product **22cb** respectively, Scheme 15). ^{1}H NMR analysis reveals that the borate group is transferred to the alkoxide when the dimeric catalyst



Scheme 14 Asymmetric oxidative Heck couplings with excellent enantioselectivities.



Scheme 15 Significant enantioselectivity difference with monomeric and dimeric NHC–Pd catalysts.

12 is used (see borate intermediate **IV**, Scheme 16). In contrast, the borate group does not remain after transmetallation with the monomeric catalyst **23**. The authors therefore suggest that the steric effect of the borate group in **IV** results in the higher enantioselectivities using dimeric catalyst **12**.

As before, the migratory insertion step is thought to be enantiodetermining. Fig. 2 shows the possible transition states for orientation of the alkene to the Pd complex **IV**. Approach by pathway A should be disfavoured by steric hindrance due to steric repulsion on the concave face. The alkene must therefore approach *via* pathway B. Of the two possible alkene coordination models **E** and **F**, coordination model **E** is disfavoured by steric hindrance between the alkenyl methyl substituent and the borate group. Therefore, coordination model **F** is

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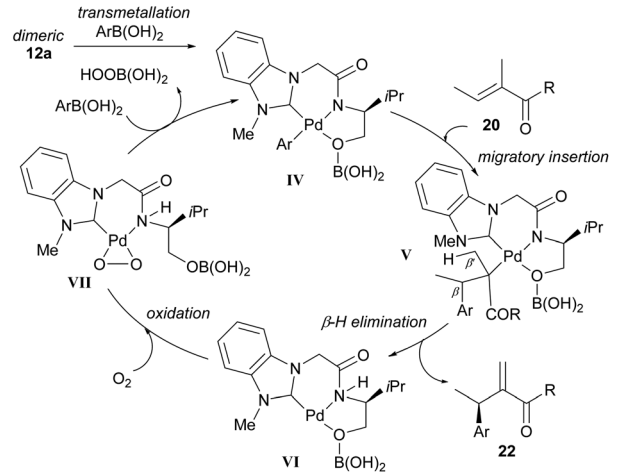


Scheme 16 Proposed mechanism of the enantioselective oxidative Heck reaction using dimeric catalyst **12a**.

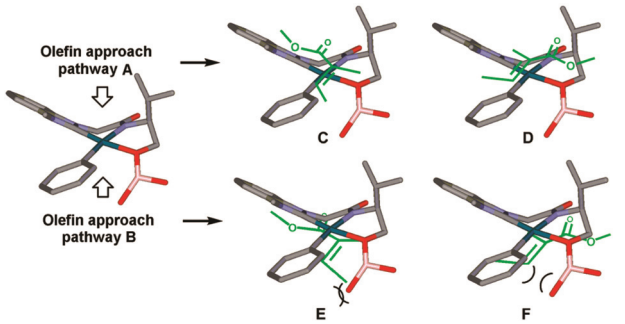


Fig. 2 Possible transition states for orientation of the alkene to Pd complex **IV**. Reprinted with permission from K. S. Yoo, J. O'Neill, S. Sakaguchi, R. Giles, J. H. Lee and K. W. Jung, *J. Org. Chem.*, 2010, **75**, 95. Copyright (2010) American Chemical Society.[32]

favoured and results in the observed stereochemical (*R*)-configuration of product **22**. The opposite alignment of the isopropyl and borate group in **IV** was termed "counter axial groups" by the authors, and is thought to be the key factor for achieving high enantioselectivities. As such, the axial borate group governs the facial selectivity of the incoming alkene starting material when dimeric catalyst **12** is employed, and in contrast, this group is not present in monomeric catalyst **23**, thereby resulting in lower enantioselectivities using the latter.

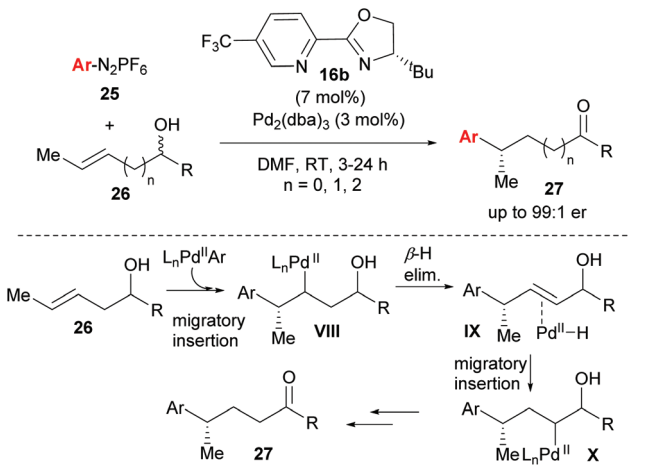
The proposed mechanism is shown in Scheme 16 and commences with transmetallation to produce the key borate species **IV**. Migratory insertion to form **V** and subsequent β-H elimination at position β′ produces the migrated cross-coupled product **22**. Oxidation of the Pd(0) species **VI** by molecular oxygen produces a peroxo–palladium complex **VII**, which then reacts with arylboronic acid to regenerate the borate complex **IV**.

As described above, the enantioselectivities in this study are good to excellent (82%–94% ee, 11 examples), but the yields are poor to moderate (29%–61%). These poor yields are attributed to a significant amount of oxidative deborylation to produce phenolic side-products (*e.g.* in Scheme 15, **22cb** is produced in 52% yield with side reactions: 43% deborylation, 2% homocoupling). Therefore, any further developments in the field will no doubt be centred upon achieving a highly enantioselective and high yielding catalytic system.

3.3 Redox–relay oxidative Heck Reaction

One of the most significant advances in asymmetric Heck-type chemistry in recent years is the redox–relay Heck-type reaction developed by Sigman and co-workers. The concept was first conceived using the Heck–Matsuda coupling[27,33] (Heck-type variant using diazonium salts **25** as coupling partners, Scheme 17), but subsequent developments utilised the oxidative Heck reaction in order to improve the scope and practical application of the method. The work is exceptional because it not only allows for the formation of remote stereocentres, but also because of its excellent site selectivity and ability to distinguish between almost identical C–H bonds in the β-H elimination (see **VIII→IX**). The catalyst system imparts notable regioselectivity (from 80 : 20 for $n = 2$ to full selectivity for $n = 0$ in **27**) during migratory insertion onto **26** and also promotes the migration of the alkene's unsaturation towards the alcohol in a redox isomerisation termed "redox–relay strategy" by the authors, to ultimately form the ketone product **27** (Scheme 17). While the racemic nature of the alkenol substrate does not bias enantioselection, the alkene configuration does ($E \rightarrow S$ and $Z \rightarrow R$). Notably, the PyOX ligand **16b** not only provides enantioinduction and regioselectivity, but also renders the Pd(II) hydride intermediates sufficiently electrophilic to reinsert into the alkene rather than dissociate from it.

As described above, the redox–relay reaction was subsequently expanded to the oxidative Heck coupling (Scheme 18) and mechanistic investigations were carried out in order to determine what controls the regioselectivity of the reaction.[34] Firstly, optimisation studies revealed that both



Scheme 17 Enantioselective redox–relay Heck-Matsuda arylations of acyclic alkenyl alcohols by Sigman and co-workers.

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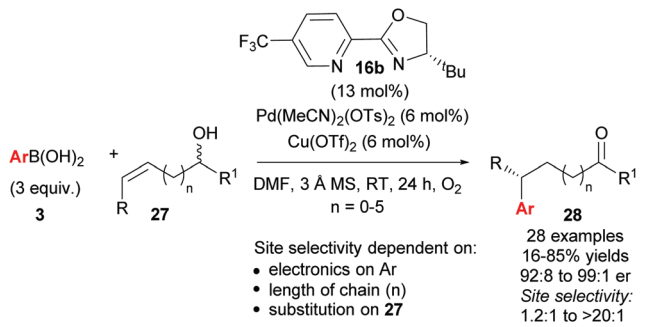
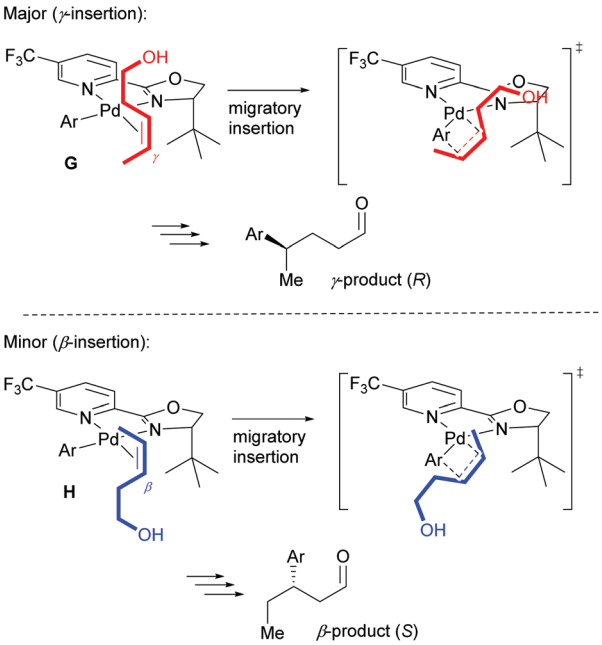
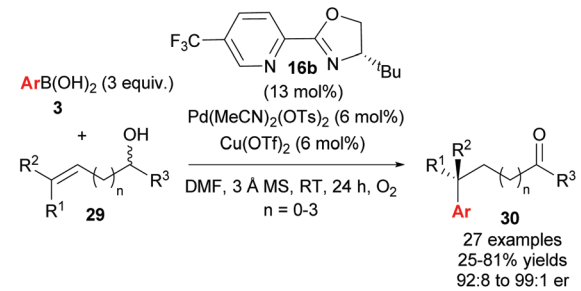


Scheme 18 Enantioselective redox–relay oxidative Heck arylations of acyclic alkenyl alcohols.



Scheme 19 Proposed conformations towards the major and minor products.



Scheme 20 Enantioselective construction of remote quaternary centres by Sigman and co-workers.

$Cu(OTf)_2$ and O_2 oxidants as well as molecular sieves [to prevent retarded oxidation of Pd(0) to Pd(II) using just O_2 or Cu(II)] were required for high conversions (Scheme 18). A thorough substrate scope investigation led to the conclusion that the (generally excellent) enantioselectivity is essentially independent of the nature of both reaction partners. In contrast, site selectivity is controlled by the nature of the arylboronic acid as well as substitution and chain length of the alkenyl alcohol substrate **27**. A plot of site selectivity ratios *vs.* Hammett σ-values shows a clear correlation between the regioselectivity and the electronic nature of the arylboronic acid, with electron poor aryls providing high selectivities and electron rich aryls giving poor selectivity. A plot of site selectivity ratios *vs.* ^{13}C chemical shifts of the alkene (the most downfield-shifted C is distal from the alcohol) also reveals a clear trend (decreased selectivity as *n* increases), suggestive once again of electronic effects governing the site selectivity. The minor isomers also all exhibit high enantioselectivities. Using the evidence above, the authors suggest that the major and minor products arise from opposite faces of the alkene being presented to the catalyst during the migratory insertion step (Scheme 19). Additional support for the electronically influenced site selectivity was subsequently disclosed by DFT calculations on the reaction.[35]

Following their initial study, the method was subsequently extended to enantioselective construction of remote quaternary centres (Scheme 20).[36,37] Typically, quaternary stereocentres are prepared from substrates with pre-existing functional groups adjacent to the reaction site, with the location of the C–C bond formation strictly defined relative to the functional group in question. As such, the ability to install quaternary chiral centres which are remote from existing functional groups, using the oxidative Heck redox relay strategy, is truly exceptional. The reaction is highly site selective for the more hindered position of the alkene **29**, which corroborates the authors' earlier conclusion that the migratory insertion step is selective for the more downfield-shifted carbon, which is proposed to be controlled by remote dipole interactions of the alcohol functional group. In contrast to their results with disubstituted alkenes **27** (Scheme 18), the reaction with trisubstituted alkenes **29** is remarkably site selective irrespective of chain length as well as the electronics on the arylboronic acid **3**, thereby providing an excellent substrate scope of various alkenyl alcohols **29** as well as aryls on **3**. Enantioselectivities are once again excellent (92 : 8 to 99 : 1 er) and a highlight example is shown in Scheme 21: an alkene with sterically similar *n*-ethyl and *n*-butyl groups (**29a**) still provides product **30ba** with a remarkable 97 : 3 er.

An exciting prospect for complex natural product synthesis is that the reaction has the ability to migrate through an existing chiral centre with preservation of enantiomeric composition, as well as catalyst controlled face-selection – two distinct diastereomers of **32** are formed by using different enantiomers of the catalyst (**31**→**32**, Scheme 22). This result implies that the catalyst remains ligated to the substrate and on the same face of the alkene throughout the relay process.

Following this groundbreaking 2014 report, an area of further study was noted to be the expansion of the chemistry

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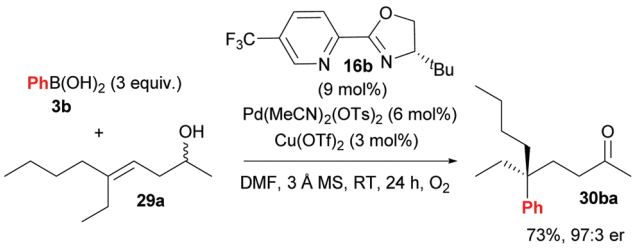
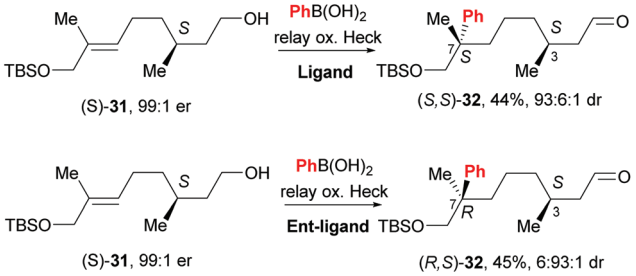
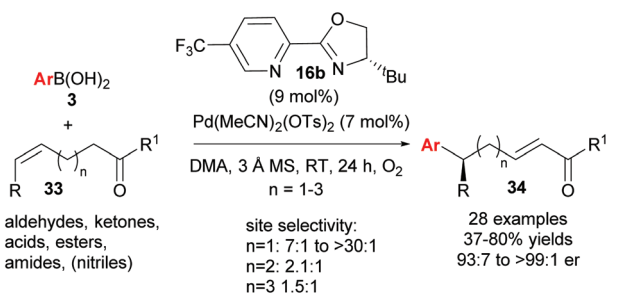


Scheme 21 Remarkable enantioselectivity even for substrates with sterically similar substituents (*n*-ethyl *vs.* *n*-butyl).

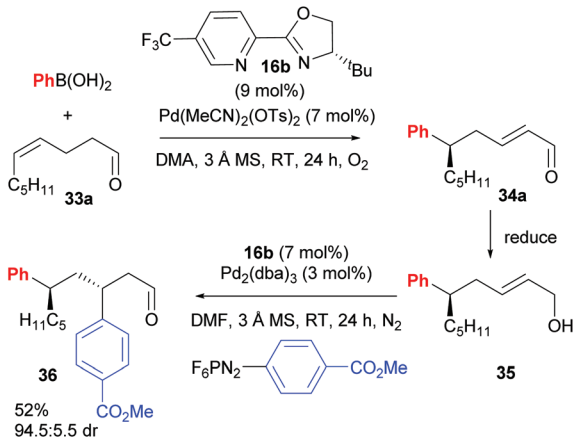


Scheme 22 Configuration of pre-existing chiral centre is retained during chain walking process and face selectivity is catalyst controlled.

beyond the coupling of aryls to other saturated and unsaturated groups, and the ability of groups other than alcohol to intercept the chain-walking Pd-catalyst.[38] Very recently, Sigman and co-workers have successfully demonstrated the ability of carbonyl groups to perform the latter chemistry (**33**→**34**, Scheme 23).[39] There was a significant solvent effect on site selectivity and the use of DMA as solvent provided good to excellent regioselectivites for cases where n = 1. The advantage of using these alkenyl carbonyl substrates is that it now allows for iterative relay Heck reactions *via* a three-step approach (Scheme 24). An oxidative Heck redox–relay reaction on **33a** followed by 1,2-reduction of **34a** provides allylic alcohol **35**, which can subsequently undergo an enantioselective Heck–Matsuda coupling to yield product **36**, with two new stereocentres installed over the 3 steps.



Scheme 23 Enantioselective redox–relay oxidative Heck arylations of alkenyl carbonyl derivatives.



Scheme 24 Iterative relay Heck reaction.

4. Conclusions

Significant progress has been made in the field of enantioselective intermolecular Heck-type reactions in recent years, and in particular, enantioselective oxidative boron Heck couplings have contributed substantial advances. The field of enantioselective intermolecular Heck-type couplings has so far yet to achieve the same generality and application as the intramolecular counterpart; therefore, the advances highlighted in this review are of significance and bode well for the future of the field. Advances enabled by utilising the oxidative boron Heck reaction include enantioselective intermolecular couplings of more challenging systems such as desymmetrisation of quaternary centres, cyclic enones, acyclic alkenes and even site selectively on remote alkenes *via* a redox–relay coupling. Of note is the use of PyOX ligands, which appears to be instrumental in almost all of the most recent developments. Nevertheless, there is still plenty of room for improvement, including expansion of the chemistry beyond the coupling of aryls as well as to other challenging alkenes. Further developments in the field can therefore be anticipated.

Acknowledgements

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