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The Asymmetric Heck Reaction

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Contents

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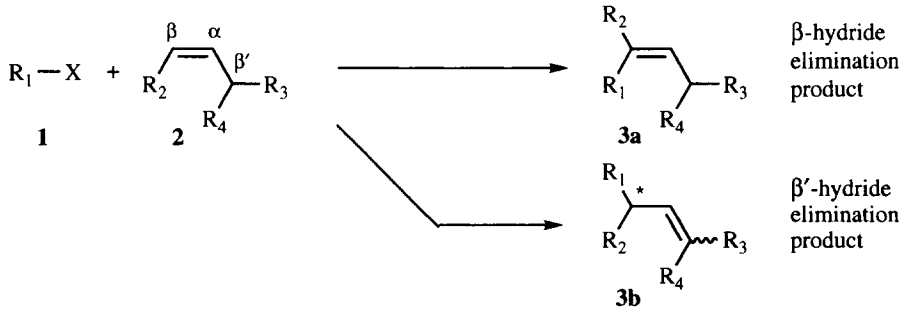
1) Introduction

The Pd -catalysed arylation or vinylation of alkenes, generally referred to as the Heck reaction, has been known to synthetic chemists since the late 1960s.[1-3] Despite displaying many of the advantages usually associated with Pd-mediated reactions[4] (particularly 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 the most significant development 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 a little surprising that the phosphine-mediated Heck reaction did not succumb to asymmetrisation attempts until the late 1980s, although in fairness 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] Reports of successful examples of the asymmetric Heck reaction (hereafter abbreviated AHR) were, however, 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 ≥80%. The bulk of the reported examples involve intramolecular reactions (i.e. ring closures),[11] which have the advantage of allowing 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. What follows is a survey of the relevant literature up to the end of 1996, beginning with a discussion of the AHR's mechanistic aspects and concluding with an assessment of likely future developments.

2) Mechanism

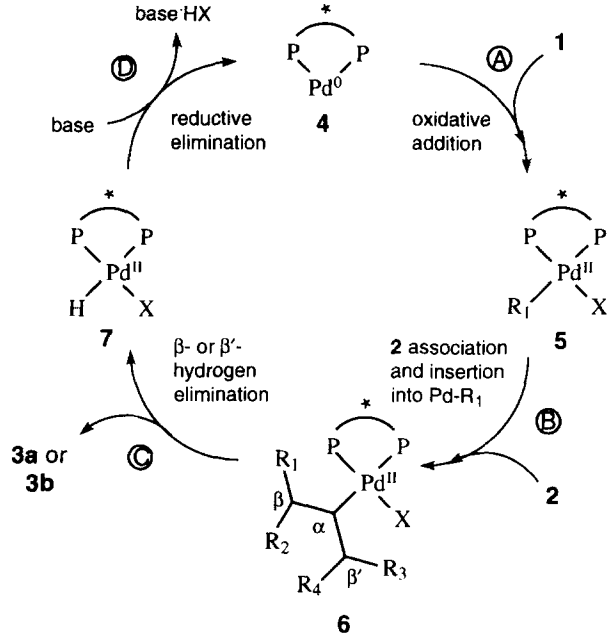
Comprehensive overviews of the current state of mechanistic theory regarding the Heck reaction have been provided in two recent review articles,[5,12] and so the discussion which follows will be a selective one, focusing primarily on the factors which impart the regio- and enantiocontrol necessary for a successful AHR.[13,14]



Scheme 1a. Heck reaction with disubstituted alkenes bearing β- and β′-hydrogens.

a) 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 bidentate phosphine ligand-bearing Pd^0 catalytic species **4** to give the Pd^{II} species **5**, B) co-ordination and then *syn*-insertion of alkene substrate **2** into the **5** Pd-R_1 bond 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**.



Scheme 1b. Catalytic cycle for the Heck reaction.

The three major factors governing regioselectivity are:

i) The regioselectivity of the insertion into Pd-R_1 is heavily dependant upon the nature of the steric and electronic environment provided by R_2, R_3 and R_4 for unsymmetrical alkenes, which has tended to limit the scope of the reaction somewhat.

ii) 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 aryl acrylates, by eliminating the possibility of β′-hydride elimination an opportunity to form a tertiary chiral centre is lost.

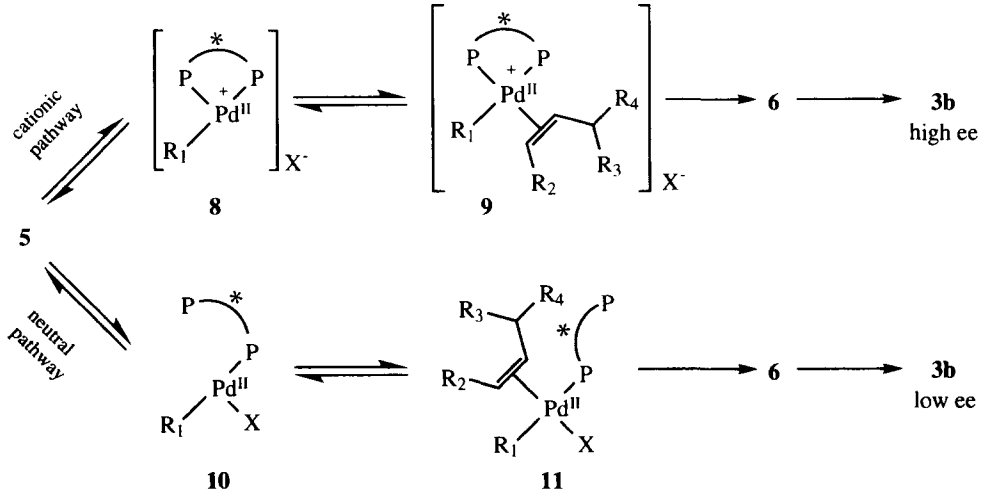
iii) Even if the regioselectivity of step C can be controlled a further problem lies in its reversibility, which can result in reinsertion of the **3b** alkene into the Pd-H bond in **7** either to regenerate **6** or to form a regioisomer of it with the Pd atom attached to the same carbon atom as R_3 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 3b). 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, which might be expected to make β′-hydride elimination the kinetically more favourable pathway. More significantly, for endocyclic alkenes the necessary σ-bond rotation is *disallowed*, making β′-hydride elimination the only possible course. It is primarily for this reason that all the AHRs forming 3° centres which have been reported (with the exception of Tietze *et al.*'s allylsilane work - see section 3av) *involve endocyclic alkene substrates*. Other possible methods of step C regiocontrol involve choosing suitable R_n groups so as to control the relative thermodynamic stabilities of the possible products, the most common tactic being to make R_3 or R_4 = OH or OR, resulting in the formation of an enol (which subsequently tautomerises to the aldehyde or ketone) or enol ether. Another strategy commonly employed in AHRs is 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.

b) Factors Governing Enantioselectivity

The key step in the catalytic cycle with regard to enantioselectivity is clearly B), association of 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]



Scheme 2. Cationic and neutral pathways for the AHR mechanism.

Two possible routes are proposed (Scheme 2), the former ("cationic") pathway beginning with the dissociation of X from **5** to generate the tri-coordinate 14e cationic complex **8** with accompanying X^-

counterion. Complexation of **2** into the vacant site then gives the 16e 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 giving 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 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. There is a significant exception to this rule, however, which is discussed section 4a. 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 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]

3) Formation of Tertiary Centres

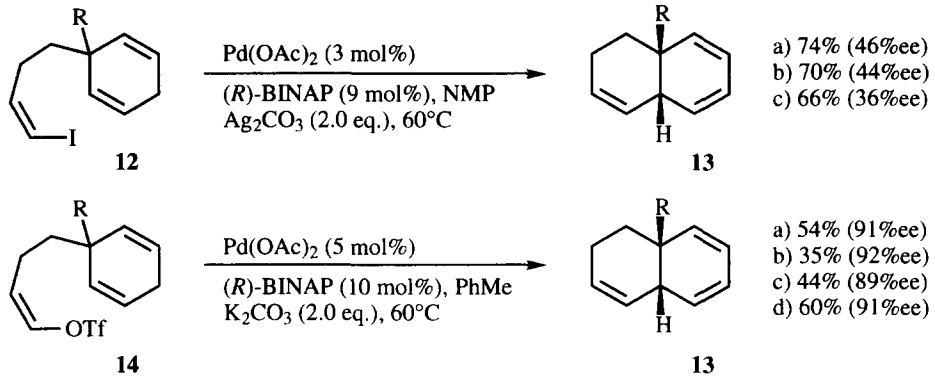
a) Intramolecular

i) 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.[23] The reaction conditions (dipolar aprotic solvent and added 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 BPPM and 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 3aiii) 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 3° centre-generating AHRs reported by the Shibasaki group.

The modest ees reported (33-46%ee) for the **12**→**13** conversion 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,[24] (*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 orthophosphate trianion), 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 use of the vinyl triflates **14a-d** in place of iodides

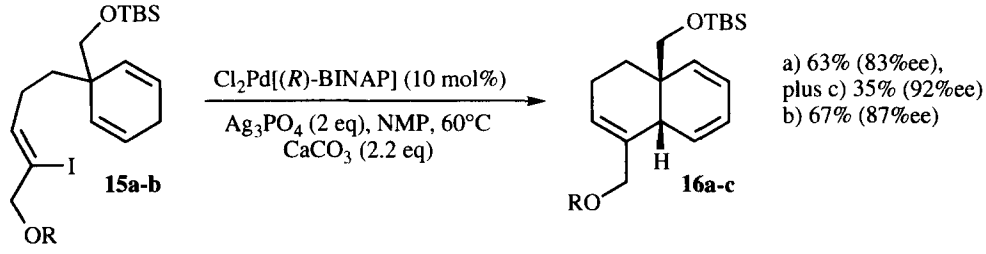
12a-c gave still better results,[25] as well as allowing the omission of expensive silver salts and the use of hydrocarbon solvents (PhMe or PhH), in which the deleterious effects of $Pd(OAc)_2$ on ee seen in NMP are not repeated. Thus products **13a-d** were obtained in 35-60% yields and uniformly excellent (89-92%) ees under the conditions indicated.



R-groups : a) R=CO_2Me, b) R=CH_2OTBS, c) R=CH_2OAc, d) R=CH_2OPv

Scheme 3

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).[25] The deleterious effect of the acetate counterion on ee and primacy of the Ag_3PO_4 / $CaCO_3$ additive combination seen for the **12**→**13** AHR are reproduced here. Interestingly, **16a** was accompanied by a minor amount (35%) of the desilylated alcohol **16c**, which displayed a higher enantiomeric excess (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**.

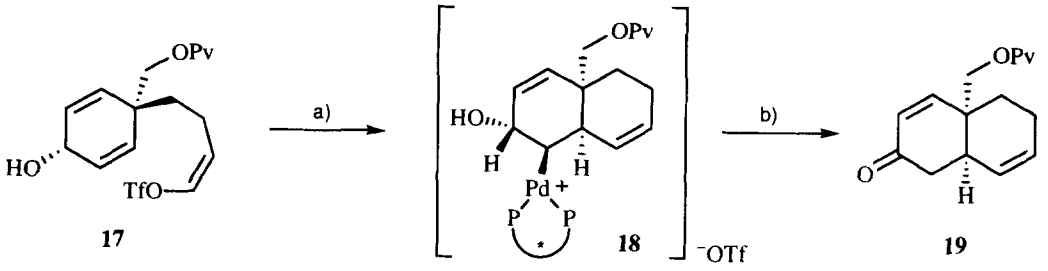


R-groups: a) R=TBS, b) R=Ac, c) R=H

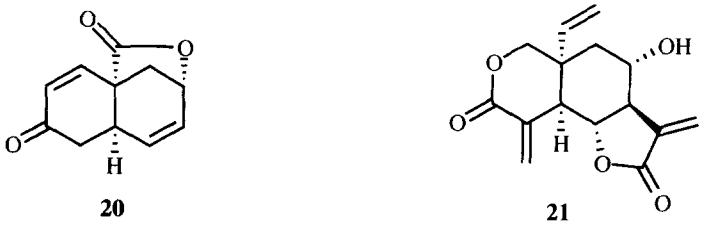
Scheme 4

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[26] 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).[27] 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 enantiomeric excess.[28] Compound **19** was converted to **20** via a 9-step process; an alternative approach was also found which started from the more

readily available **13a**.[29] Application of the DCE/tertiary alcohol solvent system to the **14a**→**13a** conversion 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.



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

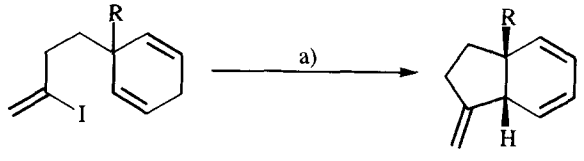


Scheme 5. Synthesis of a key intermediate for vernolepin

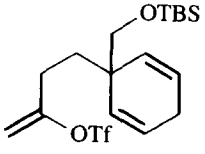
ii) Hydrindans

The general method described in 3ai for decalin synthesis has also been applied to the synthesis of 6,5-ring systems through the formation of hydrindans (Scheme 6).[30]

22a: R=CO_2Me
22b: R=CH_2OTBS
22c: R=CH_2OAc
22d: R=$CH_2OTBDPS$
22e: R=CH_2OPv



23a: 73% (83%ee)
23b: 78% (82%ee)
23c: 73% (84%ee)
23d: 53% (73%ee)
23e: 74% (80%ee)



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b) → **23b**

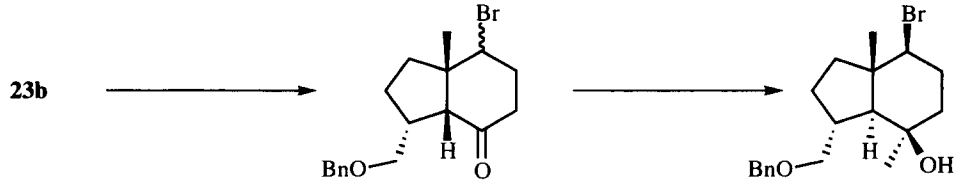
a) $PdCl_2$[(*R*)-BINAP] (10 mol%), Ag_3PO_4 (2.0 eq.), $CaCO_3$ (2.2 eq.), NMP, 60°C. b) $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP (10 mol%), K_2CO_3 (2.0 eq.), PhH, 60°C, 64 hrs, 63% (73%ee).

Scheme 6

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 (≤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 conversion of **22b**, with potassium carbonate being found to be the most effective base.

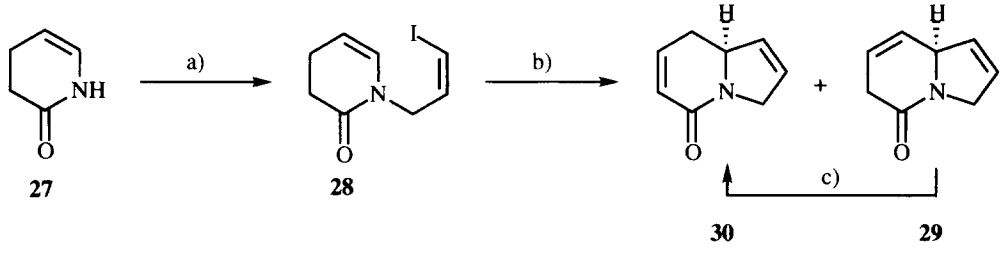
The hydrindan **23b** was later converted by the same workers into **26** (Scheme 7),[31] which is a key intermediate in the syntheses of (–)-oppositol and (–)-prepinnaterpene.[32] The conversion involved oxidation of the diene moiety with singlet oxygen, and is notable for the clean epimerisation of the ring junction to give the *trans*-configuration (**25** to **26**), which demonstrates that both *cis*- and *trans*- junctions can be obtained from the AHR products.



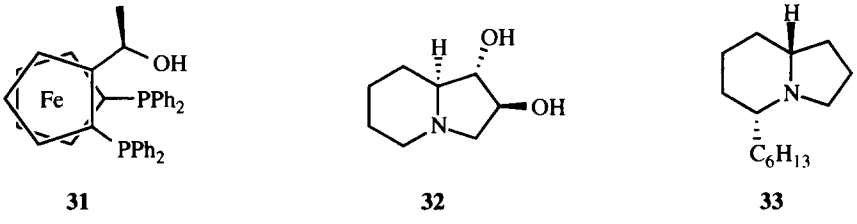
Scheme 7

iii) 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 BPPFOH ((*R*)-α-[(*S*)-1',2-*bis*(diphenylphosphino)ferrocenyl]ethyl alcohol) **31**,[33] which gives results clearly superior to those obtained with BINAP (Scheme 8).[34,35]



a) NaH, DMF, then (*Z*)-CHI=CH-CH_2I, 68%. b) $Pd_2dba_3{\cdot}CHCl_3$ (4 mol% Pd), (*R*)-(*S*)-BPPFOH (9.6 mol%), Ag-exchanged zeolite (≡ ca. 6 eq. Ag), $CaCO_3$, DMSO-DMF, 0°C, 94% (86%ee). c) Pd/C, MeOH, 23°C, quantitative.



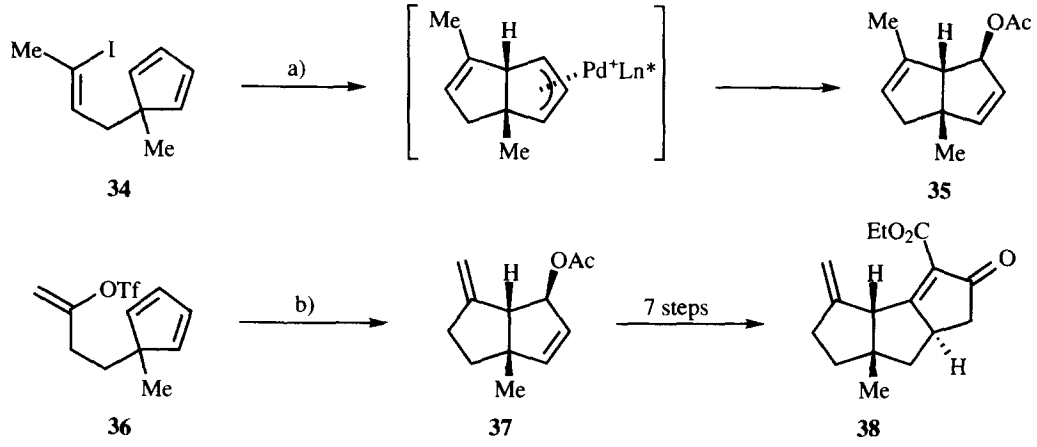
Scheme 8

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

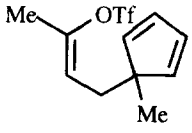
29; however, treatment of the mixture with catalytic Pd/C in MeOH at room temperature gives clean isomerisation to **30** in essentially quantitative yield. Compound **30** has been converted to the natural products lentiginosine **32**, 1,2-diepilentiginosine and gephyrotoxin 209D **33**.[36]

iv) 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.[37] 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).[38,39]



a) $[Pd(allyl)Cl]_2$, (*R,R*)-CHIRAPHOS, Bu_4NOAc, PhMe, 60°C, 6 days, 61% (20%ee). b) $Pd(OAc)_2$, (*S*)-BINAP, Bu_4NOAc, DMSO, 25°C, 2.5 hrs, 89% (80%ee).



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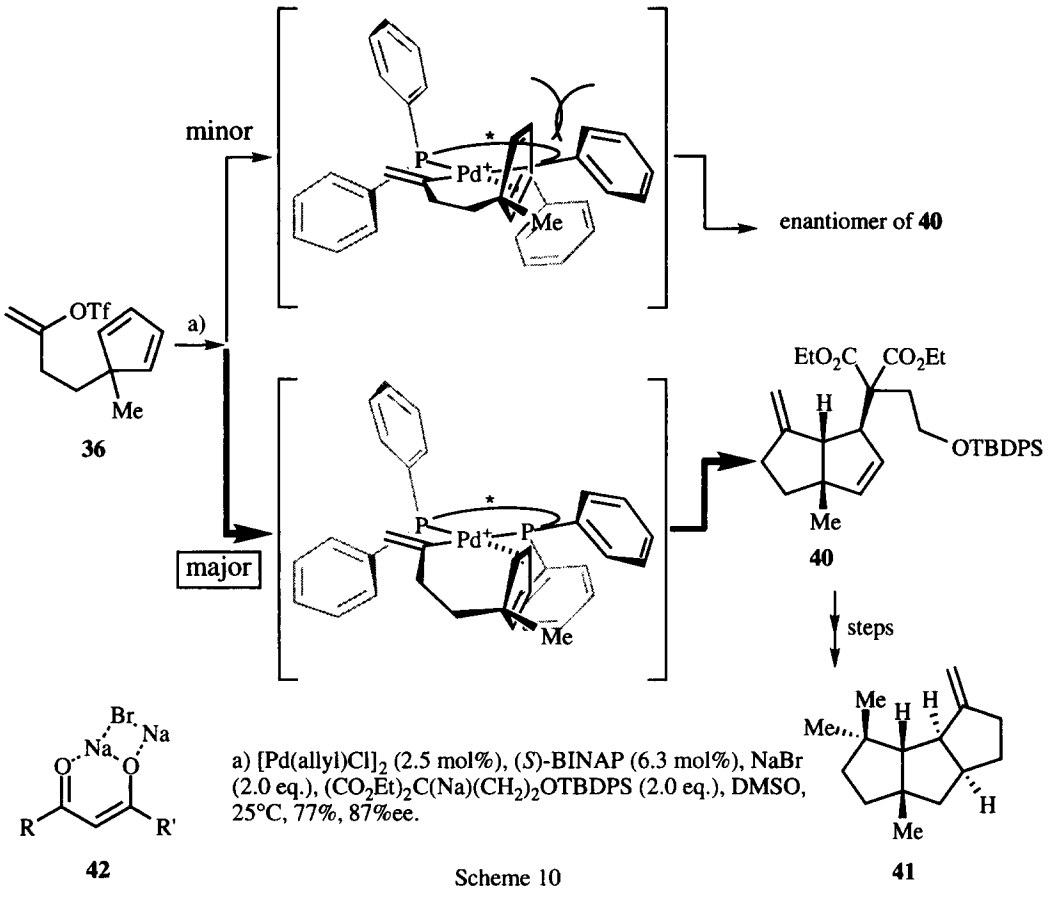
Scheme 9

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,[40] 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).[41]



Scheme 10

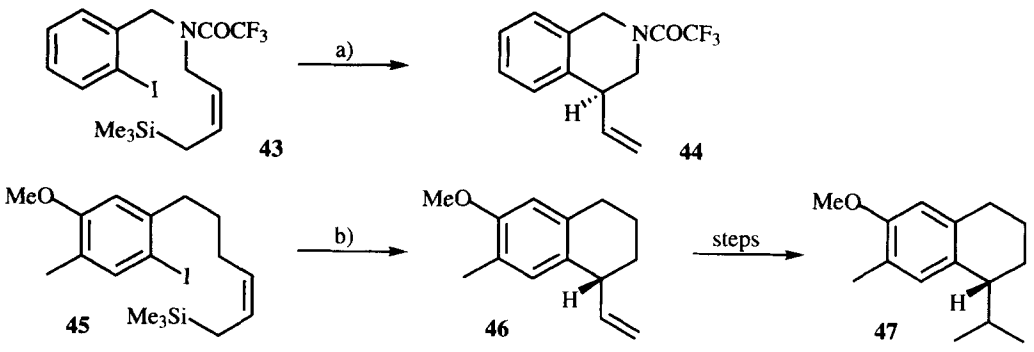
In this case BINAP was found to be the most effective ligand, and the addition of sodium bromide to significantly improve the ees in all cases studied. The latter effect is attributed to a suppression (due to formation of a stabilising complex of type **42** with the sodium enolate) of small amounts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

v) Allylsilanes

All of the examples discussed so far have relied on the use of an endocyclic alkene substrate to resolve the β- vs. β′-hydride elimination regiocontrol problem discussed in section 2a. A more general approach to the problem has been described by Tietze *et al.*, and involves the use of allyl silanes as the alkene component (Scheme 11).[42]

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. **43**→**44**). Yields and enantiomeric excesses appear to be satisfactory, and the

method has been successfully applied to the synthesis of the norsequiterpene 7-demethyl-2-methoxycalamene **47**, via the key cyclisation **45**→**46**.[43,44]



a) $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%), (*S*)-BINAP (7.0 mol%), Ag_3PO_4 (1 equiv.), 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 equiv.), DMF, 80°C, 48 hrs, 91% (92%ee).

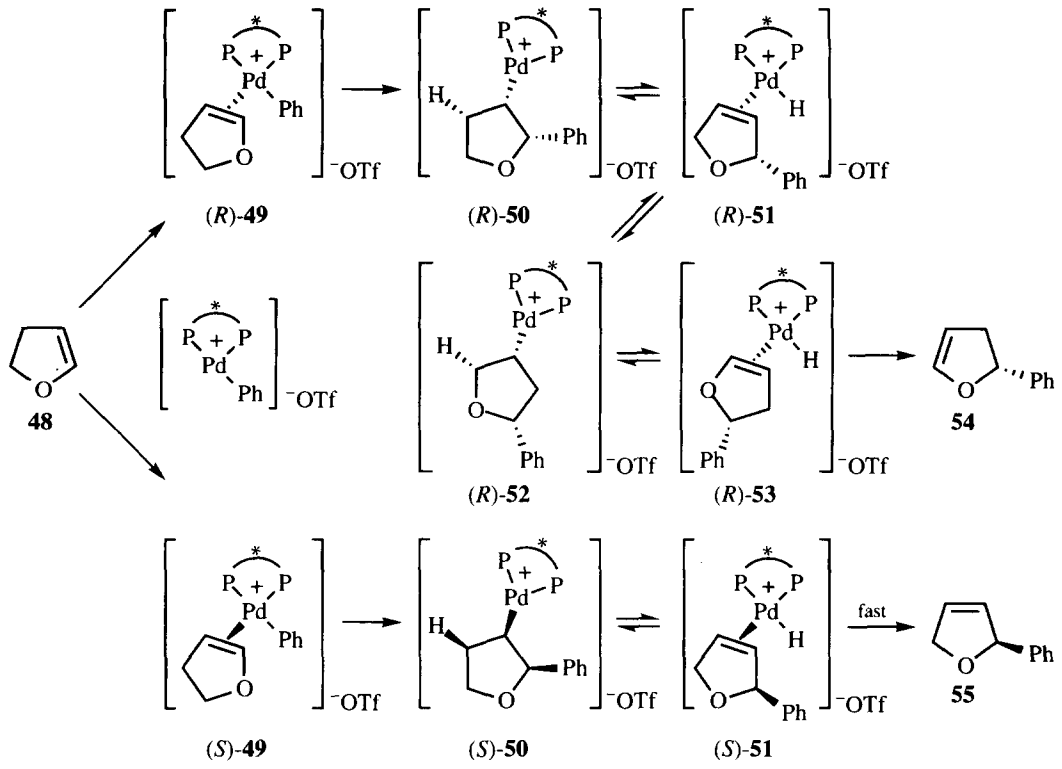
Scheme 11

b) Intermolecular

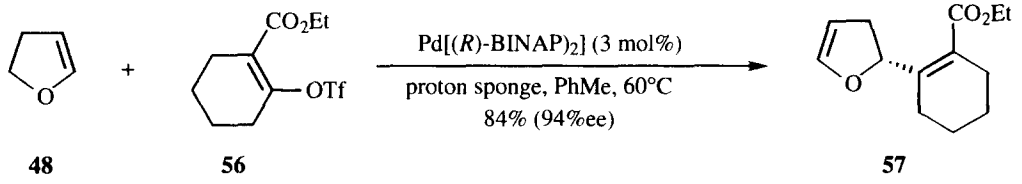
i) Dihydrofurans and Cyclic Enol Ethers

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 enantiomeric excess 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 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 **48**→**49** step 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).[45] 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**.[46] 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).[47]



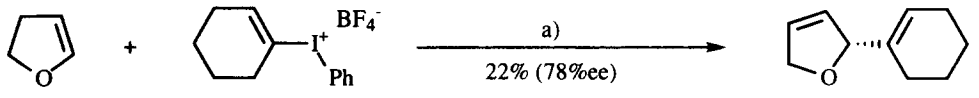
Scheme 12. Mechanism for intermolecular AHR with dihydrofurans.



Scheme 13

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 **48**→**54/55** conversion is dramatically increased, suggesting that such conditions enhance the kinetic resolution process.[48] Also, Shibasaki *et al.* have shown that the reaction can be carried out using alkenyliodonium salts instead of vinyl triflates (*viz* **58**→**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.[49] 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.

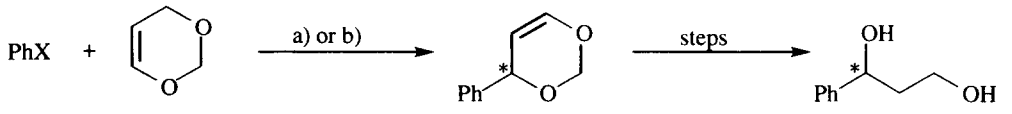
Finally, the asymmetric arylation of **60** has also been reported, although the yields and ees are more modest (Scheme 15).[50] Hydrolysis of the product **61** conveniently gives the 1,3-diol **62**, an intermediate in Sharpless's synthesis of fluoxetine.[51]



48 **58** **59**

a) $Pd(OAc)_2$ (40 mol%), (*R*)-BINAP (60 mol%), proton sponge, CH_2Cl_2, 25°C, 20 hrs.

Scheme 14



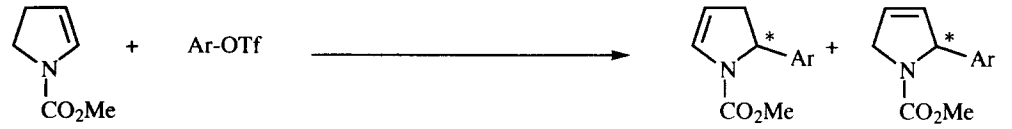
60 **61** **62**

a) for X=I; $Pd(OAc)_2$, (*R*)-BINAP, Ag_2CO_3, DMF, 60°C, 48 hrs, 62%, 43%ee; for X=OTf: $Pd(OAc)_2$, (*R*)-BINAP, i-Pr_2NEt, DMF, 60°C, 48 hrs, 37% (~35%ee).

Scheme 15

ii) Dihydropyrroles

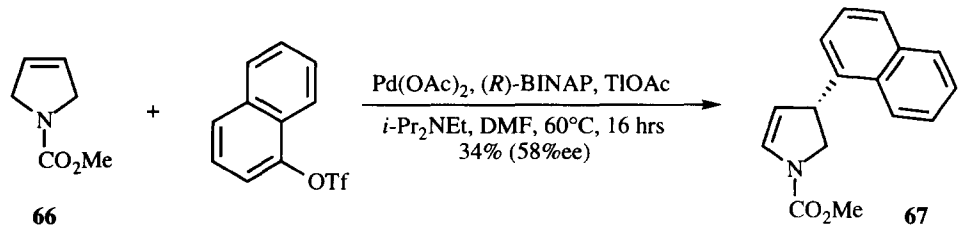
The methods described for arylation of dihydrofurans described above have also been applied to 2,3-dihydropyrroles such as **63**,[52] with similar patterns of regio- and enantioselectivity being observed. Thus little or no ee was obtained when using aryl iodides, but aryl triflates gave mixtures of 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.[47]



63 **64** **65**

Scheme 16

An example of reaction with 2,5-dihydropyrroles has also been recently disclosed.[53] Arylation of **66** using 1-naphthyl triflate and an (*R*)-BINAP / $Pd(OAc)_2$ / *i*-Pr_2NEt system in DMF gave with moderate yield and ee the 3-arylation product **67** (Scheme 17): it was found that the addition of excess acetate served to suppress formation of the undesired 2-arylation product, 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, as was an attempt to asymmetrise a similar Heck reaction with 1,2,3,4-tetrahydropyridines.[54]

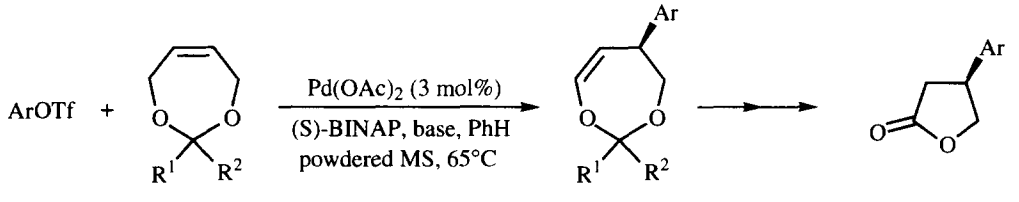


66 67

Scheme 17

iii) Dihydrodioxepins

Arylation, once again using the triflate, of the 4,7-dihydro-1,3-dioxepin system **68** (easily derived from *cis*-2-butene-1,4,-diol) was reported by Shibasaki *et al.* in 1994.[55] The reaction is significant in that the product 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).[56] Also noteworthy is the important role played by added molecular sieves, which enhance both chemical yield *and* ee, the first time such an effect had been noted for the AHR.



68 69 70

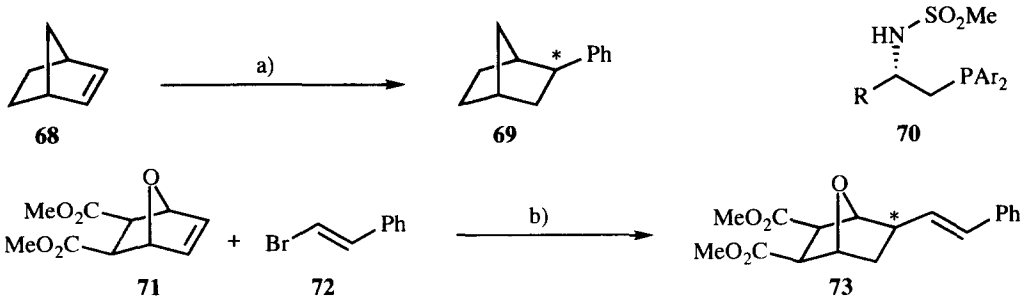
Scheme 18

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 5).[57]

iv) Hydroarylations of [2.2.1]Bicyclics

Asymmetric hydroarylation/hydrovinylation, although not strictly a Heck reaction as the β-hydride elimination step is replaced by protonolysis, nevertheless shares a common mechanistic pathway with regard to the enantioselective step and so will be discussed briefly. Hydrophenylations of norbornene and norbornadiene using aryl iodides were first reported by Brunner *et al.* in 1991, although the ees obtained were low (<40%). The preferred ligand was (–)-Norphos: BINAP does not appear to have been tested.[58] The system has since been revisited by Achiwa *et al.* as a means of testing the novel phosphine ligands of general structure **70**.[59,60] Using these the conversion **68**→**69** 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 hetero-analogues such as **71**: excellent ees and satisfactory yields were obtained.[61] Hydrophenylation of a similar system has been reported by Fiaud.[62]



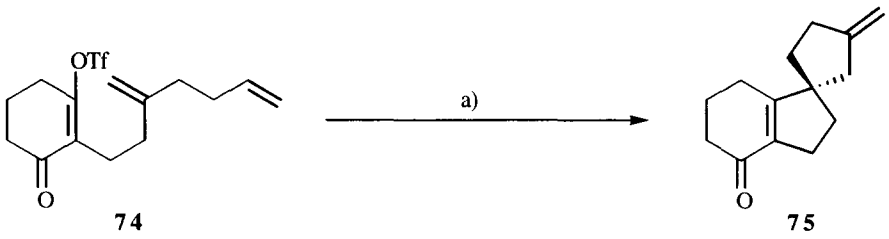
a) Ph-OTf, $Pd(OAc)_2$, **70** (R=$CHMe_2$, Ar=Ph), *i*-Pr_2NEt, HCO_2H, DMSO, 65°C, 20 hrs, 81%, 74%ee. b) Pd{(*R*)-BINAP}$_2$ (1 mol%), HCO_2H, Et_3N, $Cl(CH_2)_2Cl$, 40°C, 63%, >96%ee.

Scheme 19

4) Formation of Quaternary Centres

a) Spirocyclisations and Alkaloid Synthesis

The enantioselective formation of quaternary carbon centres remains a significant challenge to the synthetic chemist.[63] Using the AHR in this role has the obvious attraction of removing the problem of competing pathways in step C, 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.

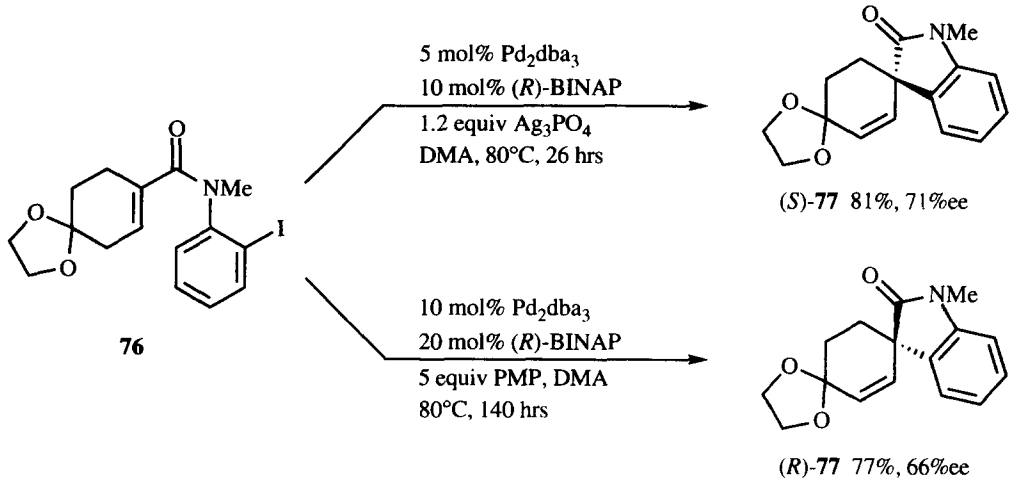


a) 10 mol% $Pd(OAc)_2$, 10 mol% (*S,S*)-DIOP, Et_3N, PhH, 25°C, 1hr, 90% (45%ee).

Scheme 20

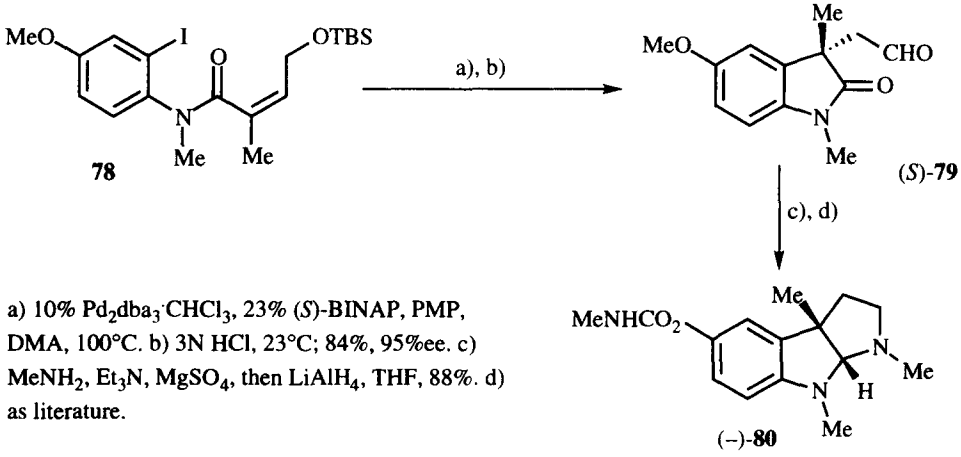
The first successful case was reported by Overman *et al.* in 1989,[64] a pioneering discovery which may be thought of as a non-identical twin to the contemporaneous work of Shibasaki *et al.* described in section 3. As with that work the enantiomeric excesses obtained at the outset were modest, with the spirocyclic system **75** being obtained in good yield and moderate ee when (*S,S*)-DIOP was substituted for triphenylphosphine (Scheme 20). 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 21).[65]

Carrying out the AH cyclisation of iodoanilide **76** in a dipolar aprotic solvent (in this case dimethylacetamide, DMA) in the presence of Ag_3PO_4 gave (*S*)-**77** 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



Scheme 21

the reaction in the absence of Ag salts and using 1,2,2,6,6-pentamethylpiperidine (PMP) as the base the opposite (*R*)-**77** enantiomer was obtained *using the same enantiomer of BINAP*. Similar studies of the cyclisation of alkene **78** revealed that when (*E*)-**78** is used the effect is reproduced, although the ees of the enantiomer obtained when using PMP are low (30-40%). In contrast, when (*Z*)-**78** is used in conjunction with (*R*)-BINAP *both* sets of conditions give the expected (*R*)-enantiomer of **79** with good yields and excellent (>90%) ees.[66] 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*)-**79**, which can be converted to the natural product physostigmine **80** *via* methylimine formation and reductive cyclisation (Scheme 22), followed by anisole demethylation and reaction of the resulting phenol with methyl isocyanate.[67]



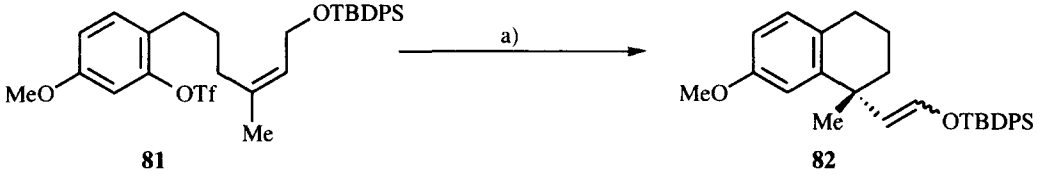
a) 10% $Pd_2dba_3{\cdot}CHCl_3$, 23% (*S*)-BINAP, PMP, DMA, 100°C. b) 3N HCl, 23°C; 84%, 95%ee. c) $MeNH_2$, Et_3N, $MgSO_4$, then $LiAlH_4$, THF, 88%. d) as literature.

Scheme 22

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.

b) Eptazocine and Halenaquinol

The synthesis of benzylic quaternary centres by AHR has also been reported by the Shibasaki group, in connection with syntheses of (–)-eptazocine[68] and of halenaquinone and halenaquinol **86**.[69] As in section 4a) the key steps in both syntheses involve the formation of a quaternary carbon centre by AH 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 **81**→**82** step in the eptazocine synthesis, the opposite enantiomer to that obtained when using the *E*-alkene. The conversion of **81** to **82** (Scheme 23) was achieved with excellent yield and ee: desilylation gave the corresponding aldehyde,[70] which was converted to (–)-eptazocine *via* a 5-step sequence.



81 **82**

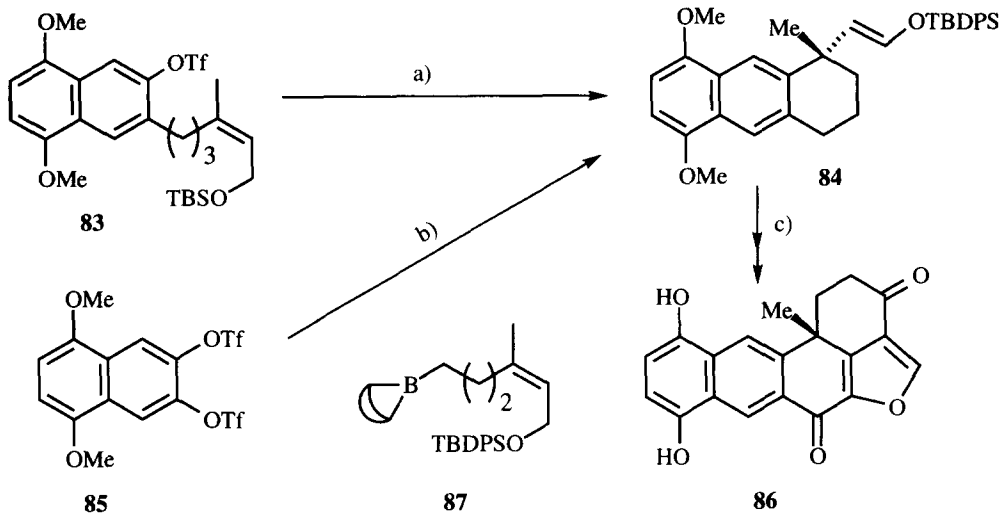
a) $Pd(OAc)_2$ (7 mol%), (*R*)-BINAP (17 mol%), K_2CO_3 (3 eq.), THF, 60°C, 72 hrs, 90%, 90% ee, *E*:*Z* = 21:3.

Scheme 23

The synthesis of halenaquinol **86** (and its oxidation product halenaquinone) initially featured the key step **83**→**84** (Scheme 24), which gave the desired product in 78% yield and 87%ee under very similar conditions to those used for **81**→**82**. However, in line with the current trend towards sequential or "one-pot" transformations,[71,72] (*vide infra*) the authors were able to combine the AHR step with a Suzuki-type coupling of the trialkylborane **87** (itself pre-generated *in situ* by hydroboration) with the C2-symmetric ditriflate **85** and so obtain **84** rather more directly. Whilst the chemical yield of this step 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.

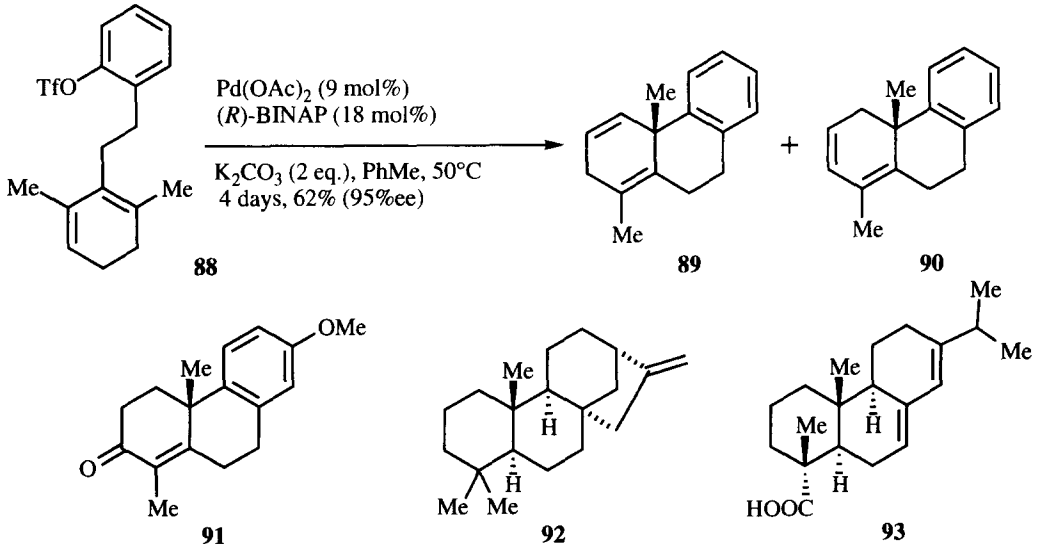
c) Sesquiterpenes

One further example of quaternary centre formation by AHR has been reported, this being the conversion of the aryl triflate **88** to a 3:1 mixture of the tricycle **89** and its isomer **90**, both of which can be converted to the enone **91**, a key intermediate in the syntheses of kaurene **92** and abietic acid **93** (Scheme 25).[73,74] Compound **89** can also be quantitatively isomerised to **90**. 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.



a) $Pd(OAc)_2$ (10 mol%), (*S*)-BINAP (20 mol%), K_2CO_3, THF, 60°C, 78%(87%ee). b) **87** (1.1 eq.), $Pd(OAc)_2$ (20 mol%), (*S*)-BINAP (40 mol%), K_2CO_3, THF, 20% (85%ee). c) 12 steps, 12% overall.

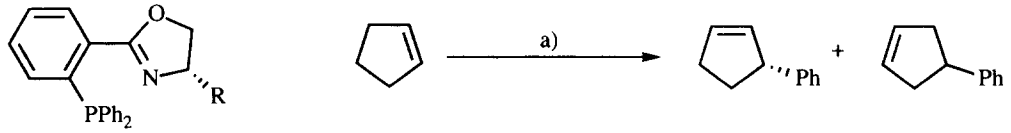
Scheme 24



Scheme 25

5) Recent Developments and New Directions

The great majority of AHRs reported so far have utilised the BINAP ligand system, which has proven to be the most effective in most of the cases in which the performances 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 of late has been the introduction by Pfaltz *et al.* of the oxazoline-based ligands **94**,[75] which appear to give dramatically improved ees with several previously reported AHRs.[57] For example, the Hayashi-type AHR of dihydrofuran **48** with cyclohexenyl triflate catalysed by $Pd(dba)_2$ and **94** (R=*tert*-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.[76] As with the Shibasaki group's vinylation of **48** using iodonium salt **58**, no trace of the isomeric 2-alkenyl-3,4-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 **95** with high yields, good to excellent ees and only small amounts (<5%) of the unwanted regioisomers such as **96** (Scheme 26). Also interesting are the increased reaction rates and decreased catalyst loading, indicating higher catalyst turnover. This has recently been achieved for the standard Heck reaction by the use of high pressure conditions,[77] and its improvement for the AHR remains an important goal.



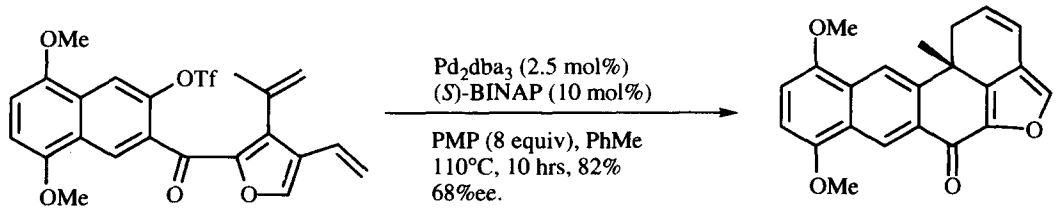
94 **95** **96**

a) PhOTf, $Pd(dba)_2$ (3 mol%), **94** (R=$C(CH_3)_3$, 6 mol%), *i*-P_2NEt, THF, 70°C, 5 days, 80%, 86%ee, **95**:**96** 99:1.

Scheme 26

The recent surge of interest in combinatorial chemistry[78,79] may also prove to be highly significant to the development of new ligands, as both Heck reactions on solid support[80] and the generation and screening of chiral phosphine ligand libraries[81] 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.[82-84]

Finally, a very recent synthesis of the halenaquinol-related natural product (+)-xestoquinone by Keay and co-workers[85] has provided confirmation of the suitability of the AHR for inclusion in Pd-mediated "cascade" polyene reactions.[86] The one-pot transformation of triflate **97** into the pentacycle **98** (Scheme 27) is achieved using conditions typical for the AHR, and gives (+)-**98** with a respectable 68%ee. Interestingly, the iodide analogue of **97** gives little or no asymmetric induction, even in the presence of silver salts.



97 **98**

Scheme 27

6) Conclusions

From its modest beginnings in the late 1980s the AHR has developed into a powerful method for the formation of both tertiary and quaternary chiral carbon centres, with enantiomeric excesses typically in excess of 80% and in some cases much higher. 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, which dissociate more rapidly from the products, may improve both enantio- and regiocontrol. It is to be hoped that the search for improved ligand systems will be greatly assisted by combinatorial screening methods, to which the mild and functionality-tolerant AHR may prove to be well suited. Certainly the reaction has proven to be useful in one-pot multi-step processes. This also makes it attractive in situations where "atom economy" is a significant concern.[87,88]

Acknowledgements

Thanks are extended to the many present and former Shibasaki group members listed in the references, in particular Dr. Mikiko Sodeoka (currently with Sagami Chemical Research Institute).

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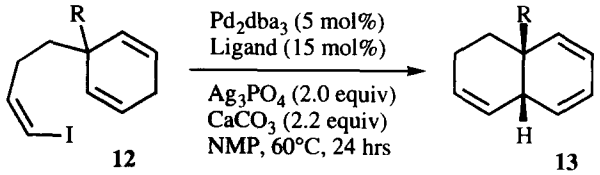
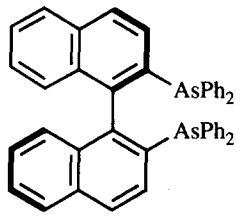


Ligand	yield (%)	ee (%)	
(*R*)-BINAs	90	82	
(*R*)-BINAP	55	32	(R=CH_2OTBS)



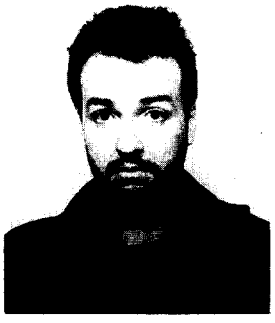
(*R*)-BINAs

Scheme 28

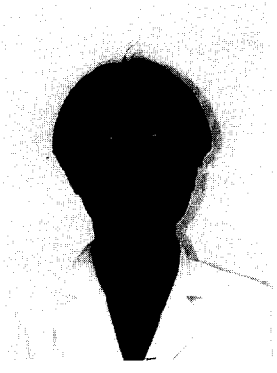
(*Received* 15 *April* 1997)

Biographical Sketch

Masakatsu Shibasaki



Christopher D. J. Boden



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Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his PhD. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E.J.Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Centre as a group leader, and in 1986 took up a professorship at the University of Hokkaido, before returning to the University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young Scientists, Inoue Academic Prize and Fluka Prize (Reagent of the Year, 1996). His research interests include asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by asymmetric heterobimetallic complexes, and also the medicinal chemistry of biologically significant compounds.

Chris Boden was born in 1967 in Rotherham, England and received his BSc, MPhil. and PhD. degrees from the University of Southampton, the latter under the supervision of Dr. Ian Stevens and bridging the areas of Organic Chemistry and Chemical Ecology. In 1993 he moved to the University of Nottingham to take up a postdoctoral fellowship with Professor Gerald Pattenden.
He was a JSPS postdoctoral fellow in Prof. Shibasaki's research group from 1996 to 1997, and is currently employed by Nippon Glaxo in Tsukuba, Japan.

Akihiko Kojima was born in 1965 in Kanagawa, Japan, and received his M.S. in 1990 from the Tokyo College of Pharmacy (now the Tokyo University of Pharmacy and Life Science). He has been employed by Kyorin Pharmaceutical Company since 1991, and since 1995 has also been carrying out research towards a PhD. in the research group of Prof. Shibasaki.