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Review

The palladium-catalysed arylation and vinylation of alkenes—enantioselective fashion☆

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Abstract

The enantioselective Heck reaction is a powerful method for the synthesis of both tertiary and quaternary chiral carbon centres, with enantiomeric excesses (ees) often around 80% and in some cases much higher. A variety of carbocyclic and heterocyclic systems can be constructed or modified including spirocyclic systems. Although problems of regioselectivity with respect to the product alkene continue to limit the scope of the reaction somewhat, there are indications that these may be surmountable and that a new generation of ligands and a refined methodology, may improve both enantio- and regiocontrol. All the relevant literature is discussed. © 1999 Elsevier Science S.A. All rights reserved.

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1. Introduction

The palladium mediated coupling of aryl or vinyl iodides, bromides or triflates with alkenes in the presence of base, in other words the Pd-catalysed arylation or vinylation of alkenes, is generally referred to as the Heck reaction. It has been known to synthetic chemists since the late 1960s [1–3]. As a great advantage this reaction is not limited to activated alkenes. The substrate can be a simple olefin (with ethylene being the most reactive one), or it can contain a variety of functional groups, such as ester, ether, carboxyl, phenolic, or cyano groups. Despite displaying many of the benefits usually associated with Pd-mediated reactions [4] (for example ease of scale up and tolerance of water and/or other functional groups), interest in the reaction has been sporadic, largely due to problems of regiocontrol in the case of unsymmetrical alkene substrates and to an incomplete understanding of the reaction mechanism. In recent years, however, the attention paid to the reaction has increased dramatically [5], and perhaps one of the most significant developments to date has been the advent of an enantioselective variant [6,7].

Given the many reports of chiral phosphine ligands dating from the early 1970s [8], it is perhaps somewhat surprising that the phosphine-mediated Heck reaction was not subjected to asymmetrisation attempts until the late 1980s. However, it can be pointed out, that the reaction has not usually been used to generate stereogenic centres [9], and that for many years chelating diphosphines in general were thought to be unsuitable catalysts [10]. First reports of successful examples of the asymmetric Heck reaction (AHR) were received in 1989 and the reaction has since been successfully developed to the point where both tertiary and quaternary centres can be generated with ees $\geq 80\%$. The bulk of the reported examples involve intramolecular reactions (i.e. ring closures) [11], which have the advantage of allow-

☆ Dedicated to Professor Richard F. Heck and to Professor Jiro Tsuji.

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ing relatively easy control of alkene regiochemistry and geometry in the product and of tolerating less reactive alkene substrates. In contrast, successful intermolecular reactions have until very recently been limited to quite reactive substrates, principally *O*- and *N*-heterocycles, and to the formation of tertiary centres on ring carbon atoms, which again simplifies the question of alkene regiochemistry (but see Section 6).

What follows is a survey of the relevant literature up to the middle of 1998, including a discussion of the mechanistic aspects relevant for stereoselection in the AHR. The classification of the chapters proceeds according to the various types of underlying carbon skeletons or natural product fragments of the resulting compounds. Diastereoselective variations [5] which have been frequently utilized for the construction of natural products are generally not included.

2. Reaction conditions

The AHR is carried out under similar or identical reaction conditions generally associated with racemic versions of the Heck reaction using standard laboratory glassware. The solvents which have been used include benzene, dichloroethane, diglyme, dimethylacetamide, DMSO, THF or even mixtures containing water. The reaction usually requires elevated temperatures (reflux, about 60–100°C) to proceed with reasonable speed. Generally, degassed solvents and an inert atmosphere (nitrogen or argon) are necessary to avoid decomposition of the Pd–intermediates or oxidation of the phosphine ligand and the formation of other side products. Numerous bases have been applied, ranging from K_2CO_3 to proton sponge. The catalyst is conveniently prepared in situ. Examples for palladium precursors are $Pd(OAc)_2$ or $Pd_2dba_3CHCl_3$ (dba = dibenzylideneacetone) among others, with usually at least about 3–10 mol% catalyst required for reasonable yields and reaction rates. The catalyst stability and the turnover numbers are relatively low compared to other catalytic processes and recovery of the catalyst is usually not practical. However, as AHRs can be employed for the construction of valuable natural products a somewhat higher catalyst cost is acceptable.

3. Mechanistic aspects

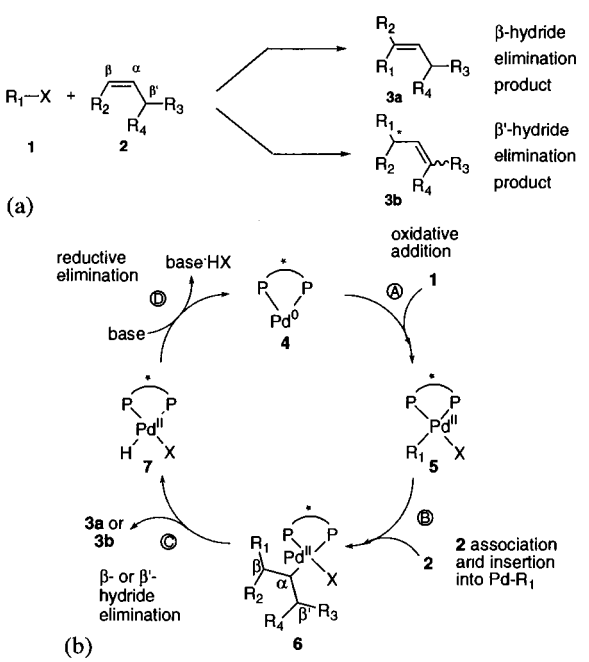
The current state of mechanistic theory regarding the Heck reaction in general has been provided in recent review articles [5,12]. In the following, the discussion will be a selective one, focusing primarily on the factors which influence the regio- and enantiocontrol [13,14].

3.1. Factors governing regioselectivity

The mechanism of the Heck reaction (Scheme 1a) with bidentate phosphine ligands is generally thought to follow the four-step catalytic cycle shown in Scheme 1b, with the individual steps being: (a) oxidative addition of **1** to the Pd^0 species **4**, bearing a bidentate phosphine ligand, to give the Pd^{II} species **5**; (b) coordination and then *syn*-insertion of the alkene substrate **2** into the Pd–R_1 bond of **5** to give **6**; (c) β- or β′-hydride elimination from **6** to give either **3a** or **3b**, and finally; (d) regeneration of **4** by reductive elimination of HX from **7**.

The three major factors governing regioselectivity are:

1. The regioselectivity of the insertion into Pd–R_1 is heavily dependent upon the nature of the steric and electronic environment provided by R_2, R_3 and R_4 for unsymmetrical alkenes. This lack of selectivity, which has tended to limit the scope of the reaction somewhat, can be overcome by selecting appropriate chiral ligands and reaction conditions.
2. The problem of competing β- and β′-hydride elimination from **6** further complicates the regioselectivity issue, to the extent that the majority of reported Heck reactions simply avoid the problem by using simple acrylate ester substrates (R_2=CO_2R, monosubstituted alkene), which through their highly unsymmetrical steric and electronic environment also avoid any problems with regioselectivity in step B. Whilst this constitutes a mild and quite powerful method for the synthesis of arylacrylates, by eliminating the possibility of β′-hydride elimination an opportunity to form a tertiary chiral centre is lost.



Scheme 1.

3. Even if the regioselectivity of step C can be controlled a further problem lies in its reversibility, which can result in re-insertion of the **3b** alkene into the Pd–H bond in **7** either to regenerate **6** or to form a regioisomer of it with the Pd atom attached to the same carbon atom as R_3 and R_4. If either of these substituents contains a suitably positioned hydrogen atom then the possibility exists of isomerisation of the α,β′-alkene into a β′,γ′-position, a problem which is especially prone to occur for endocyclic alkene products (see Section 4.2). Fortunately methods have been developed to suppress this, involving the addition of thallium [15] or silver [16,17] salts to the reaction mixture-the latter are usually preferred owing to their lower toxicity and fortuitous double role as enhancers of enantioselectivity (vide infra).

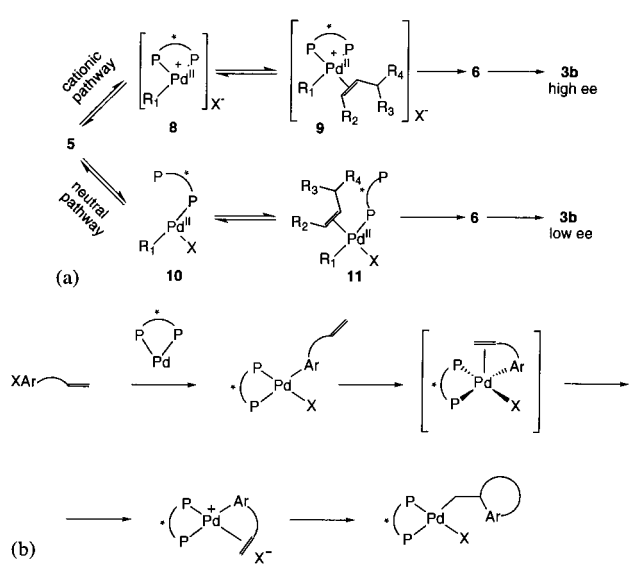
A preference for **3b** rather than **3a** formation is essential for the AHR to occur, and thus an examination of the factors controlling the competing elimination processes in step C and the consequent prerequisites for ensuring the predominance of the desired pathway is clearly apropos. As both insertion into **5** and elimination from **6** are *syn*-processes, rotation about the alkene σ-bond is required before β-hydride elimination can occur. This might be expected to make β′-hydride elimination the kinetically more favourable pathway. More significantly, for endocyclic alkenes the necessary σ-bond rotation is not feasible for steric reasons, making β′-hydride elimination the only possible course. It is primarily for this reason that all the AHRs forming tertiary centres which have been reported (with the exception of Tietze et al.'s allylsilane work—see Section 4.1.5) involve endocyclic alkene substrates. Other methods to direct the selectivity of step C involve choosing suitable R_n groups to influence the relative thermodynamic stabilities of the possible products, the most common tactic being to make $R_3/R_4 =$ OH or OR, resulting in the formation of an enol (which subsequently tautomerises to the aldehyde or ketone) or enol ether. A similar strategy commonly employed in AHRs is to choose $R_3/R_4 =$ alkenyl, resulting in the formation of a conjugated diene product. Either approach may be used in addition to the choice of a cyclic substrate as a way of providing an extra driving force to the reaction, and this indeed occurs in many of the published AHR examples.

3.2. Factors governing enantioselectivity

The key step in the catalytic cycle with regard to enantioselectivity is clearly B, association of the alkene **2** and insertion of it into the Pd–R_1 bond. As with the Heck reaction itself the mechanism for this process remains a matter for conjecture, with the overall rationale currently in favour having been proposed in 1991 by Ozawa and Hayashi [18] and independently by Cabri [19] (although the cationic pathway via **8** and **9** had been proposed as early as 1990 [20]). Its development and subsequent evolution has recently been reviewed by the latter author [12].

Two possible routes are proposed (Scheme 2a), the former ('cationic') pathway beginning with the dissociation of X from **5** to generate the tri-coordinate 14 e^- cationic complex **8** with the accompanying counterion X^-. Complexation of **2** into the vacant site then gives the 16 e^- species **9**, and insertion of **2** into the Pd–R_1 bond followed by reformation of the Pd–X bond gives **6** as desired, with the chiral bidentate ligand having remained fully chelated throughout and so having maximised the asymmetric induction. The alternative ('neutral') pathway starts with dissociation of one arm of the bidentate ligand resulting in the neutral species **10**; association and complexation into the vacant site of **2** gives the neutral species **11**, which by alkene insertion into Pd–R_1 and re-complexation of the previously displaced phosphine moiety also gives **6**.

The nature of X in **1** (and thus the strength of the Pd–X bond in **5**) is clearly an important factor; unless the reaction conditions are modified aryl and vinyl triflates are generally assumed to follow the cationic pathway (the Pd–OTf bond being weak [21]) with either route being available to reactions using aryl/vinyl halides. In practice it has proven possible to influence which pathway will be followed in a given Heck process, either by adding silver salts to the reaction of an aryl/vinyl halide (the halophilic Ag^+ salt sequestering the halide from **5** and replacing it with its own anionic component [6]), or by adding excesses of halide anions to reactions using triflates (resulting in nucleophilic displacement of the triflate anion from **5** [22]). The nature of the alkene substrate is also important, with



Scheme 2.

electron-rich olefins favouring the cationic pathway (and so being the most suitable for the AHR) while the neutral pathway makes for faster reaction with electron-poor substrates [19].

The partial dissociation of the chiral ligand during the neutral process would seem to make it less well suited to asymmetric induction, however, and the evidence of most of the AHRs reported so far seems to indicate that conditions which favour the cationic route also give the best enantiomeric excesses (ees). However, a significant exception to this rule has been found (see also Section 5.1.). Overman et al. observed that for a special aryl *triflate* [(*Z*)-butenanilide triflate] the addition of halide salts to the reaction mixture resulted in a dramatic increase in ee of the intramolecular Heck reaction product [23]. If on the other hand the corresponding aryl *iodide* was used as starting material high ees could be obtained without further additives. Overman concluded that in the case of this substrate the neutral pathway must be the more enantioselective one. Furthermore it was shown that when the bidentate diphosphine ligand (*R*)-BINAP was substituted by potentially monodentate analogues of (*R*)-BINAP only low enantioselections were obtained for this example. This can be seen as an evidence that both phosphines of the diphosphine ligand remain coordinated to the Pd center during the enantioselective step. To account for these findings mechanistically a 'refined' neutral pathway for the AHR involving a pentacoordinate intermediate without partial dissociation of the diphosphine was suggested (Scheme 2b).

It is clear that considerations on the geometry of the palladium center during the catalytic cycle are fundamental for further developments of more detailed descriptions of the stereoinduction. Explicit three dimensional rationalisations on how the chirality is transferred from the ligand to the substrate are not available for the AHR at present or just beginning to emerge (see Section 4.1.4).

4. Formation of tertiary carbon centres

4.1. Intramolecular

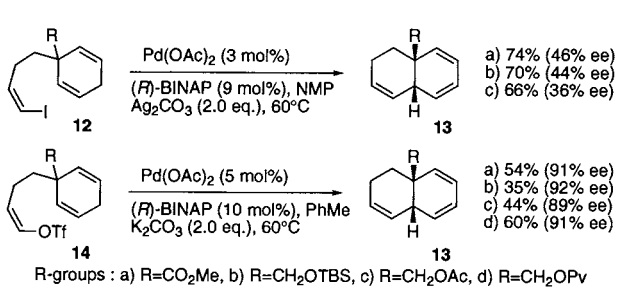
4.1.1. Decalins

The first example of the AHR was reported in 1989, and involved the conversion of the prochiral vinyl iodides **12a**–**c** into the chiral decalin systems **13a**–**c**, as shown in Scheme 3 [24]. The reaction conditions (dipolar aprotic solvent and presence of silver salts), whilst similar to those of a previously reported non-enantioselective method [16] differ crucially in respect of the choice of chiral ligand and of solvent—very low or negligible ees were obtained using THF, MeCN or DMSO, with the preferred solvent being *N*-methyl-2-pyrrolidinone (NMP). Similarly the widely used chiral phosphine ligands 1-*t*-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)azolidine (BPPM) and *N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (BPPFA) failed to give significant asymmetric induction, with (*R*)-BINAP proving to be the ligand of choice, a pattern which has been repeated in most (though not all—see Section 4.1.3) of the reported examples of the AHR. By using a prochiral substrate two stereocentres can be set in one step, a tactic which is used repeatedly in the tertiary centre-generating AHRs reported by the Shibasaki group.

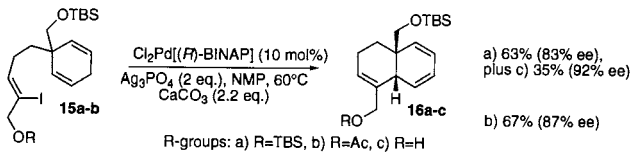
The modest ees reported (33–46%) for the conversion from **12** to **13** were greatly improved as a result of a study of the effects on the reaction of varying the anionic component of both the Pd source and more particularly the silver salt [20]. It was found that the use of a Pd^0 catalyst complex pre-formed in situ from Cl_2Pd(*R*)-BINAP [25], (*R*)-BINAP and cyclohexene, gave greatly improved ees relative to the 1:3 $Pd(OAc)_2$/(*R*)-BINAP pre-reduced catalyst used in the original work; in contrast, the use of AgOAc as the Ag^+ source reduced the ee to almost zero, clearly indicating the undesirability of the nucleophilic acetate counterion, which perhaps forms a Pd–OAc bond to replace the dissociated Pd–I bond and so inhibits the cationic pathway. The best Ag^+ source in terms of ee was found to be Ag_3PO_4 (most likely due to the very low nucleophilicity of the $Ag_2PO_4^-$ anion), with the sparingly soluble $CaCO_3$ being added as the basic component. Under these conditions **13b** was obtained in 80% ee and 67% yield.

The very recent introduction of the new ligand 2,2′-bis(diphenylarsino)-1,1′-binaphthyl (BINAs) [26], the diarsine equivalent of BINAP, helped to considerably increase the yield for the conversion of **12b** to **13b**. After optimization the product **13b** could be prepared in 90% chemical yield and with 82% ee [26].

The use of the vinyl triflates **14a**–**d** in place of iodides **12a**–**c** gave still better results [27] as well as allowing



Scheme 3.

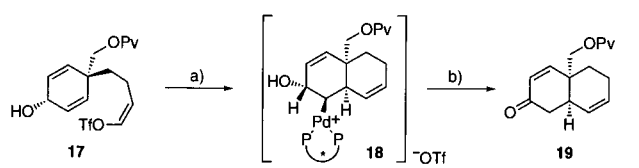


Scheme 4.

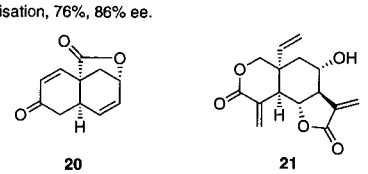
the omission of expensive silver salts and the use of hydrocarbon solvents (PhMe or PhH), in which the deleterious effects of $Pd(OAc)_2$ on ee seen in NMP are not repeated. Thus products **13a–d** were obtained in 35–60% yields and uniformly excellent (89–92%) ees under the conditions indicated.

The scope of the reaction was extended somewhat by the use of the trisubstituted vinyl iodide **15**, which gave the decalin systems **16a** and **16b** in yields of 63% (83% ee) and 67% (87% ee) respectively (Scheme 4) [27]. The deleterious effect of the acetate counterion on ee and primacy of the $Ag_3PO_4/CaCO_3$ additive combination seen for the AHR converting from **12** to **13** are reproduced here. Interestingly, **16a** was accompanied by a minor amount (35%) of the desilylated alcohol **16c**, which displayed a higher ee (92%)—control experiments indicated that desilylation was occurring via transmetalation to Pd after completion of the ring closure. No such free hydroxyl formation was seen in the case of acetate **15b**.

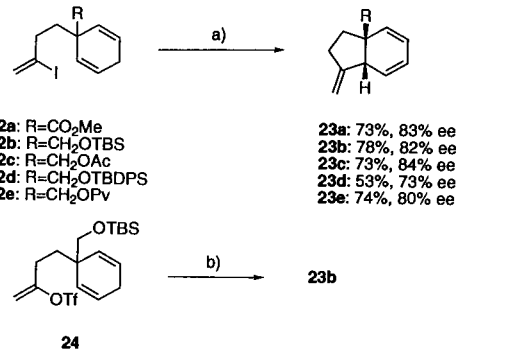
A more significant extension in scope was the synthesis of a range of bicyclic enones and dienones, including a key intermediate **20** in Danishefsky's synthesis [28] of vernolepin **21**. The AHR involved was initially the conversion of divinylalcohol **17** to the chiral decalin system **19**, via the intermediate **18** (Scheme 5) [29]. The best solvent for this was found to be 1,2-dichloroethane (DCE), with the addition of *t*-BuOH having a beneficial effect on reaction rate and chemical yield without reducing the ee [30]. Compound **19** was converted to **20** via a nine-step process; an alternative approach was also



a) $Pd_2dba_3{\cdot}CHCl_3$ (9 mol% Pd), (*R*)-BINAP (11.3 mol%), K_2CO_3 (2 eq.), *t*-BuOH (11 eq.), $ClCH_2CH_2Cl$, 60°C, 3 days. b) β-hydride elimination, then tautomerisation, 76%, 86% ee.



Scheme 5.



a) $PdCl_2$[(*R*)-BINAP] (10 mol%), Ag_3PO_4 (2.0 eq.), $CaCO_3$ (2.2 eq.), NMP, 60°C. b) $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP (10 mol%), K_2CO_3 (2.0 eq.), benzene, 60°C, 64 hrs, 63% (73% ee).

Scheme 6.

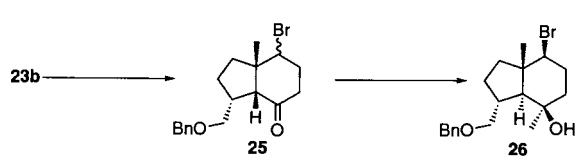
found which started from the more readily available **13a** [31]. Application of the DCE/tertiary alcohol solvent system for the conversion of **14a** to **13a** gave improved yield relative to that previously reported; a study of the various tertiary alcohols found pinacol to be the most efficacious, giving **13a** in 78% yield with 95% ee. The authors successfully synthesised (+)-**21**, thereby enabling assignment of its absolute configuration.

4.1.2. Hydrindans

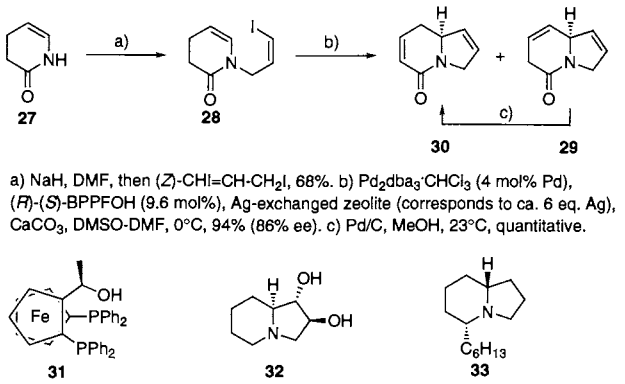
The general method described in Section 4.1.1 for decalin synthesis has also been applied to the synthesis of 6,5-ring systems through the formation of hydrindans (Scheme 6) [32].

Both iodides **22a–e** and triflate **24** could be converted to the corresponding *cis*-hydrindans by similar methods to those used for decalins; once again Ag_3PO_4 was found to be the most effective silver salt in the conversion of the former. Small increases ($\leq 5\%$) in ee could be obtained for **22a–c** by pre-reducing the palladium catalyst in situ. The triflate **24** gave **23b** in slightly lower ee than seen for the corresponding conversion of **22b**, with potassium carbonate being found to be the most effective base.

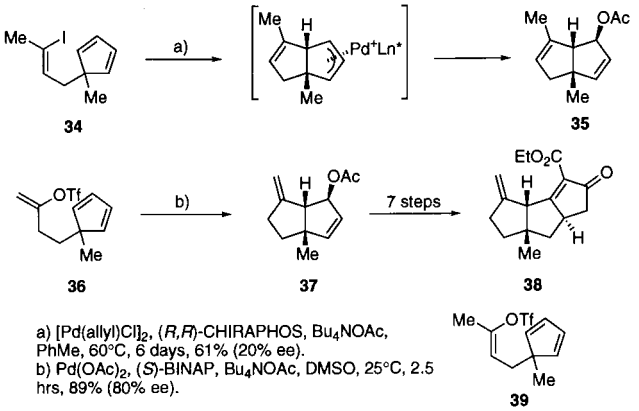
The hydrindan **23b** was later converted by the same group into **26** (Scheme 7) [33], which is a key intermediate in the syntheses of (–)-oppositol and (–)-prepinnaterpene [34]. The conversion involved oxidation of the diene moiety with singlet oxygen, and is notable for the clean epimerisation of the ring junction to give the *trans*-configuration (from **25** to **26**), which demonstrates that both *cis*- and *trans*- junctions can be obtained from the AHR products.



Scheme 7.



Scheme 8.



Scheme 9.

4.1.3. Indolizidines

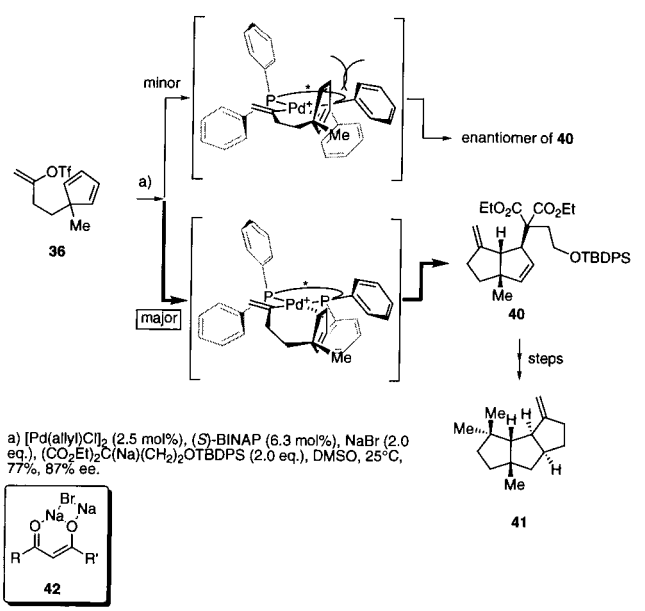
The 6,5-bicycle synthesis outlined above has been extended to indolizidines, formed by AHR of a suitable prochiral alkenyl iodide such as **28**, which can be easily prepared by allylation of the lactam **27**. In contrast to purely carbogenic systems, however, the most effective ligand proves to be (*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol (BPPFOH) **31** [35] which gives results clearly superior to those obtained with BINAP (Scheme 8) [36,37].

The use of an Ag-exchanged zeolite also appears to give somewhat better results than the more usual Ag_3PO_4 silver source. The desired indolizidine **30** is obtained as a mixture (94% yield, 86% ee) with the isomer **29**; however, treatment of the mixture with catalytic Pd/C in MeOH at room temperature gives clean isomerisation to **30** in essentially quantitative yield. Compound **30** has been converted to the natural products lentiginosine **32**, 1,2-diepilentiginosine and gephyrotoxin 209D **33** [38].

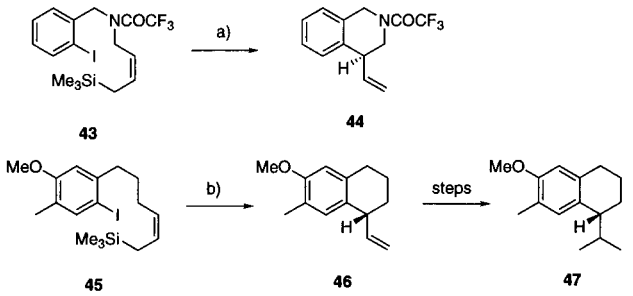
4.1.4. Diquinanes

The successful execution of AHRs for the formation of 6,6- and 6,5- ring systems from prochiral substrates clearly suggested an extension of the method to the formation of 5,5-systems, which form the backbone of a large number of natural products. The use of prochiral cyclopentadienyl systems, however, involves the generation of a π-allyl palladium species, which must then be trapped out with a suitable nucleophile [39]. The greater reactivity of the 1,3-diene substrate towards the silver salts used in the reactions and the propensity for undesirable side-reactions such as Diels–Alder cycloadditions must also be born in mind. The former problem, in fact, figures prominently in the first example to be published of AHR-based diquinane synthesis (Scheme 9) [40,41].

Although cyclisation of iodide **34** could be carried out to give the bicyclo[3.3.0]octane **35** in reasonable yield, the observed ees were low (ca. 20%; a slightly higher ee was obtained with (*S*)-BINAP, but at the cost of greatly reduced yield). The authors attribute this failing in large part to a clearly observed instability of **34** in the presence of silver salts, necessitating their omission from the reaction medium and so forfeiting the beneficial effects noted in earlier work [20]. The presence of tetrabutylammonium acetate, a source of nucleophilic acetate appears to be essential, as the reaction does not proceed in its absence; this was in fact the first example of an AHR followed by anion capture. The problem of low ee was circumvented by employing the triflate **36** (chosen instead of the more obvious analog **39** on the grounds of ease of synthesis), which gave the diquinane **37** with 80% ee and in 89% yield. The authors converted this to the triquinane **38**, an intermediate in a previously described synthesis of $\Delta^{9(12)}$-capnellene-3β,8β,10α-triol [42], and later developed the first *catalytic* asymmetric synthesis of $\Delta^{9(12)}$-capnellene **41** itself by trapping the π-allyl Pd intermediate with a suitable β-dicarbonyl carbanion (Scheme 10) [43].



Scheme 10.



a) $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), (*S*)-BINAP (7.0 mol%), Ag_3PO_4 (1 eq.), DMF, 75°C, 48 hrs, 63% (72% ee); b) $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), (*R*)-BINAP (7.0 mol%), Ag_3PO_4 (1.1 eq.), DMF, 80°C, 48 hrs, 91% (92% ee).

Scheme 11.

In this case BINAP was found to be the most effective ligand, and the addition of sodium bromide too significantly improve the ees in all cases studied. The latter effect is attributed to a suppression (due to formation of a stabilising complex of type **42** with the sodium enolate) of small amounts of anion exchange which may be taking place between free malonate anions and the triflate anion in the cationic intermediate of type **9**.

4.1.5. Allylsilanes

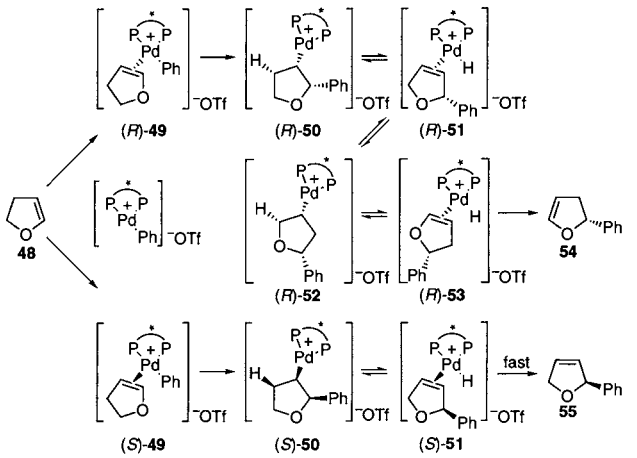
All of the examples discussed so far have relied on the use of an endocyclic alkene substrate to resolve the β- versus β′-hydride elimination regiocontrol problem discussed in Section 2.1. A more general approach to the problem has been described by Tietze et al. and involves the use of allylsilanes as the alkene component (Scheme 11) [44].

By careful choice of reaction conditions either a vinyl- or a trimethylsilylvinyl- substituted carbocycle can be produced in the non-enantioselective reaction. Under conditions suitable for the AHR, however, the former product predominates (e.g. reaction from **43** to **44**). Yields and ees appear to be good, and the method has been successfully applied to the synthesis of the norsequiterpene 7-demethyl-2-methoxycalamene **47**, via the key cyclisation from **45** to **46** [45,46].

4.2. Intermolecular

4.2.1. Dihydrofurans and cyclic enol ethers

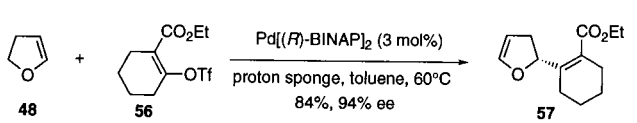
The first example of the intermolecular AHR was reported by Hayashi et al. and involved the asymmetric arylation of 2,3-dihydrofurans using aryl triflates [18]. Although little or no ee was obtained when aryl iodide/silver salt combinations were used, the use of triflates along with the familiar $Pd(OAc)_2$/BINAP catalyst system resulted in the formation of the 2-aryl-2,3-dihydrofuran product **54**, together with minor amounts of the 2,5-dihydrofuran isomer **55**. The rationale proposed by the authors for this outcome is shown in Scheme 12; it



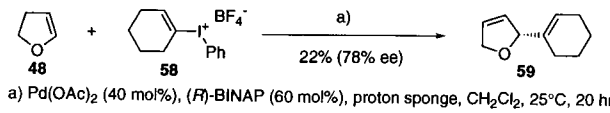
Scheme 12.

is hypothesised that addition of the catalytic complex to either face of the substrate can take place, ultimately producing the complexes (*R*)-**51** and (*S*)-**51**, but that in the case of the latter unfavourable steric factors cause an immediate dissociation of the Pd species, producing the minor product **55**.

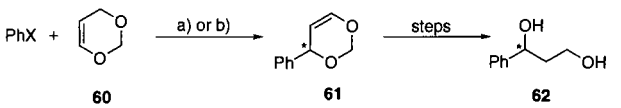
In contrast (*R*)-**51** is able to undergo a reinsertion of the alkene into the Pd–H bond followed by a second β-hydride elimination to produce the product **54**. The overall effect is a kinetic resolution of (*R*) and (*S*)-**51**, effectively enhancing the facial selectivity shown in the initial transformation from **48** to **49** by selectively removing the **51** enantiomer produced by complexation to the undesired face of **48**. As might be expected from the above argument, reaction conditions which give proportionally larger amounts of **55** also appear to give the best ees for the major product **54**; thus, when proton sponge is used as the base the product **54** is obtained with $>96\%$ ee, at the cost of a 71:29 ratio of **54**:**55**, whereas in contrast using Na_2CO_3 gives a lower ee (75%) but much better regioselectivity (97:3) [47,48]. The authors note that the presence of the nucleophilic acetate anion in the reaction medium assists the dissociation of (*S*)-**51** (and presumably (*R*)-**51** as well), making possible the formation of **55** [49]. Even more impressive results have been obtained using vinyl triflates—for example the AHR between **48** and triflate **56** gives the expected major product **57** with 94% ee, without formation of the undesired regioisomer (Scheme 13) [50].



Scheme 13.



Scheme 14.



Scheme 15.

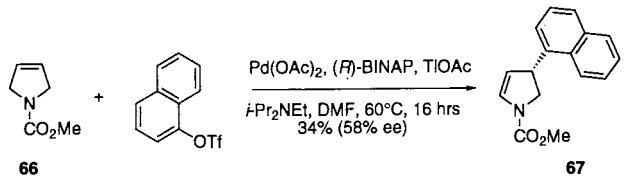
An interesting corollary to this work has been reported by Reiser et al. who found that at high pressure the ee of the major product in the conversion from **48** to **54**/**55** is dramatically increased, suggesting that such conditions enhance the kinetic resolution process [51]. Shibasaki et al. have shown that the reaction can be carried out using alkenyliodonium salts instead of vinyl triflates (transformation from **58** to **59**, Scheme 14), although yields are lower due to the highly reactive nature of the salts, which leads to competition from uncatalysed and/or non-phosphine mediated processes [52]. Interestingly, only the 2-vinyl-2,5-dihydrofuran product is obtained, suggesting that dissociation from the Pd complex formed after the first β-hydride elimination is more rapid than when using triflates.

Finally, the asymmetric arylation of **60** has also been reported, although the yields and ees are more modest (Scheme 15) [53]. Hydrolysis of the product **61** conveniently gives the 1,3-diol **62**, an intermediate in Sharpless's synthesis of fluoxetine [54].

4.2.2. Dihydropyrroles

The methods described for arylation of dihydrofurans (see above) have also been applied to 2,3-dihydropyrroles such as **63** [55], with similar patterns of regio- and enantioselectivity being observed. Thus little or no ee was obtained when using aryl iodides, but aryl triflates gave mixtures of 2-aryl-2,3-dihydropyrroles **64** and 2-aryl-2,5-dihydropyrroles **65**, with the former predominating and the kinetic resolution process again being in effect, as evidenced by another inverse relationship between the ee of **64** and the **64**:**65** ratio (Scheme 16). The reaction was also successfully extended to vinyl triflates, which gave even better ees than obtained for the dihydrofurans [50].

Scheme 16.



Scheme 17.

An example of a reaction with 2,5-dihydropyrroles has also been recently disclosed [56]. Arylation of **66** using 1-naphthyl triflate and an (*R*)-BINAP/$Pd(OAc)_2$/*i*-Pr_2NEt system in DMF gave the 3-arylation product **67** (Scheme 17) with moderate yield and ee. It was found that the addition of excess acetate served to suppress formation of the undesired 2-arylation product (which was formed after initial isomerization of the double bond in **66**), and this was conveniently achieved by adding TlOAc, with the thallium cation acting as a co-catalyst. Unfortunately, attempts to carry out this reaction with other aryl triflates or with aryl iodides were unsuccessful.

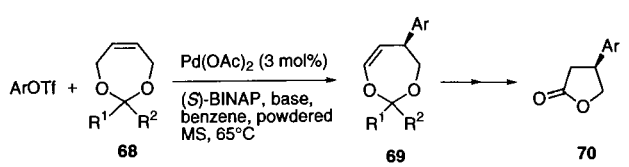
4.2.3. Dihydrodioxepins

Arylation of the 4,7-dihydro-1,3-dioxepin system **68** (easily derived from *cis*-2-butene-1,4-diol), once again using the triflate, was reported by Shibasaki et al. in 1994 [57]. The reaction is significant in that the resulting enol ethers are easily converted (by hydrolysis and then oxidation of the intermediate lactol) to chiral β-aryl-γ-butyrolactones **70**, which are themselves useful synthetic intermediates (Scheme 18) [58]. Also noteworthy is the important role played by added molecular sieves, which enhance both chemical yield *and* ee. This was the first time that such an effect had been noted for the AHR.

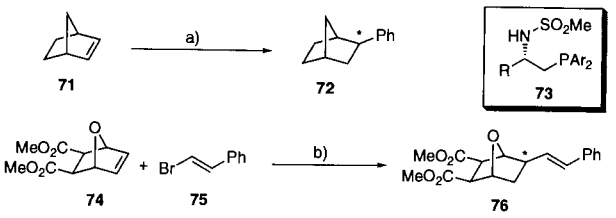
A combination of MS 3Å and potassium carbonate base was found to be the most effective, with the best auxiliary system ($R^1 = R^2 = H$) giving **69** with a satisfactory 72% ee and in 84% yield. Gratifyingly, these figures showed only minor perturbations when the Ar ring substituents were varied. Significantly improved ees have recently been reported for this process using a new ligand system (see Section 6) [59].

4.2.4. Hydroarylations of [2.2.1]bicyclics

Asymmetric hydroarylation/hydrovinylation, although not strictly a Heck reaction as the β-hydride elimination step is replaced by reductive elimination,



Scheme 18.



Scheme 19.

nevertheless shares a common mechanistic pathway with regard to the enantioselective step and so will be discussed briefly. In 1991 Brunner et al. first reported hydrophenylations of norbornene and norbornadiene using aryl iodides, although the ees obtained were low ($<40\%$). The preferred ligand was (–)-Norphos—BINAP does not appear to have been tested [60]. The system has since been revisited by Achiwa et al. as a means of testing novel phosphine ligands of the general structure **73** [61,62]. Using these the conversion from **71** to **72** could be carried out in 81% yield and 74% ee (Scheme 19).

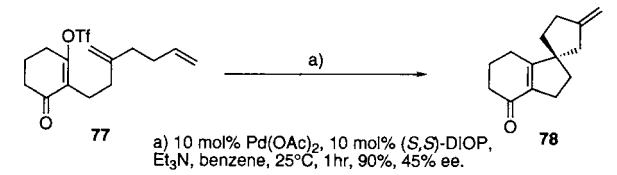
Hayashi et al. have carried out AHRs using vinyl iodides and triflates both on norbornene and on heteroanalogues such as **74**: excellent ees and satisfactory yields were obtained [63]. Hydrophenylation of a similar system has been reported by Fiaud [64].

5. Formation of quaternary carbon centres

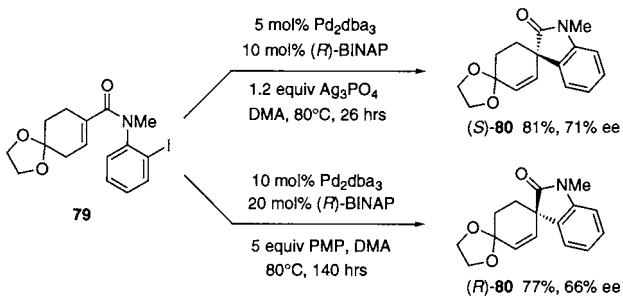
5.1. Spirocyclisations and alkaloid synthesis

The enantioselective formation of quaternary carbon centres remains a significant challenge to the synthetic chemist [65]. To use the AHR in this role has the obvious attraction of removing the problem of competing pathways in step C (see Scheme 1b), as no β-hydrogen is present to compete with the desired β′-hydride elimination step-the need to use endocyclic alkene substrates is thus removed.

The first successful case was reported by Overman et al. in 1989 [66], a pioneering strategy, which opened the way for the development of AHRs leading to quaternary centres. Furthermore it was outlined that polycyclizations are well within the scope of the Heck reaction. According to Scheme 20 it can be expected



Scheme 21.



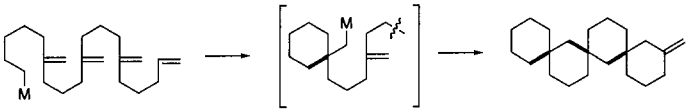
Scheme 22.

that contrary to the case of polycyclizations of carbocations and free radicals, cyclizations resulting from sequential intramolecular insertions of palladium metal alkyls will be most effective when the transition metal propagates at the least substituted termini of the participating alkene units.

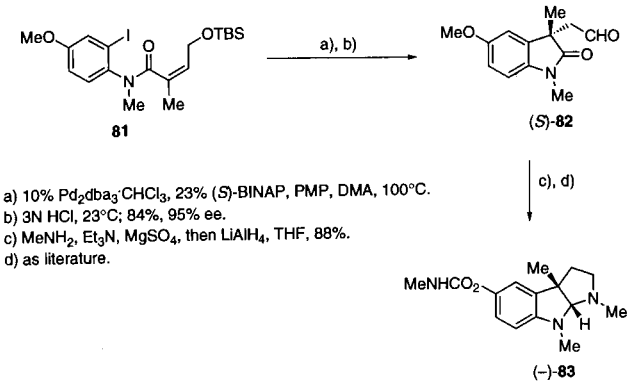
As with the work creating tertiary centres reported by Shibasaki et. al. which was described in Section 4, the ees of the cylizations obtained at the outset were modest, with the spirocyclic system **78** being obtained in good yield and moderate ee when (*S*,*S*)-DIOP was substituted for triphenylphosphine (Scheme 21).

Although this work clearly demonstrated the viability of such a process, the full potential of the approach did not become fully apparent until the publication of a remarkable study concerning the synthesis of spiroxindoles (Scheme 22) [67].

Carrying out the AH cyclisation of iodoanilide **79** in a dipolar aprotic solvent (in this case dimethylacetamide, DMA) in the presence of Ag_3PO_4 gave (*S*)-**80** in 81% yield and with 71% ee, results very similar to those achieved by other workers for tertiary centres under such conditions. However, by carrying out the reaction in the absence of Ag salts and using 1,2,2,6,6-pentamethylpiperidine (PMP) as the base the opposite (*R*)-**80** enantiomer was obtained *using the same enantiomer* of BINAP.Similar studies of the cyclisation of alkene **81** revealed that when (*E*)-**81** is used the effect is



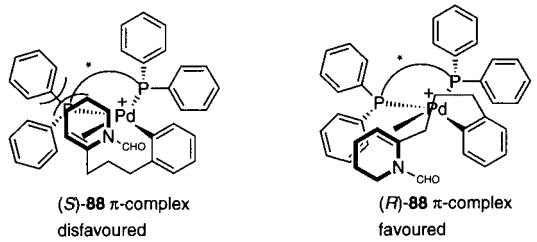
Scheme 20.



Scheme 23.

reproduced, although the ees of the enantiomer obtained when using PMP are low (30–40%). In contrast, when (*Z*)-**81** is used in conjunction with (*R*)-BINAP *both* sets of conditions give the expected (*R*)-enantiomer of **82** with good yields and excellent (>90%) ees [68]. These results appear to suggest that the observed 'geometry effect' (identical to that observed by Shibasaki et al. for carbocycle formation, vide infra) is rather more powerful than the 'base/additive effect' in determining the sense of chiral induction. The use of (*S*)-BINAP under otherwise identical conditions of course gives (*S*)-**82**, which can be converted to the natural product physostigmine **83** via methylimine formation and reductive cyclisation (Scheme 23), followed by anisole demethylation and reaction of the resulting phenol with methyl isocyanate [69].

These surprising results proved to be a powerful spur to mechanistic investigation of the AHR, as they effectively rebutted the prevailing view that the cationic pathway is the only mechanism capable of producing high ees, by demonstrating that the alternative neutral pathway is also apt to do so with certain substrates. The 'base/additive effect' has, however, yet to be reported for substrates other than acrylamides, a substrate-specificity which must be taken into account before broader conclusions can be drawn regarding the AHR mechanism, especially the means by which the enantioselectivity reversal occurs.



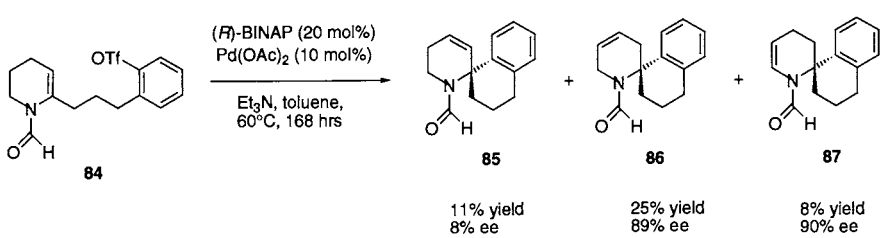
Scheme 25.

5.2. Tetrahydropyridines

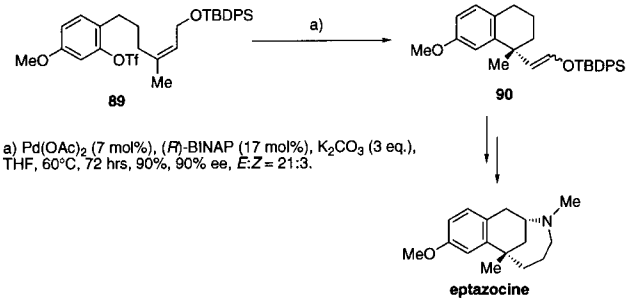
Interesting attempts to asymmetrise an intramolecular Heck reaction with 1,2,3,4-tetrahydropyridines also giving access to spirocyclic systems have not been successful at the beginning [70]. However, by using *N*-formyl-1,2,3,4-tetrahydropyridines Ripa and Hallberg succeeded in preparing various spirocyclic derivatives of tetrahydropyridines in moderate yields (Scheme 24) [71]. The asymmetric cyclization of **84** using (*R*)-BINAP as chiral ligand resulted in the formation of three isomers **85**, **86** and **87** with a rather long reaction time required. Good ees have been obtained for the products **86** and **87** (89 and 90%).

The migration of the double bond could not be controlled effectively by varying the reaction conditions. Interestingly, the introduction of the chiral (phosphinoaryl)oxazoline (first reported by Pfaltz; see Section 6) as a ligand helped to suppress the formation of the double bond isomer **87**. At the same time the regioselectivity could be considerably changed in favour of the formation of **85** to yield a 6:1 mixture of (*R*)-**85** (87% ee) and (*R*)-**86** (>99% ee) after 48 h at 110°C, using $(i\text{-Pr})_2$NEt as base [71]. A rationalization for the observed excellent enantioselectivities in the case of (*R*)-BINAP is shown in Scheme 25. It was suggested that one of the diastereomeric π-complexes ((*S*)-**88**), formed after oxidative addition of the triflate could be sterically more crowded. A similar argumentation, based on steric arguments, was used to explain the subsequent migration of the double bond and the considerably differing ees of the double bond isomers.

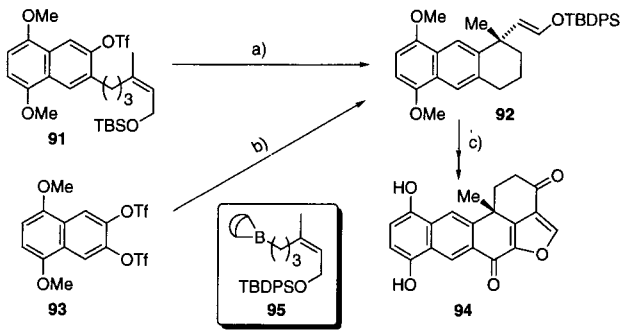
If the corresponding iodide was used instead of the triflate **84** only low to moderate ees have been observed. Furthermore, it seems that the role of the N-formyl



Scheme 24.



Scheme 26.



Scheme 27.

moiety could be important for chiral induction and this could provide further information about the mechanism.

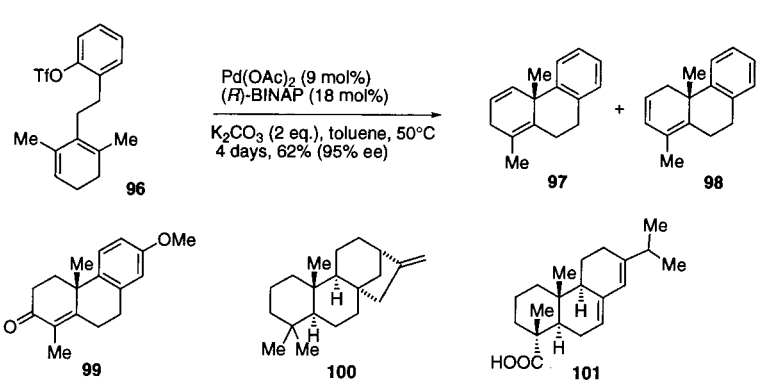
5.3. Eptazocine and halenaquinol

The synthesis of benzylic quaternary centres by an AHR has also been reported by Shibasaki et al. in connection with syntheses of (–)-eptazocine [72] and of halenaquinone and halenaquinol **94** [73]. As in Section 5.1 the key steps in both syntheses involve the formation of a quaternary carbon centre by asymmetric Heck arylation of a trisubstituted alkene, with BINAP being the preferred ligand. The 'geometry effect' seen by Overman for spiroxindoles (vide supra) is clearly present, with the *Z*-alkene giving much better enantioselectivity and, in the case of model studies of the step **89**–**90** in the eptazocine synthesis the opposite enantiomer to that obtained when using the *E*-alkene. The conversion from **89** to **90** (Scheme 26) was achieved with excellent yield and ee; desilylation gave the corresponding aldehyde [74], which was converted to (–)-eptazocine via a five-step sequence.

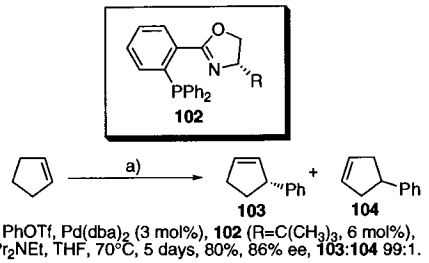
The synthesis of halenaquinol **94** (and its oxidation product halenaquinone) initially featured the conversion from **91** to **92** as a key step (Scheme 27), which gave the desired product in 78% yield and 87% ee under very similar conditions used for the conversion from **89** to **90**. However, in line with the current trend towards sequential or 'one-pot' transformations [75,76] (vide infra), the authors were able to combine the AHR step with a Suzuki-type coupling of the trialkylborane **95** (itself pre-generated in situ by hydroboration) with the C_2-symmetric ditriflate **93** and so obtain **92** rather more directly. Whilst the chemical yield of this sequence is still low (20%) and the catalyst loading rather high (20 mol%) the ee is excellent (85%), suggesting that further development of the method should be feasible.

5.4. Sesquiterpenes

One further example of quaternary centre formation by AHR has been reported, this being the conversion of the aryl triflate **96** to a 3:1 mixture of the tricycle **97** and its isomer **98**, both of which can be converted to the enone **99**, a key intermediate in the syntheses of kaurene **100** and abietic acid **101** (Scheme 28) [77,78]. Compound **97** can also be quantitatively isomerised to **98**. The essentially complete selectivity towards 6-*exo* cyclisation is noteworthy. The authors rationalise this on the basis of unfavourable steric interactions in the alternative intermediates.



Scheme 28.



a) PhOTf, $Pd(dba)_2$ (3 mol%), **102** (R=$C(CH_3)_3$, 6 mol%), *i*-Pr_2NEt, THF, 70°C, 5 days, 80%, 86% ee, **103**:**104** 99:1.

Scheme 29.

6. Future developments

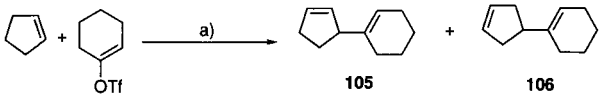
6.1. Ligands

The great majority of AHRs reported so far have utilised the BINAP ligand system, which has usually proven to be the most effective, when the performance of different ligands has been assessed. The significant number of exceptions to this rule, however, suggest that experimentation with alternatives may prove worthwhile. The most dramatic development in that direction has definitely been the introduction by Pfaltz et al. of the oxazoline-based ligands **102** [79], which give distinctly improved ees with several previously reported AHRs [59]. For example, the Hayashi-type AHR of dihydrofuran **48** with cyclohexenyl triflate catalysed by $Pd(dba)_2$ and **102** (R = *t*-butyl) with *i*-Pr_2NEt as the base gives the 2-alkenyl-2,5-dihydrofuran product **59** in 92% yield and with >99% ee, a major improvement on the ees obtained with BINAP[1]. Similar to the vinylation of **48** using iodonium salt **58**, no trace of the isomeric 2-alkenyl-2,3-dihydrofuran product is formed, indicating that rapid dissociation of the catalyst from the initial product of β′-hydride elimination occurs. Remarkably, the resistance of the first-formed product alkene to isomerisation by this catalyst is so pronounced as to allow the arylation and/or alkenylation of cyclopentene, giving regiodefined products such as **103** with high yields, excellent ees and only small amounts (<5%) of the unwanted regioisomers such as **104** (Scheme 29). This catalyst system is also interesting in terms of reaction rates and decreased catalyst loading, indicating higher catalyst turnover compared to BINAP (see Section 6.2).

An example for an alkenylation reaction utilizing **102** (R = $C(CH_3)_3$) is given in Scheme 30. Again, excellent selectivity towards the less isomerized product **105** as well as high ees have been observed [59].

The conversions outlined in Scheme 29 and Scheme 30 are also noteworthy in so far as they constitute examples of intermolecular AHRs of very simple starting materials

[1] One must be careful in making this comparison, however, as the major products obtained using the different ligand systems are isomeric.



a) $Pd(dba)_2$ (3 mol%), **102** (R=$C(CH_3)_3$, 6 mol%), *i*-Pr_2NEt, C_6H_6, 40°C, 4 - 5 d.

Scheme 30.

with no other functionality or heteroatom present than is required for the Heck reaction to proceed. Simple hydrocarbon skeletons are the resulting products.

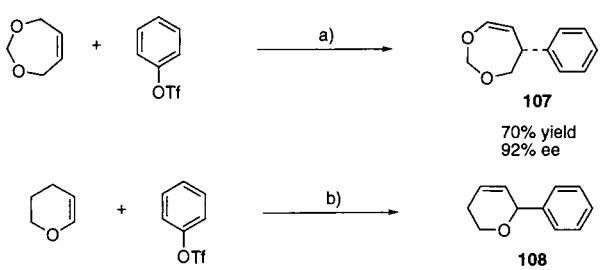
Two further examples for arylation reactions catalyzed by phosphanyldihydrooxazole-palladium complexes are shown in Scheme 31 with the formation of **107** and **108** as products in high yields and excellent ees [80].

The application of ligand **102** has successfully been extended to derivatizations of nitrogen containing substrates: Arylation of the 2,3-dihydropyrrole **63** with phenyl triflate catalyzed by the **102**-palladium complex (R = $C(CH_3)_3$) gave the single isomer **65** in 88% yield and 85% ee [80].

Interestingly, phosphinooxazolines **102** with smaller R-groups than R = $C(CH_3)_3$ have been found to produce less reactive catalysts. This finding was very unusual as with $C(CH_3)_3$ being a very bulky group the steric hindrance near the metal center could actually be expected to slow down a metal catalyzed process.

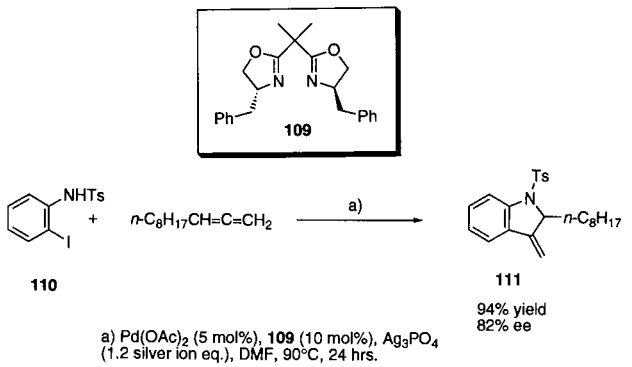
The use of a chiral bisoxazoline ligand **109** for the enantioselective palladium-catalyzed annulation of allenes has been reported by Larock and Zenner (an example is given in Scheme 32) [81]. Even though in this case the alkene insertion step is followed by an intramolecular nucleophilic attack of the amine functionality (which could be described as an 'intramolecular anion capture process') and the reaction is not strictly a AHR, the high yields and ees obtained for various substrates are remarkable.

Looking at the results obtained with BINAP, with the new diarsine ligand mentioned in Section 4.1.1 and with bisoxazoline **109**, it seems evident, that various donor atoms (N, P, As) can be contained in ligands



a) $Pd(dba)_2$ (3 mol%), **102** (R=$C(CH_3)_3$, 6 mol%), *i*-Pr_2NEt, THF, 70°C, 7 d.
b) $Pd(dba)_2$ (5 mol%), **102** (R=$C(CH_3)_3$, 10 mol%), *i*-Pr_2NEt, C_6H_6, 80°C, 5 d.

Scheme 31.



Scheme 32.

which provide the best solution to a given AHR problem. Accordingly, recently 2-diphenylarsino-2′-diphenylphosphino-1,1′-binaphthyl (BINAPAs, **112**) has been synthesized and successfully applied to the AHR of a system similar to **91** (Scheme 33) with superior reactivity compared to BINAP [82].

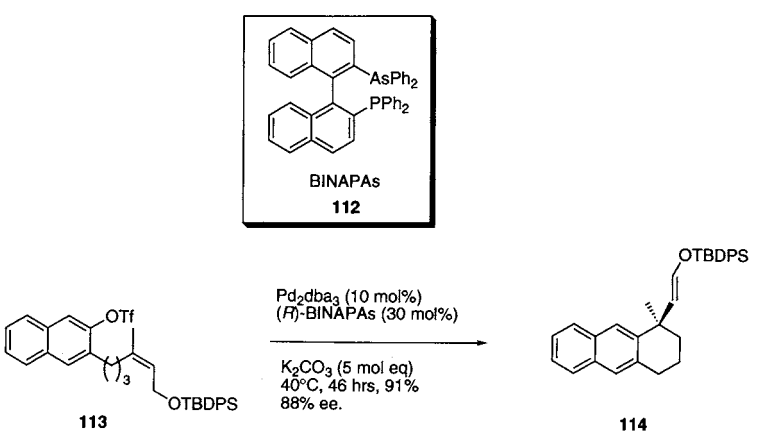
Whereas the yield for the conversion from **113** to **114** has been 74% using BINAP it could be improved to 91% by using BINAPAS under otherwise identical conditions. The ee remained virtually unchanged.

Another new direction was recently pointed out by Shibasaki et al. by successfully carrying out an AHR which allowed a kinetic resolution of the racemic starting material (Scheme 34) [83]. With that method, a possible intermediate (**116-β**) for the total synthesis of wortmannin could be isolated in 96% ee after subjecting the racemic triflate (±)-**115** to Heck conditions (the absolute stereochemistry was determined using Mosher's method). Such reaction sequences could eventually prove to be extremely valuable and convenient for the enantioselective synthesis of natural products in general.

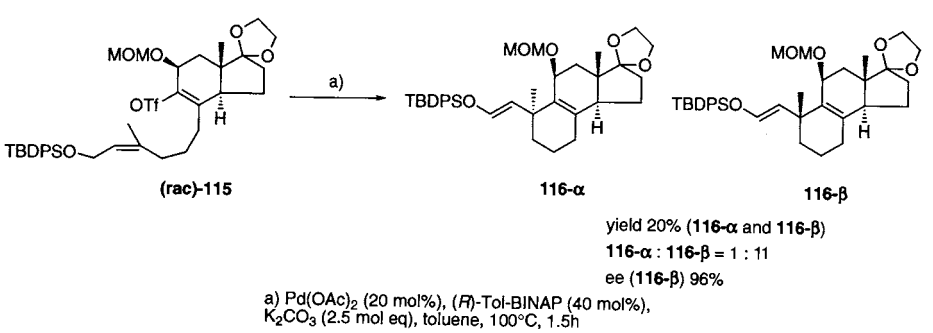
Remarkable *diastereoselectivities* have also been observed for AHR with the chiral auxiliaries RAMP or SAMP present in the substrate using triphenylphosphine as a ligand [84]. Even a 'ligandless' version of a palladium(0) catalyst has been described for an intramolecular Heck reaction with very good diastereoselectivity of the resulting spirocyclic oxindole. This catalyst could still be tailored by adding Ag_3PO_4, resulting in the formation of the opposite diastereomer [85].

6.2. Methodological directions

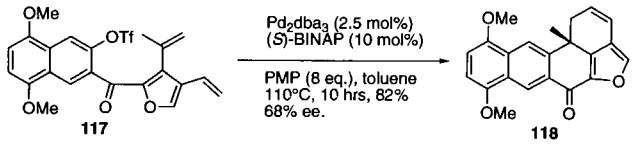
Efforts to increase the catalyst turnover number are indeed another major area where further improvements could be expected. Such improvements have recently been achieved for the standard Heck reaction by the use of high pressure conditions [86], the use of pre-



Scheme 33.



Scheme 34.



Scheme 35.

formed palladacycles as catalysts [87] or by using a macrocyclic tetraphole as ligand [88]. Dendritic diphosphine palladium complexes as catalysts for Heck reactions have also been reported to possess superior stability compared to the monomeric parent compounds [89]. In addition, the same research group could considerably activate the rate of the Heck reaction of chlorobenzene and styrene by addition of tetraphenylphosphonium salts and *N*,*N*-dimethylglycine [90]. Transferring such innovations to the AHR remains an important goal.

The current surge of interest in combinatorial chemistry [91,92] may also prove to be highly significant to the development of new ligands, as both Heck reactions on solid support [93] and the generation and screening of chiral phosphine ligand libraries [94] have recently been demonstrated, potentially opening the way to combinatorial screening of AHR catalyst systems.

The move away from bulky BINAP ligands which Pfaltz's work may foreshadow would certainly simplify library construction. The ready availability of chiral oxazolines from peptide residues may also be helpful in this respect [95–97].

Microwave-promoted Heck reactions are another recent development. It was shown that Heck reactions of common substrates like *p*-iodoanisol and methyl acrylate, which under standard conditions need several hours for reasonable conversions, can be carried out in just a few minutes if DMF is used as a solvent and microwave irradiation is applied [98].

Finally, a very recent synthesis of the halenaquinol-related natural product (+)-xestoquinone by Keay and co-workers [99] has provided confirmation of the suitability of the AHR for inclusion in Pd-mediated 'cascade' polyene reactions [100]. The one-pot transformation of triflate **117** into the pentacycle **118** (Scheme 35) is achieved using conditions typical for the AHR, and gives (+)-**118** with a respectable 68% ee. Interestingly, the iodide analogue of **117** gives little or no asymmetric induction, even in the presence of silver salts.

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