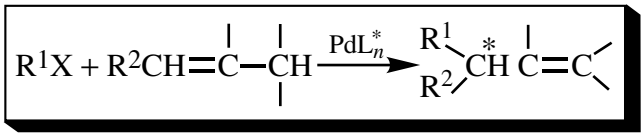

IV.2.3 Asymmetric Heck Reactions

MASAKATSU SHIBASAKI and FUTOSHI MIYAZAKI

A. INTRODUCTION

The Pd-mediated coupling of aryl or vinyl iodides, bromides, or triflates with alkenes in the presence of a base, in other words, the Pd-catalyzed 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] It is a great advantage that 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, hydroxyl including phenolic ones, or cyano groups. Despite displaying many of the benefits usually associated with Pd-mediated reactions[4] (e.g., 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 dissymmetrization attempts until the late 1980s. However, it can be pointed out that the reaction has not usually been used to generate stereogenic centers,[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 centers can be generated with ee values ≧80%. The bulk of the reported examples involves 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, mainly *O*- and *N*-heterocycles, and to the formation of tertiary centers on ring carbon atoms, which again simplifies the question of alkene regiochemistry (but see **Sect. F**).

What follows is a survey of the relevant literature up to late 2000, including a discussion of the mechanistic aspects relevant for stereoselection in the AHR. The classification of the sections proceeds according to the various types of underlying carbon skeletons or natural product fragments of the resulting compounds. Diastereoselective variations,[5]

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which have frequently been utilized for the construction of natual products, are generally not included.

B. REACTION CONDITIONS

The AHR is carried out under similar or identical reaction conditions generally associated with versions of the Heck reaction leading to racemic products using standard laboratory glassware. The solvents that 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 at a reasonable rate. 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 generated *in situ*. Examples for palladium catalyst precursors are $Pd(OAc)_2$ or $Pd_2(dba)_3 \cdot CHCl_3$ (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.

C. MECHANISTIC ASPECTS

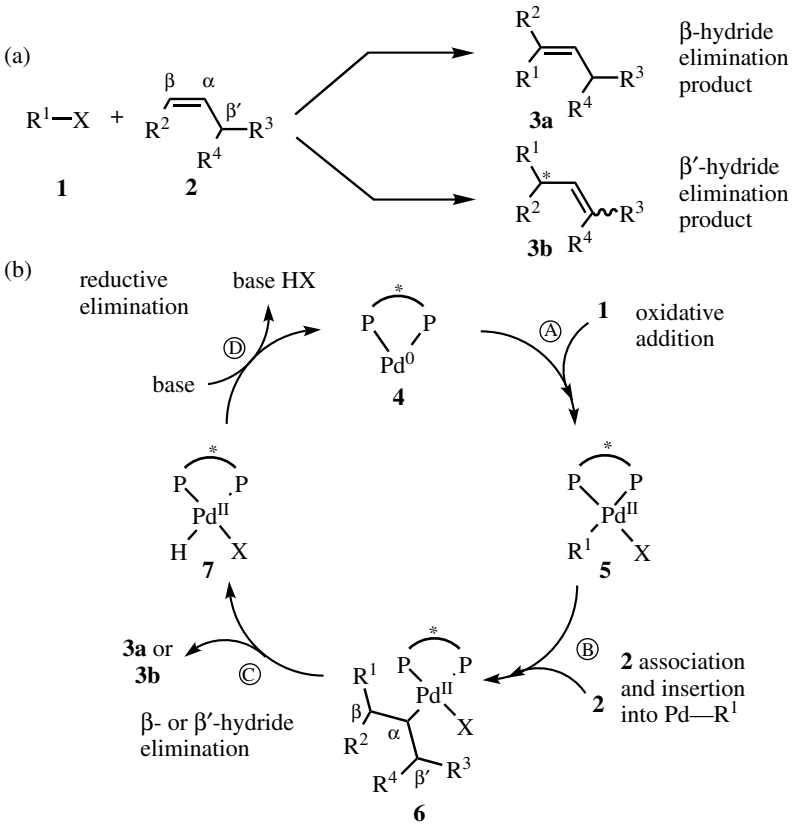
The current state of mechanistic theory regarding the Heck reaction in general has been provided in recent review articles.[5],[12] In the following, the discussion will be a selective one, focusing primarily on the factors that influence the regio- and enantiocontrol.[13],[14]

C.i. 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: (i) oxidative addition of **1** to the Pd^0 species **4**, bearing a bidentate phosphine ligand, to give the Pd^{II} species **5**; (ii) coordination and then *syn*-insertion of the alkene substrate **2** into the Pd—R^1 bond of **5** to give **6**; (iii) β- or β'-hydride elimination from **6** to give either **3a** or **3b**; and finally; (iv) regeneration of **4** by reductive elimination of HX from **7**.

The three major factors governing regioselectivity are:

1. The regioselectivity of the insertion into the Pd—R^1 bond heavily depends on the nature of the steric and electronic environment provided by R^2, R^3, and R^4 for unsymmetrically substituted 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- or 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 substrates ($R^2 = CO_2R$,



Scheme 1

monosubstituted alkene), which through their highly unsymmetrical steric and electronic environment also avoid any problems with regioselectivity in step **B**. While this constitues 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 center is lost.

3. Even if the regioselectivity of step © can be controlled, a further problem lies in its reversibility, which can result in reinsertion of the alkene **3b** 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 a formal shift of the double bond in the alkene from the α,β'- into a β',γ'-position, a problem that is especially prone to occur for endocyclic alkene products (see **Sect. D.ii**). 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*).

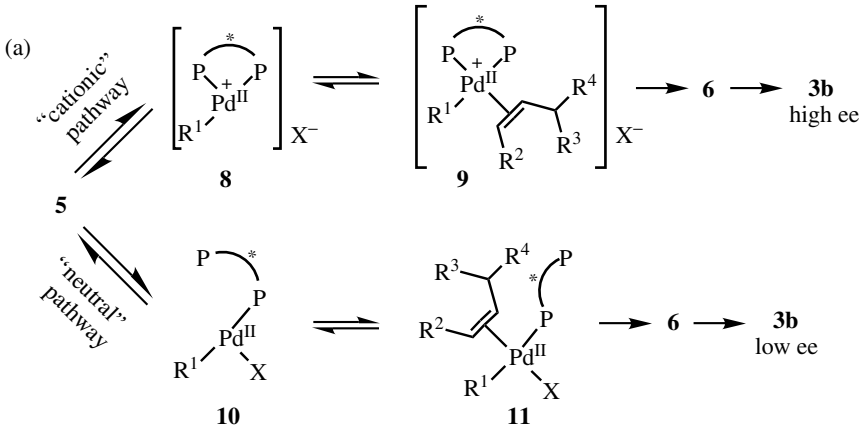
A preference for **3b** rather than **3a** formation is essential for the AHR to occur, and thus an examination of the factors controlling the competing elimination processes in step ©

and the consequent prerequisites for ensuring the predominance of the desired pathway is clearly apropos. As both the insertion into **5** and the elimination from **6** are *syn*-processes, rotation around the alkene σ-bond is required before β-hydride elimination can occur. This might be expected to make β'-hydride elimination the kinetically more favorable 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 centers, which have been reported (with the exception of the allylsilane reactions by Tietze and colleagues—see **Sect. D.i.e**), involve endocyclic alkene substrates. Other methods to direct the selectivity of step © 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 tautomerizes 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.

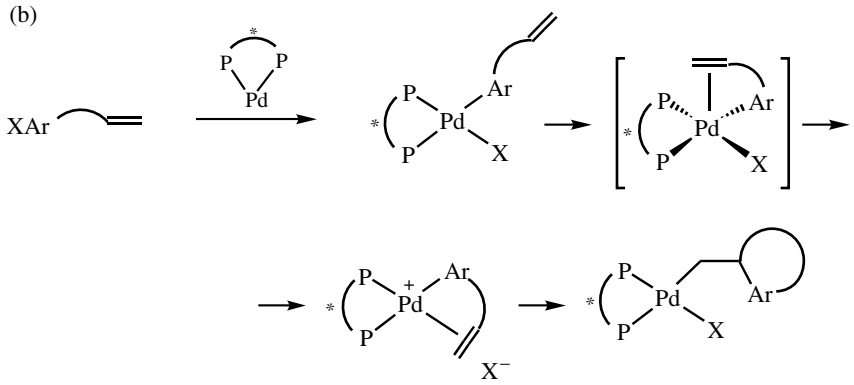
C.ii. Factors Governing Enantioselectivity

The key step in the catalytic cycle with regard to enantioselectivity is clearly Ⓑ, 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 favor having been proposed in 1991 by Ozawa, Kubo, and Hayashi,[18] and independently by Cabri et al.[19] (although the cationic pathway via **8** and **9** had been proposed as early as 1990[20]). Its development and subsequent evolution have recently been reviewed by Cabri and Candiani.[12]

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



Scheme 2a



Scheme 2b

remained fully chelated throughout and so having maximized 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 recomplexation 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 alkenyl 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/alkenyl halides. In practice, it has proved possible to influence which pathway will be followed in a given Heck process, either by adding silver salts to the reaction of an aryl/alkenyl 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 alkenes favoring 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]

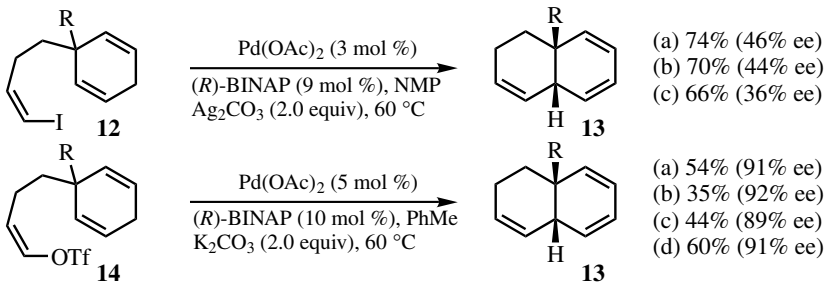
The partial dissociation of the chiral ligand during the "neutral" process would seem to make it less well suited to asymmetric induction, however, and the evidence of most of the AHRs reported so far seems to indicate that conditions which favor the "cationic" route also give the best enantiomeric excesses (ees). However, a significant exception to this rule has been found (see also **Sect. E.i**). Overman, Poon, and co-workers 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],[24] 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 analog of (*R*)-BINAP, only low enantioselectivities were obtained for this example. This can be taken as evidence that both phosphines of the diphosphine ligand remain coordinated to the Pd center during the enantioselective step. It was also shown that enantioselectivity in this neutral pathway was unchanged in going from dry DMA to DMA containing 5% water.[24] 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 rationalizations on how the chirality is transferred from the ligand to the substrate are not available for the AHR at present or are just beginning to emerge (see **Sect. D.i.d**).

D. FORMATION OF TERTIARY CARBON CENTERS

D.i. Intramolecular

D.i.a. ***Decalins.*** The first example of an asymmetric Heck reaction was reported in 1989 and involved the conversion of the prochiral alkenyl iodides **12a–c** into the chiral decalin systems **13a–c**, as shown in **Scheme 3**.[25] The reaction conditions (dipolar aprotic solvent and presence of silver salts), while similar to those of a previously reported nonenantioselective method,[16] differ crucially in respect of the choice of the 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 inductions, with (*R*)-BINAP proving to be the ligand of choice, a pattern that has been repeated in most (though not all—see **Sect. D.i.c**) of the reported examples of the AHR. By using a prochiral substrate, two stereocenters can be set in one step, a tactic that is used repeatedly in the tertiary center-generating AHRs reported by the Shibasaki group.



(a) R = CO2Me, (b) R = CH_2OTBS, (c) R = CH_2OAc, (d) R = CH_2OPiv

Scheme 3

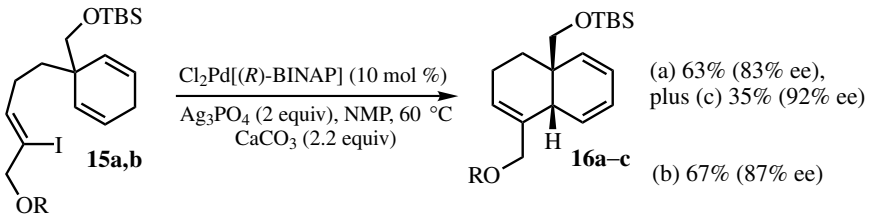
The modest ees reported (33–46%) for the conversion from **12** to **13** were greatly improved as a result of a study of the effects on the reaction of varying the anionic component of both the Pd source and more particularly the silver salt.[20] It was found that the use of a Pd^0 catalyst complex preformed *in situ* from Cl_2Pd(*R*)-BINAP,[26] (*R*)-BINAP, and cyclohexene gave greatly improved ees relative to the 1:3 $Pd(OAc)_2$/(*R*)-BINAP prereduced 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 easily 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 with 80% ee and in 67% yield.

The very recent introduction of the new ligand 2,2′-bis(diphenylarsino)-1,1′-binaphthyl (BINAs),[27] the diarsine equivalent of BINAP, helped to considerably increase the yield for the conversion of **12b** to **13b** (**Scheme 3**). After optimization, the product **13b** could be prepared in 90% chemical yield and with 82% ee.[27]

The use of the alkenyl triflates **14a–d** in place of iodides **12a–c** gave still better results[28] 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 with uniformly excellent (89–92%) ees under the conditions indicated.

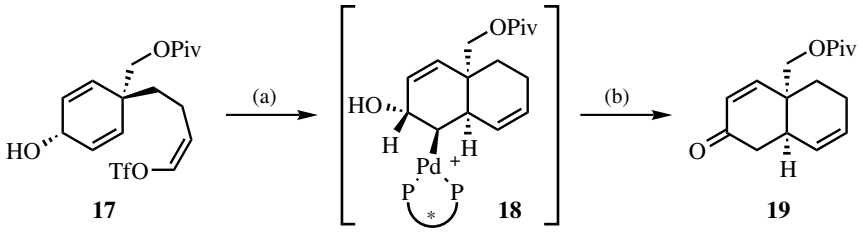
The scope of the reaction was extended somewhat by the use of the trisubstituted alkenyl iodide **15**, which gave the decalin systems **16a** and **16b** in yields of 63% (83% ee) and 67% (87% ee), respectively (**Scheme 4**).[28] The deleterious effect of the acetate counterion on ee and favorable influence of the $Ag_3PO_4/CaCO_3$ additive combination seen for the AHR conversion of **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 transmetallation to Pd after completion of the ring closure. No such free hydroxyl formation was seen in the case of the acetate **15b**.



(a) R = TBS, (b) R = Ac, (c) R = H

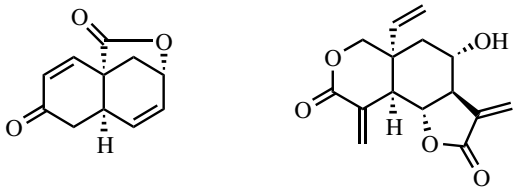
Scheme 4

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[29] of vernolepin **21**. The AHR involved was initially the conversion of the bisallylicalcohol **17** to the chiral decalin system **19**, via the intermediate **18** (**Scheme 5**).[30] The best solvent for this was found to be 1,2-dichloroethane (DCE), with the addition of *t*-BuOH having a beneficial effect on the reaction rate and the chemical yield without reducing the ee.[31] Compound **19** was converted to **20** via a nine-step process; an alternative approach was also found, which started from the more readily available **13a**.[32] Application of the DCE/tertiary alcohol solvent system for the conversion of **14a** to **13a** gave an 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 synthesized (+)-**21**, thereby making an assignment of its absolute configuration possible.



17 18 19

(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 d. (b) β-hydride elimination, then tautomerization, 76%, 86% ee.

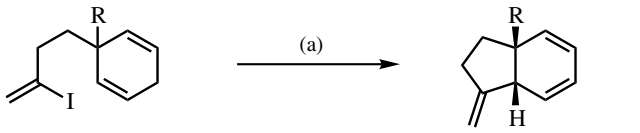


20 **21**

Scheme 5

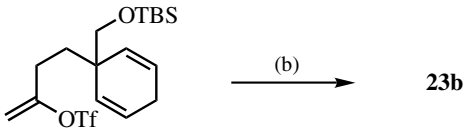
D.i.b. ***Hydrindans.*** The general method described in **Sect. D.i.a** for decalin synthesis has also been applied to the synthesis of 6,5-ring systems through the formation of hydrindans (**Scheme 6**).[33]

Both the iodides **22a–e** and the 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%)



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



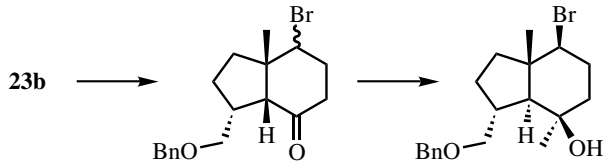
24 **23b**

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

Scheme 6

in ee could be obtained for **22a**–**c** by prereducing the palladium catalyst *in situ*. The triflate **24** gave **23b** with slightly lower ee than seen for the corresponding conversion of **22b**, with potassium carbonate being the most effective base.

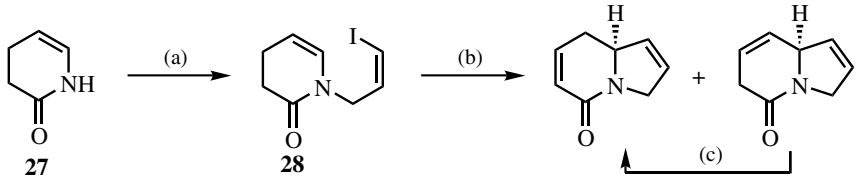
The hydrindan **23b** was later converted by the same group into **26** (**Scheme 7**),[34] which is a key intermediate in the synthesis of (−)-oppositol and (−)-prepinnaterpene.[35] The conversion involved oxidation of the diene moiety with singlet oxygen and is notable for the clean epimerization of the ring junction to give the *trans*-configuration (from **25** to **26**), which demonstrates that both *cis*- and *trans*-junctions can be obtained in the AHR products.



25 **26**

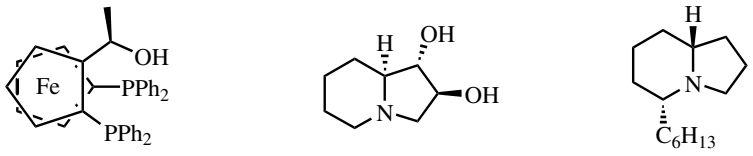
Scheme 7

D.i.c. ***Indolizidines.*** The 6,5-combination bicycle synthesis outlined above has been extended to indolizidines, formed by AHR of a suitable prochiral alkenyl iodide such as **28**, which can easily be prepared by allylation of the lactam **27**. In contrast to purely carbocyclic systems, however, the most effective ligand proves to be (*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol (BPPFOH) **31**,[36] which gives results clearly superior to those obtained with BINAP (**Scheme 8**).[37],[38]



27 **28** **30** **29**

(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 (corresponds to ca. 6 equiv Ag), $CaCO_3$, DMSO-DMF, 0 °C, 94% (86% ee). (c) Pd/C, MeOH, 23 °C, quantitative.

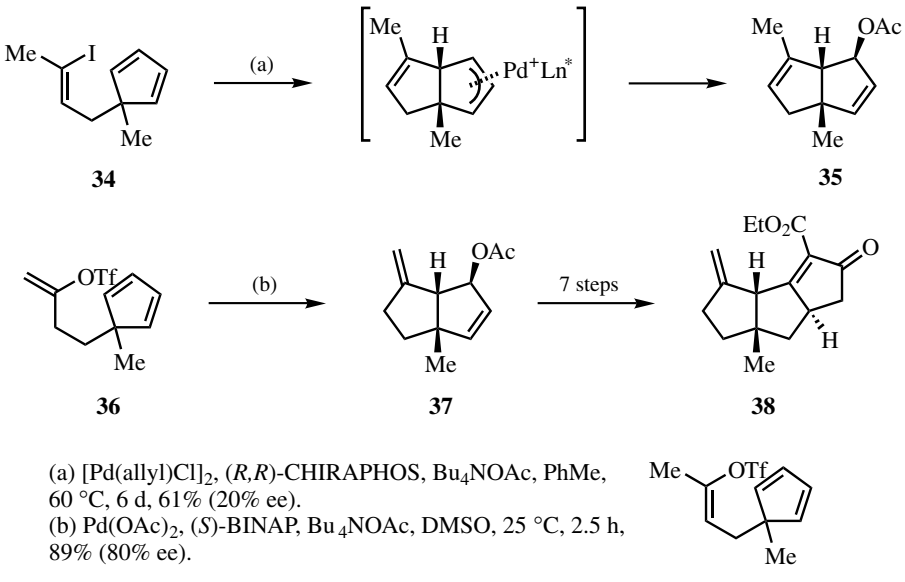


31 **32** **33**

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 isomerization to **30** in essentially quantitative yield. Compound **30** has been converted to the natural products lentiginosine **32**, 1,2-diepilentiginosine, and gephyrotoxyn 209D **33**.[39]

D.i.d. ***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-allylpalladium species, which must then be trapped with a suitable nucleophile.[40] The greater reactivity of the 1,3-diene substrate toward the silver salts used in the reactions and the propensity for undesirable side reactions such as Diels–Alder cycloadditions must also be borne in mind. The former problem, in fact, figures prominently in the first example of an AHR-based diquinane synthesis to be published (**Scheme 9**).[41],[42]

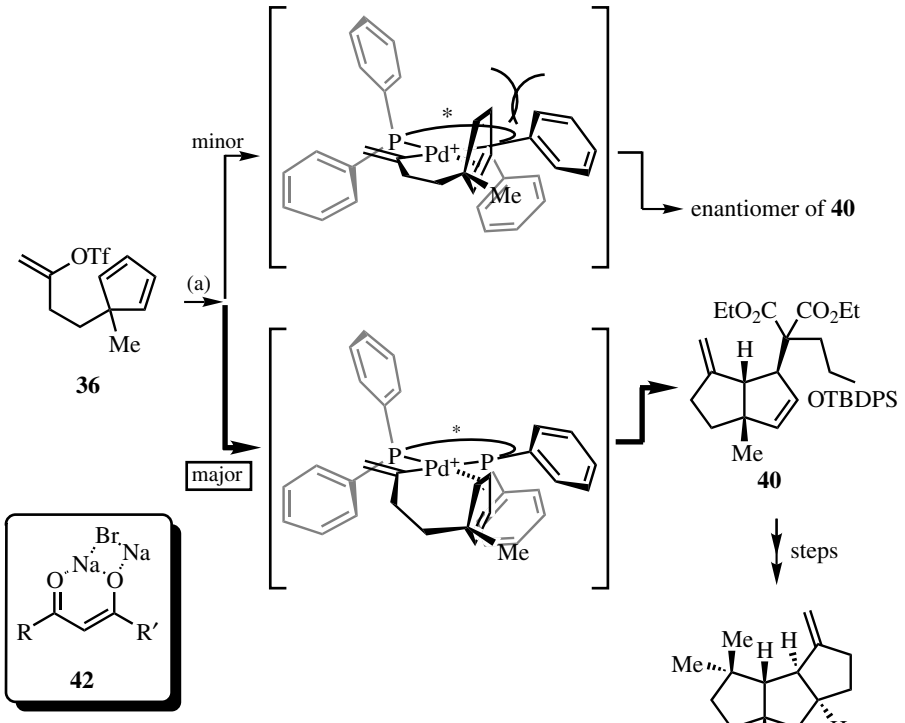


(a) $[Pd(allyl)Cl]_2$, (*R,R*)-CHIRAPHOS, Bu_4NOAc, PhMe, 60 °C, 6 d, 61% (20% ee).
(b) $Pd(OAc)_2$, (*S*)-BINAP, Bu_4NOAc, DMSO, 25 °C, 2.5 h, 89% (80% ee).

Scheme 9

Although cyclization of the 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 failure 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,[43] and later developed the first *catalytic* asymmetric synthesis of $\Delta^{9(12)}$-capnellene **41** itself by trapping the π-allylpalladium intermediate with a suitable β-dicarbonyl carbanion (**Scheme 10**).[44]

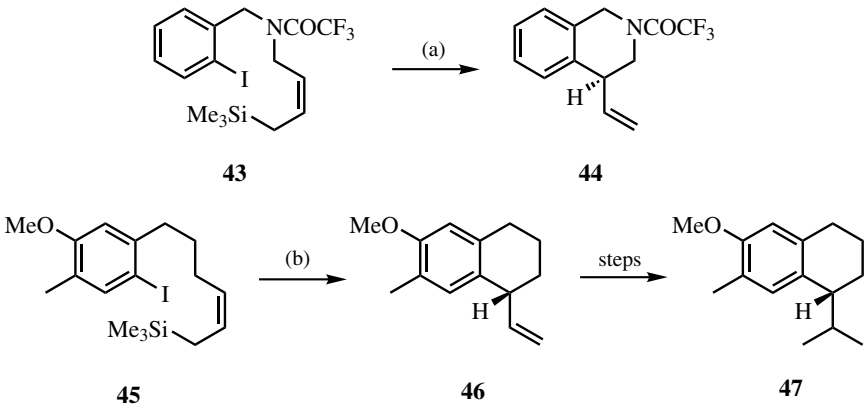


(a) $[Pd(allyl)Cl]_2$ (2.5 mol %), (*S*)-BINAP (6.3 mol %), NaBr (2.0 equiv), $(CO_2Et)_2C(Na)(CH_2)_2OTBDPS$ (2.0 equiv), DMSO, 25 °C, 77%, 87% ee.

Scheme 10

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

D.i.e. ***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 **Sect. B.i**. A more general approach to the problem has been described by Tietze and co-workers and involves the use of allylsilanes as the alkene component (**Scheme 11**).[45],[46]



(a) $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %), (*S*)-BINAP (7.0 mol %), Ag_3PO_4 (1 equiv), DMF, 75 °C, 48 h, 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 h, 91% (92% ee).

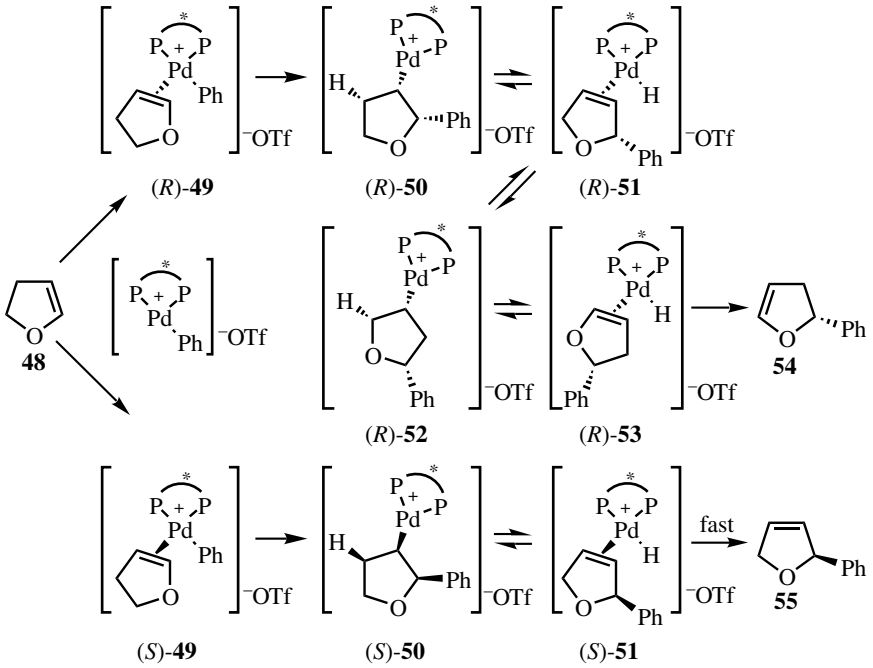
Scheme 11

By careful choise of reaction conditions either a vinyl- or trimethylsilylvinyl-substituted carbocycle can be produced in the nonenantioselective reaction. Under conditions suitable for the AHR, however, the former product predominates (e.g., transformation of **43** to **44**). Yields and ees appear to be good, and the method has been applied successfully to the synthesis of the norsesquiterpene 7-demethyl-2-methoxycalamene **47**, via the key cyclization from **45** to **46**.[47],[48]

D.ii. Intermolecular

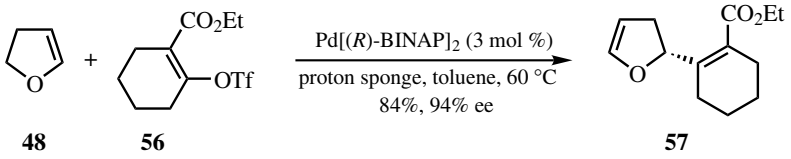
D.ii.a. ***Dihydrofurans and Cyclic Enol Ethers.*** The first example of an intermolecular AHR was reported by Hayashi and co-workers and involved the asymmetric arylation of 2,3-dihydrofurans using aryl triflates.[18] Although little or no ee was obtained when aryl iodide/silver salt combinations were 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 is hypohthesized 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 unfavorable steric factors cause an immediate dissociation of the Pd species, producing the minnor 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 that give proportionally larger amounts of **55** also appear to give the best ees for 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



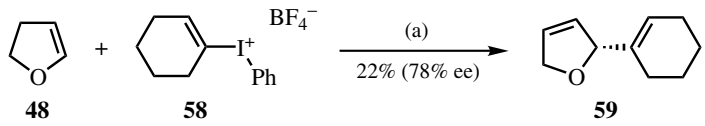
Scheme 12

much better regioselectivity (97:3).[49],[50] 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**.[51] Even more impressive results have been obtained using alkenyl 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**).[52]



Scheme 13

An interesting corollary to this work has been reported by Hillers and Reiser, 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.[53] Shibasaki and co-workers have shown that the reaction can be carried out using alkenyliodonium salts instead of alkenyl 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 an uncatalyzed and/or nonphosphine-mediated process.[54] Interestingly, only the 2-alkenyl-2,5-dihydrofuran product is obtained,



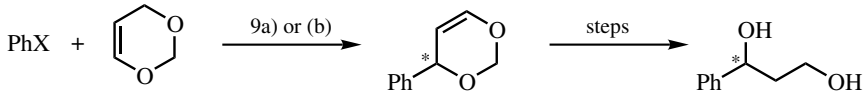
48 **58** **59**

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

Scheme 14

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**).[55] Hydrolysis of the product **61** conveniently gives the 1,3-diol **62**, an intermediate in Sharpless's synthesis of fluoxetine.[56]

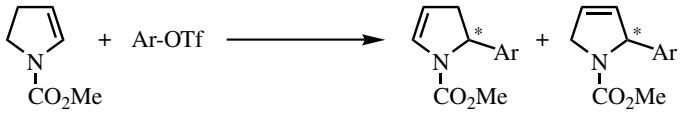


60 **61** **62**

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

Scheme 15

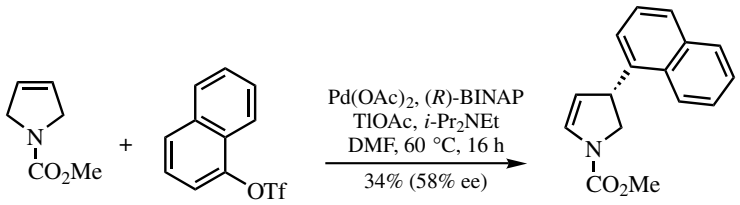
D.ii.b. ***Dihydropyrroles.*** The methods described for arylation of dihydrofurans (see above) have also been applied to 2,3-dihydropyrroles such as **63**,[57] with similar patterns of regio- and enantioselectivity being observed. Thus, little or no ee was obtained when using aryl iodides, but aryl 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 extended successfully to alkenyl triflates, which gave even better ees than obtained for the dihydrofurans.[52]



63 **64** **65**

Scheme 16

An example of a reaction with 2,5-dihydropyrroles has also been recently disclosed.[58] 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**),

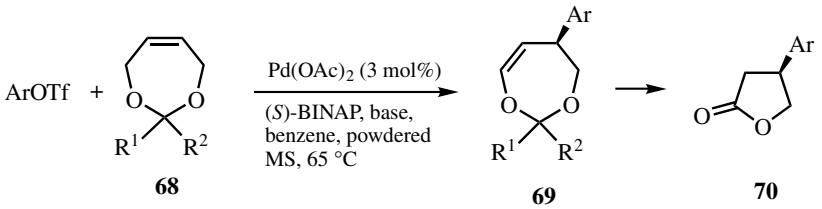


66 **67**

Scheme 17

and this was conveniently achieved by adding TlOAc, with the thallium cation acting as a cocatalyst. Unfortunately, attempts to carry out this reaction with other aryl triflates or with aryl iodides were unsuccessful.

D.ii.c. ***Dihydrodioxepines.*** 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 and co-workers in 1994.[59] 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**).[60] 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.



68 **69** **70**

Scheme 18

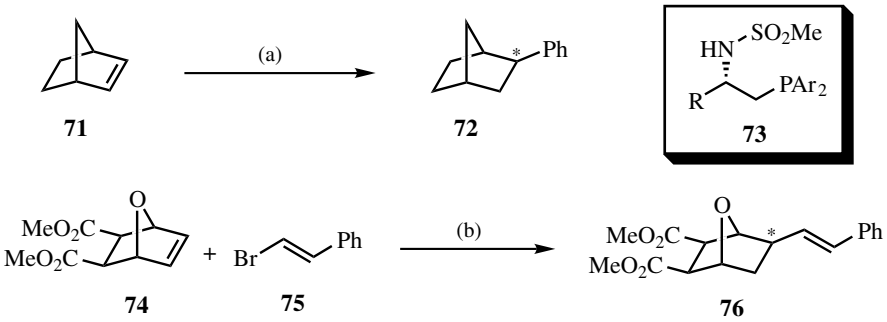
A combination of MS 3 Å and potassium carbonate base was found to be the most effective, with the best auxiliary system ($R^1 = R^2 = H$) giving **69** with a satisfactory 72% ee and in 84% yield. Gratifyingly, these figures showed only minor perturbations when the Ar ring substituents were varied. Significantly improved ees have recently been reported for this process using a new ligand system (see **Sect. F**).[61]

D.ii.d. ***Hydroarylations of Bicyclo[2.2.1]heptane Derivatives.*** Asymmetric hydroarylation/hydroalkenylation, although not strictly a Heck reaction as the β-hydride elimination step is replaced by reductive elimination, nevertheless shares a common mechanistic pathway with regard to the enantioselective step and so will be discussed briefly. In 1991 Brunner and Kramler first reported hydrophenylations of norbornene and norbornadiene using aryl iodide, although the ees obtained were low ($<40\%$). The preferred ligand was (−)-Norphos; BINAP does not appear to have been tested.[62] The system has since been revisited by Achiwa and co-workers as a means of testing novel phosphine ligands of the general structure **73**.[63],[64] Using these, the conversion of **71** to **72** could be carried out in

81% yield and with 74% ee (**Scheme 19a**). Moreover, Namyslo and Kaufmann have demonstrated that the highest enantioselectivity (86.4%) is obtained when phenyl nonaflate is used as a substrate.[65]

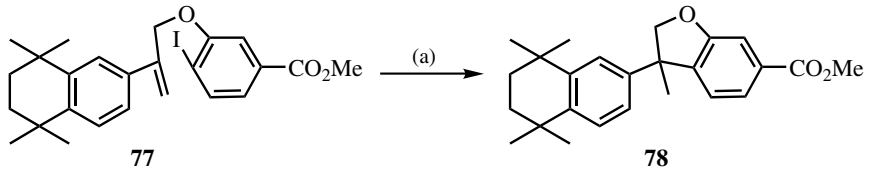
Hayashi and co-workers have carried out AHRs using alkenyl iodides and triflates both on norbornene and on heteroanalogs such as **74**: excellent ees and satisfactory yields were obtained.[66] Hydrophenylation of a similar system has been reported by Moinet and Fiaud.[67]

Quite recently, Diaz and co-workers have reported an intramolecular asymmetric hydroarylation of alkene **77**, which gives satisfactory ees and moderate yields and also showed that silver zeolites[38],[39] are very effective silver salts to obtain high enantioselectivity in this system[68] (**Scheme 19b**).



(a) Ph-OTf, $Pd(OAc)_2$, **73** (R = $CHMe_2$, Ar = Ph), *i*-Pr_2NEt, HCO_2H, DMSO, 65 °C, 20 h, 81%, 74% ee.
(b) Pd{(*R*)-BINAP}$_2$ (1 mol %), HCO_2H, Et_3N, $Cl(CH_2)_2Cl$, 40 °C, 63%, >96% ee.

Scheme 19a



(a) $Pd(OAc)_2$ (10 mol %), (*R*)-BINAP (20 mol %), $CaCO_3$ (2.2 equiv), Ag-zeolites corresponding to ca. 6 equiv of Ag, MeCN, 8 h, 60 °C, 42% yield, 81% ee.

Scheme 19b

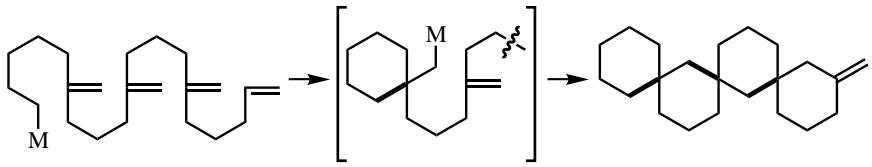
E. FORMATION OF QUATERNARY CARBON CENTERS

E.i. Spirocyclizations and Alkaloid Synthesis

The enantioselective formation of quaternary carbon centers remains a significant challenge to the synthetic chemist.[69] To use the AHR in this role has the obvious attraction of removing the problem of competing pathways in step © (see **Scheme 1b**), as no β-hydrogen is

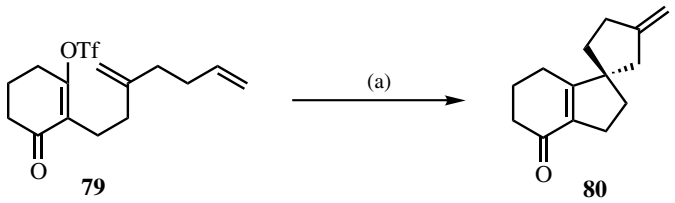
present to compete with the desired β'-hydride elimination step—the need to use endocyclic alkene substrates is thus removed.

The first successful case was reported by Overman and co-workers in 1989,[70] a pioneering strategy, which opened the way for the development of AHRs leading to quaternary centers. Furthermore, it was outlined that polycyclizations are well within the scope of the Heck reaction. According to **Scheme 20** it can be expected 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.



Scheme 20

As with the work creating tertiary centers reported by Shibasaki and co-workers, which was described in **Sect. D**, the ees of the cyclizations obtained at the outset were modest, with the spirocyclic system **80** being obtained in good yield and moderate ee when (*S*,*S*)-DIOP was substituted for triphenylphosphine (**Scheme 21**).



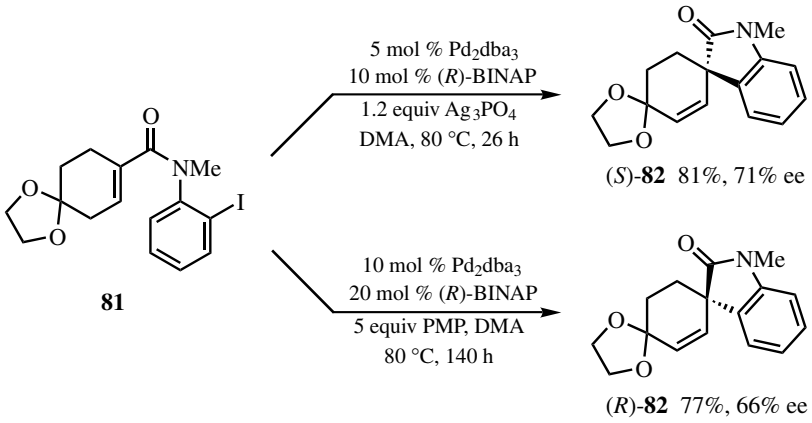
79 **80**

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

Scheme 21

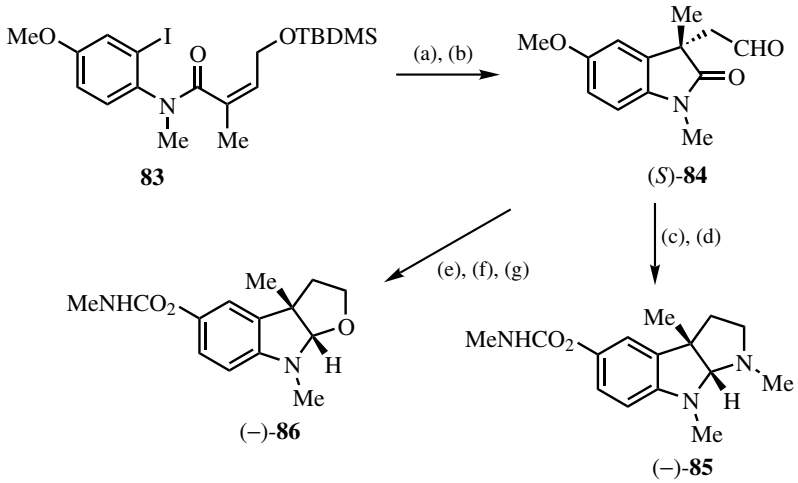
Although this work clearly demonstrated the viability of such a process, the full potential of the approach did not become fully apparent until the publication of a remarkable study concerning the synthesis of spiroxindoles (**Scheme 22**).[71]

Carrying out the AH cyclization of iodoanilide **81** in a dipolar aprotic solvent (in this case dimethylacetamide, DMA) in the presence of Ag_3PO_4 gave (*S*)-**82** in 81% yield and with 71% ee, results very similar to those achieved by other workers, for tertiary centers 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*)-**82** enantiomer was obtained *using the same enantiomer* of BINAP. Similar studies of the cyclization of alkene **81** revealed that when (*E*)-**83** was used, the effect is reproduced, although the ees of the enantiomer obtained when using PMP were low (30–40%). In



Scheme 22

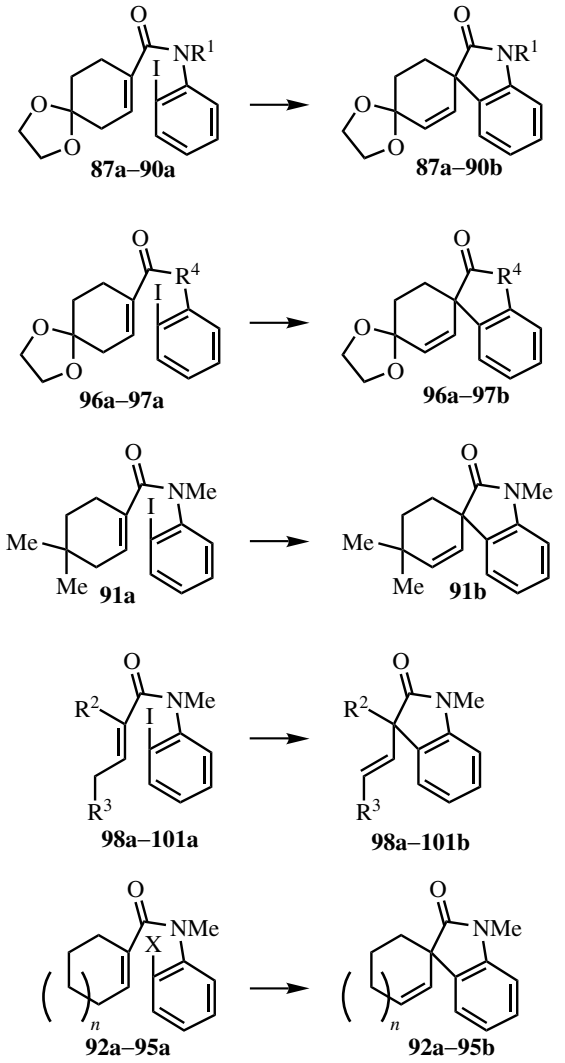
contrast, when (*Z*)-**83** was used in conjunction with (*R*)-BINAP, *both* sets of conditions gave the expected (*R*)-enantiomer of **84** with good yields and excellent (>90%) ees.[72] These results appear to suggest that the observed "geometry effect" (identical to that observed by Shibasaki and co-workers for carbocycle formation, *vide infra*) is rather more powerful than the "base/additive effect" in determining the sense of chiral induction. The use (*S*)-BINAP under otherwise identical conditions, of course, gives (*S*)-**84**, which can be converted to the natural products physostigmine **85** and physovenine **86** (**Scheme 23a**).[73],[74]



(a) 10 mol % $Pd_2dba_3 \cdot CHCl_3$, 23 mol % (*S*)-BINAP, PMP, DMA, 100 °C.
(b) 3 N HCl, 23 °C; 84%, 95% ee.
(c) $MeNH_2$, Et_3N, $MgSO_4$, then $LiAlH_4$, THF, 88%.
(d) As in the literature.
(e) $LiAlH_4$, THF, 23 °C, 94%.
(f) BBr_3, CH_2Cl_2, 23 °C.
(g) NaH, Et_2O; MeNCO.

Scheme 23a

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. In fact, Overman and co-workers reported that PMP-promoted AH cyclizations along a "neutral" pathway via a pentacoordinate intermediate were very effective when iodoanilide with an endocyclic alkenyl moiety (**87a–89a, 91a–92a**, and **94a–95a**) were used as substrates, but not so effective when **96a**, **97a**, and **98a–101a** were used as substrates[75] (**Scheme 23b**). Thus, the "base/additive effect" has yet to be reported for substrates other than acrylamides, a substrate specificity that 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 23b (*Continued*)

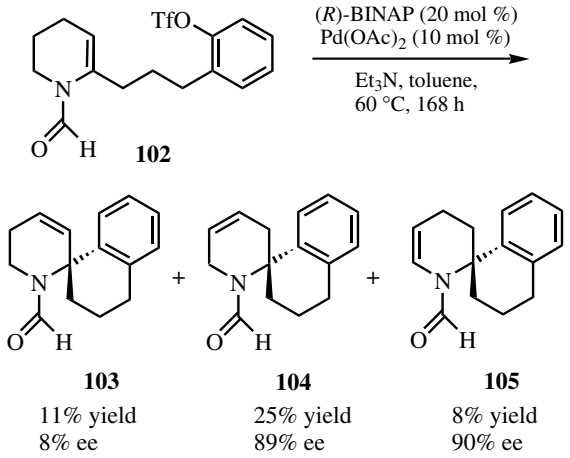
Asymmetric Heck reaction of **87–101**

Substrate	Overman's PMP-Promoted Conditions	Shibasaki's Ag Salt-Promoted Conditions
87: R^1 = Me	71% y., 66% ee	81% y., 71% ee
88: R^1 = Bn	66% y., 66% ee	91% y., 41-51%ee
89: R^1 = SEM	68% y., 75% ee	76% y., 65% ee
90: R^1 = BOC	no example	65% y., 42% ee
91	89% y., 71% ee	99% y., 72% ee
92: n = 1, X = I	45% y., 89–95% ee	74% y., 79–81% ee
93: n = 1, X = Br	51% y., 32% ee	no example
94: n = 2, X = I	50% y., 88% ee	62% y., 0% ee
95: n = 0, X = I	96% y., 56% ee	81% y., 7% ee
96: $R^4 = NCO_2Me$	51% y., 8% ee	90% y., 64% ee
97: R^4 = O	66% y., 0–7% ee	91% y., 49–55% ee
98: R^2 = Me, R^3 = Me	91% y., 25% ee	88% y., 59% ee
99: R^2 =Me, R^3 = TBDMSO	85% y., 38% ee	80% y., 45% ee
100: R^2 = *t*-Bu, R^3 = TIPSO	90% y., 27% ee	41% y., 72% ee
101: R^2 = Ph, R^3 = TIPSO	74% y., 35% ee	93% y., 73% ee

Scheme 23b

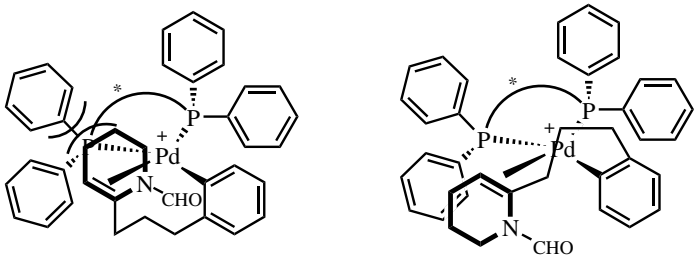
E.ii. Tetrahydropyridines

Interesting attempts to asymmetrize an intramolecular Heck reaction with 1,2,3,4-tetrahydropyridines also giving access to spirocyclic systems have not been successful at the beginning.[76] 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**).[77] The asymmetric cyclization of **102** using (*R*)-BINAP as a chiral ligand resulted in the formation of three isomers **103**, **104**, and **105**, with a rather long reaction time being required. Good ees have been obtained for the products **104** and **105** (89% and 90%).



Scheme 24

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 **Sect. F**) as a ligand helped to suppress the formation of the double bond isomer **105**. At the same time the regioselectivity could considerably be changed in favor of the formation of **103** to yield a 6:1 mixture of (*R*)-**103** (87% ee) and (*R*)-**104** (>99% ee) after 48 h at 110 °C, using $(i\text{-Pr})_2$ NEt as a base.[77] 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*)-**106**], formed after oxidative addition of the triflate, could be sterically more crowded. A similar rationalization, 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.



(*S*)-**106** p-complex disfavored

(*R*)-**106** p-complex favored

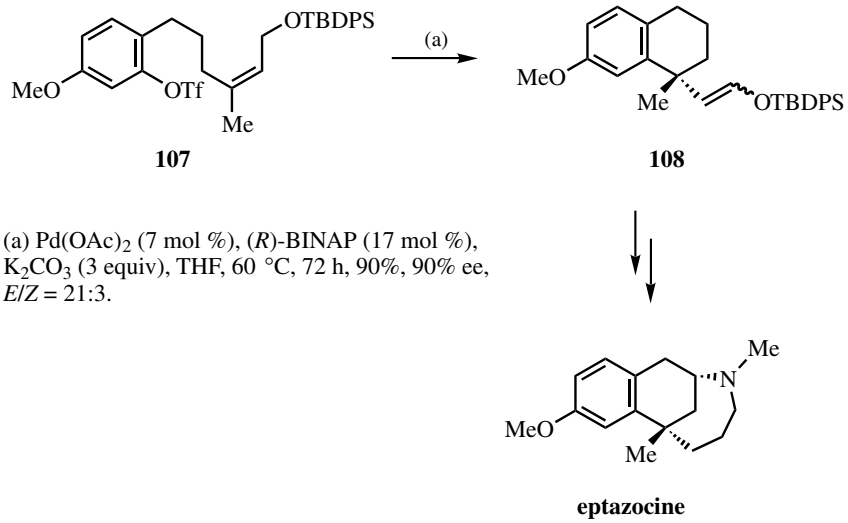
Scheme 25

If the corresponding iodide was used instead of the triflate **102**, only low to moderate ees have been observed. Furthermore, it seems that the role of the *N*-formyl moiety could be important for chiral induction and this could provide further information about the mechanism.

E.iii. Eptazocine and Halenaquinol

The synthesis of benzylic quaternary centers by an AHR has also been reported by Shibasaki and co-workers in connection with syntheses of (−)-eptazocine[78] and of halenaquinone and halenaquinol **112**.[79],[80] As in **Sect. E.i**, the key steps in both syntheses involve the formation of a quaternary carbon center by asymmetric Heck arylation of a trisubstituted alkene, with BINAP being the preferred ligand. The "geometry effect" seen by Overman and co-workers 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 **107–108** in the eptazocine synthesis, the opposite enantiomer to that obtained when using the *E*-alkene. The conversion from **107** to **108** (**Scheme 26**) was achieved with excellent yield and ee; desilylation gave the corresponding aldehyde,[81] which was converted to (−)-eptazocine via a five-step sequence.

The synthesis of halenaquinol **112** (and its oxidation product halenaquinone) initially featured the conversion from **109** to **110** as a key step (**Scheme 27**), which gave the desired product in 78% yield and with 87% ee under very similar conditions used for

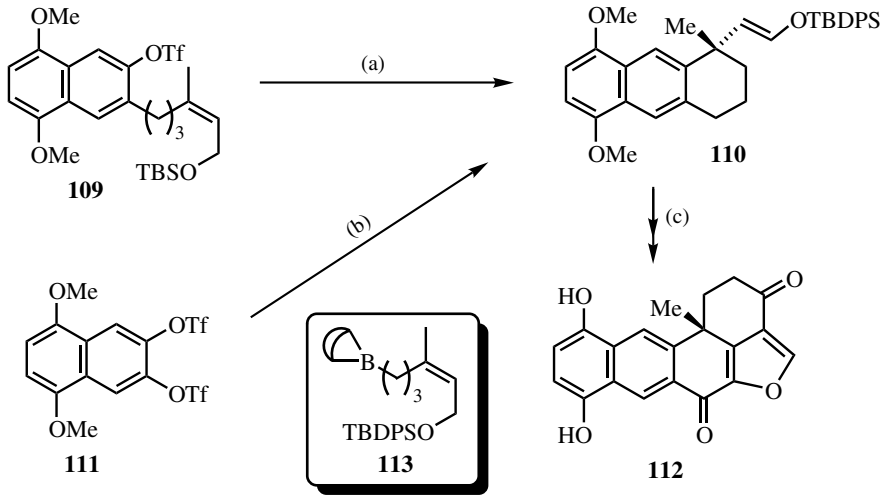


107 **108**

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

eptazocine

Scheme 26



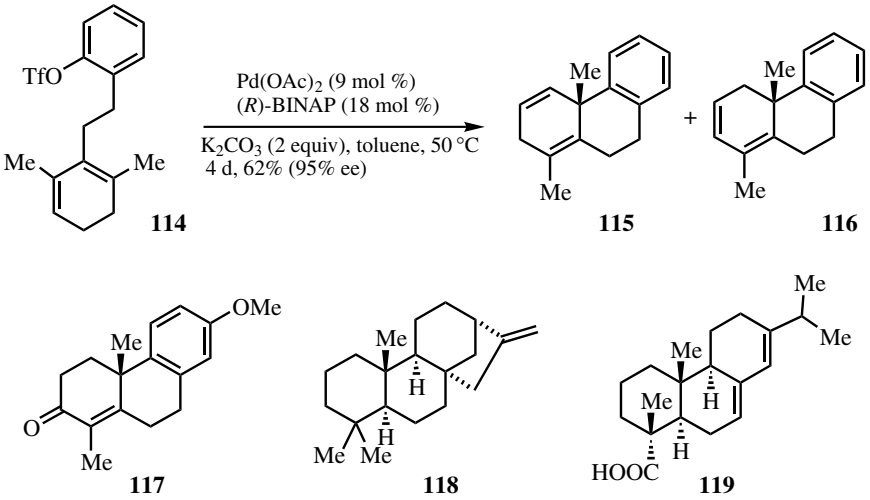
(a) $Pd(OAc)_2$ (10 mol %), (*S*)-BINAP (20 mol %), K_2CO_3, THF, 60 °C, 78%(87% ee). (b) **113** (1.1 equiv), $Pd(OAc)_2$ (20 mol %), (*S*)-BINAP (40 mol %), K_2CO_3, THF, 20% (85% ee). (c) 12 steps, 12% overall.

Scheme 27

conversion of **107** to **108**. However, in line with the current trend toward sequential or "one-pot" transformations[82],[83] (*vide infra*), the authors were able to combine the AHR step with a Suzuki-type coupling of the trialkylborane **113** (itself prepared *in situ* by hydroboration) with the C_2-symmetric ditriflate **111** and so obtain **110** rather more directly. While 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.

E.iv. Sesquiterpenes

One further example of quaternary center formation by an AHR has been reported, this being the conversion of the aryl triflate **114** to a 3:1 mixture of the tricycle **115** and its isomer **116**, both of which can be converted to the enone **117**, a key intermediate in the synthesis of kaurene **118** and abietic acid **119** (**Scheme 28**).[84],[85] Compound **115** can also be quantitatively isomerized to **116**. The essentially complete selectivity toward 6-*exo* cyclization is noteworthy. The authors rationalize this on the basis of unfavorable steric interactions in the alternative intermediates.



Scheme 28

F. FUTURE DEVELOPMENT

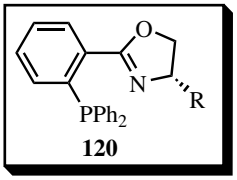
F.i. Ligands

The great majority of AHRs reported so far have utilized the BINAP ligand system, which usually has proved to be the most effective one, 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 of the oxazoline-based ligands **120**,[86] which give distinctly improved ees with several previously reported AHRs.[61] For example, the Hayashi-type AHR of dihydrofuran **48** with cyclohexenyl triflate catalyzed by $Pd(dba)_2$ and **120** (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. Similar to the alkenylation of **48** using the 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 isomerization by this catalyst is so pronounced as to allow the arylation and/or alkenylation of cyclopentene, giving regiodefined products such as **121** with high yields, excellent ees,

and only small amounts (>5%) of the unwanted regioisomers such as **122** (**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 **Sect. F.ii**).

An example for an alkenylation reaction utilizing **120** [R = $C(Me)_3$] is given in **Scheme 30**. Again, excellent selectivity toward the less isomerized product **125** as well as high ees have been observed.[61]

The conversions outlined in **Schemes 29** and **30** are also noteworthy in so far as they constitute examples of intermolecular AHRs of very simple starting materials with no other functionality or heteroatom present than is required for the Heck reaction to proceed. Simple hydrocarbon skeletons are the resulting products.

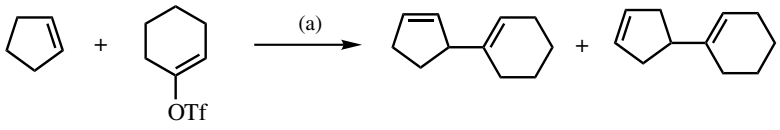


120

121 **122**

(a) PhOTf, $Pd(dba)_2$ (3 mol %), **120** [R = $C(Me)_3$, 6 mol %] *i*-Pr_2NEt, THF, 70 °C, 5 d, 80%, 86% ee, **121/122** = 99:1.

Scheme 29



123 **124** **125** **126**

(a) $Pd(dba)_2$ (3 mol %), **120** [R = $C(Me)_3$, 6 mol %], *i*-Pr_2NEt, C_6H_6, 40 °C, 4–5 d.

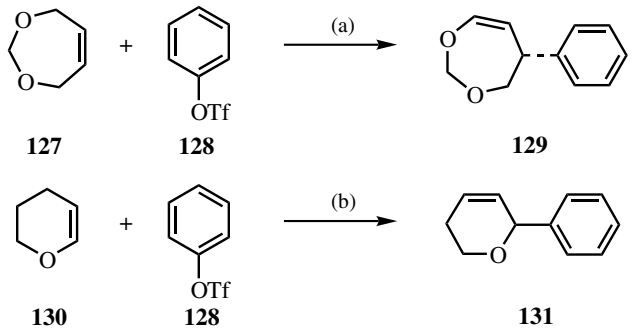
69% yield
89% ee

1% yield

Scheme 30

Two further examples for arylation reactions catalyzed by phosphinooxazoline–palladium complexes are shown in **Scheme 31** with the formation of **129** and **131** as nitrogen-containing substrates: arylation of the 2,3-dihydropyrrole **63** with phenyl triflate catalyzed by the palladium complex **120** (R = CMe_3) gave the single isomer **65** in 88% yield and with 85% ee.[87]

Interestingly, phosphinooxazolines **120** with smaller R groups than *t*-butyl have been found to produce less reactive catalysts. This finding was very unusual as with *t*-butyl being a very bulky group the steric hindrance near the metal center could actually be expected to slow down a metal-catalyzed process.

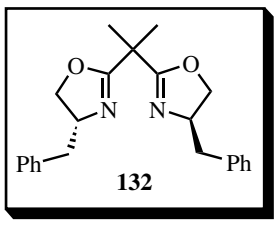


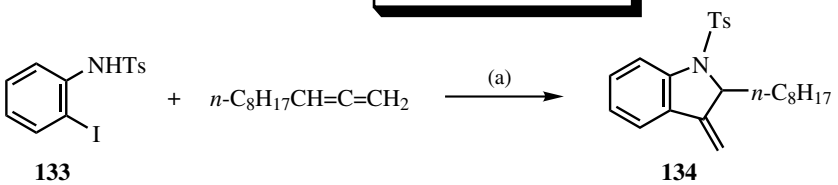
(a) $Pd(dba)_2$ (3 mol %), **120** (R = CMe_3, 6 mol %), *i*-Pr_2NEt, THF, 70 °C, 7 d, 70% y., 92% ee.
(b) $Pd(dba)_2$ (5 mol %), **120** (R = CMe_3, 10 mol %), *i*-Pr_2NEt, C_6H_6, 80 °C, 5 d, 78% y., 84% ee.

Scheme 31

The use of a chiral bisoxazoline ligand **132** for the enantioselective Pd-catalyzed annelation of allenes has been reported by Larock and Zenner (an example is given in **Scheme 32a**).[88],[89] The use of a chiral phosphinooxazoline ligand **135** for the enantioselective Pd-catalyzed annelation of diene **136** has also been reported (an example is given in **Scheme 32b**).[90] Even though in these cases 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 reactions are not strictly AHRs, the high yields and ees obtained for various substrates are remarkable.

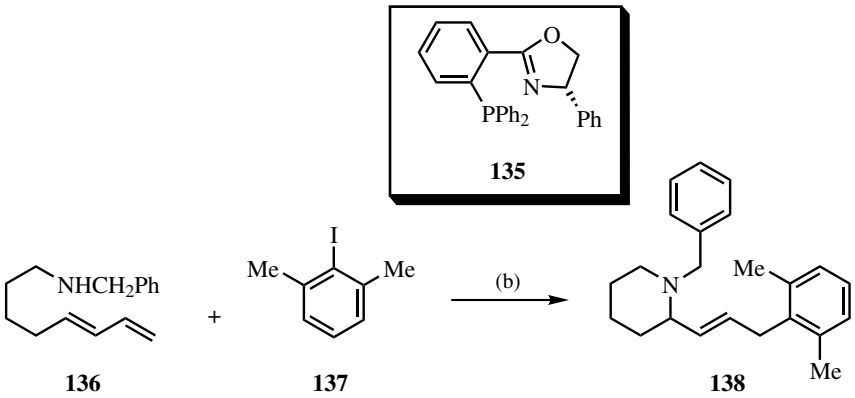
Looking at the results obtained with BINAP, with the new diarsine ligand mentioned in **Sect. D.i.a** and with bisoxazoline **132**, it seems evident that various donor atoms (N, P, As) can be contained in ligands which provide the best solution to a given AHR problem. Accordingly, recently 2-diphenylarsino-2′-diphenylphosphino-1,1′-binaphthyl





(a) $Pd(OAc)_2$ (5 mol %), **132** (10 mol %), Ag_3PO_4 (1.2 equiv of silver ion equiv), DMF, 90 °C, 24 h. — 94% yield, 82% ee

Scheme 32a

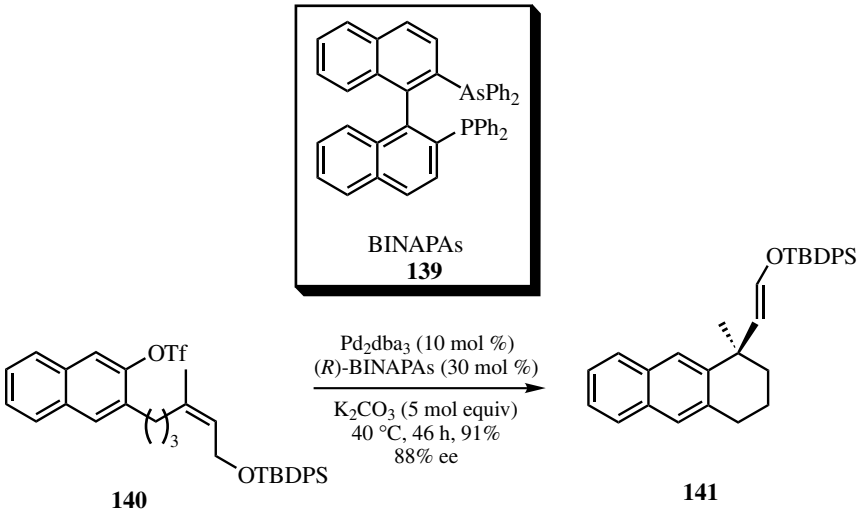


(b) $Pd(OAc)_2$ (5 mol %), **135** (10 mol %), Ag_3PO_4 (1.0 equiv of silver ion equiv), DMF, 100 °C, 48 h, 61% y., 67% ee.

Scheme 32b

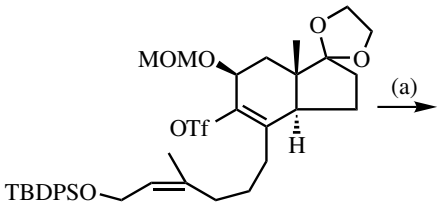
(BINAPAs, **139**) has been synthesized and successfully applied to the AHR of a system similar to **109** (**Scheme 33**) with superior efficiency compared to BINAP.[91]

Whereas the yield for the conversion of **140** to **141** has been 74% using BINAP, it could be improved to 91% by using BINAPAs under otherwise identical conditions. The ee remained virtually unchanged.



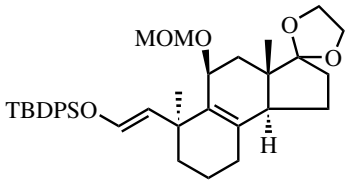
Scheme 33

Another new direction was recently pointed out by Shibasaki and co-workers by successfully carrying out an AHR that allowed a kinetic resolution of the racemic starting material (**Scheme 34**).[92] With that method, a possible intermediate (**143-β**) for the total synthesis of wortmannin could be isolated with 96% ee after subjecting the

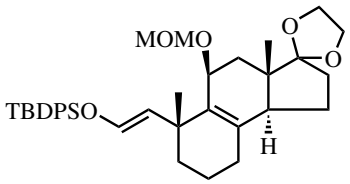


(rac)-**142**

(a) $Pd(OAc)_2$ (20 mol %), (*R*)-Tol-BINAP (40 mol %), K_2CO_3 (2.5 mol equiv), toluene, 100 °C, 1.5 h



143-α



143-β

yield 20% (**143-α** and **143-β**)
143-α : **143-β** = 1:5
ee (**143-β**) 96%

Scheme 34

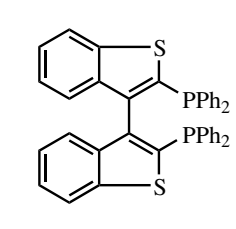
racemic triflate (±)-**142** to Heck conditions (the absolute configuration was determined using Mosher's method). Such reaction sequences could eventually prove to be extremely valuable and convenient for the enantioselective synthesis of natural products in general.

Quite recently, a highly regioselective and enantioselective AHR was reported by Tietze and co-workers by developing a new chiral ligand BITIANP.[93] With the use of BITIANP only **54** was obtained, whereas with BINAP the regioselectivity is rather low; with a substituted MeO-BIPHEP ligand a 22:1 ratio of **54** and **55** was obtained[94]; and with chiral phosphinooxazolines only **55** was obtained (**Scheme 35**).

Remarkable *diastereoselectives* have also been observed for AHR with the chiral auxiliaries RAMP or SAMP (**Scheme 36a**)[95] and with the chiral sulfoxides (**Scheme 36b**).[96],[97]

F.ii. Methodological Directions

Efforts to increase the catalyst turnover number are indeed another major area where further improvements can be expected.[98] Such improvements have recently been achieved using preformed palladacycles as catalysts[99] or by using a macrocyclic tetraphole as ligand.[100] Dendritic diphosphine–palladium complexes as catalysts for Heck reactions have also been reported to possess superior stability compared to the monomeric parent compounds.[101] 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.[102] Transferring such innovations to the AHR remains an important goal.



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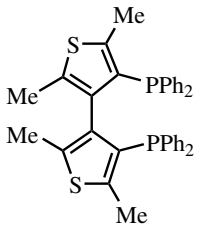

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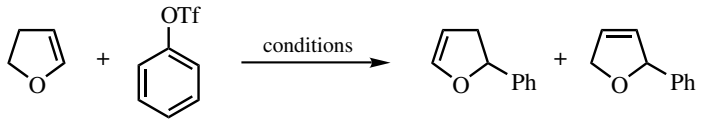


48 **128** **54** **55**

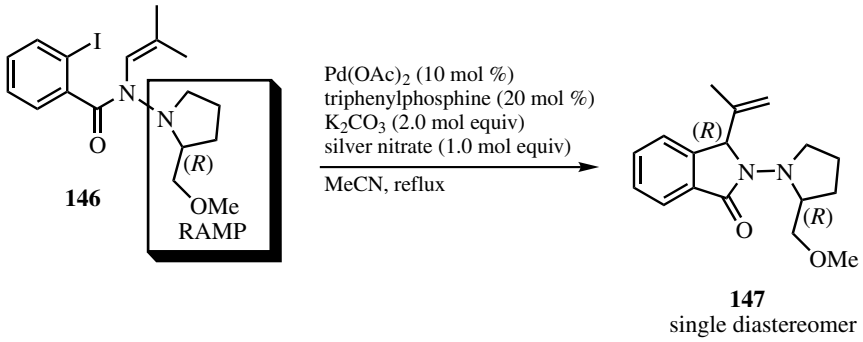
Intermolecular asymmetric Heck reaction of **48** and **128**

Run	$Pd_2(dba)_3 \cdot CHCl_3$ (mol %)	Ligand (mol %)	Base (equiv)	Solvent	Temperature (°C)	Time	Ratio[a]	Yield (%)		ee (%)[b]	
							54/55	**54**	**55**	**54**	**55**
1	3	BITIANP **144** (12)	PS (3)c	DMF	90	18 h	100:<1	84	—	91	—
2	3	BITIANP **144** (12)	*i*-Pr2NEt (3)	DMF	90	20 h	100:<1	90	—	90	—
3	5	BITIANP **144** (10)	*i*-Pr2NEt (3)	THF	70	7 d	7:1	62	—	80	—
4	3	BINAP (12)	PS (3)c	DMF	90	18 h	3:1	58	20	42	33
5	5	TMBTP **145** (10)	*i*-Pr2NEt (3)	DMF	90	3 d	1:2	27	58	4	2
6	5	TMBTP **145** (10)	*i*-Pr2NEt (3)	THF	70	4 d	3:1	54	19	14	10
7	5	TMBTP **145** (10)	PS (3)c	Benzene	70	4 d	6:1	73	12	4	0

[a] Determined by GC.
[b] Determined by chiral GC.
[c] PS = Proton sponge = 1,8-bis(dimethylamino)naphthalene.

Scheme 35

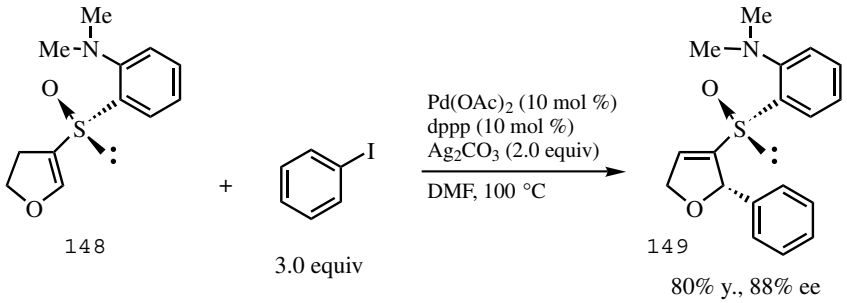
The current surge of interest in combinatorial chemistry[103],[104] may also prove to be highly significant to the development of new ligands, as both Heck reactions on solid support[105] and the generation and screening of chiral phosphine ligand libraries[106] have recently been demonstrated, potentially opening the way to combinatorial screening of AHR catalyst systems.



146

147
single diastereomer

Scheme 36a

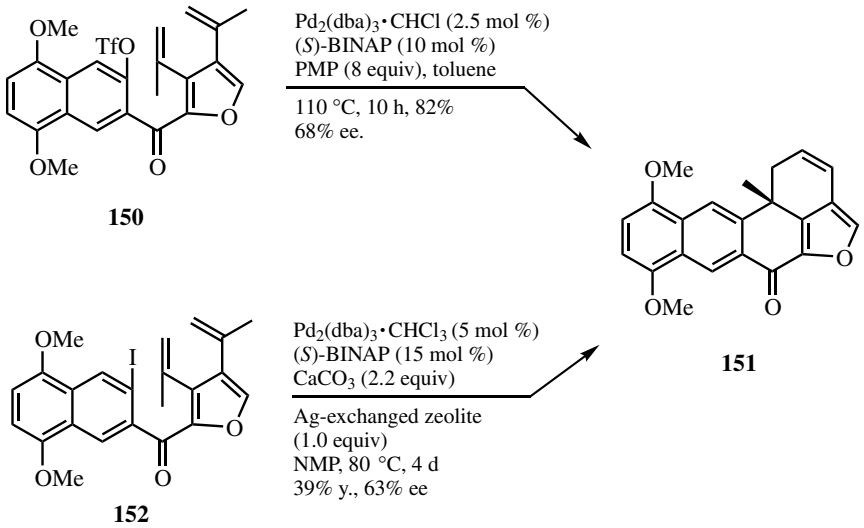


Scheme 36b

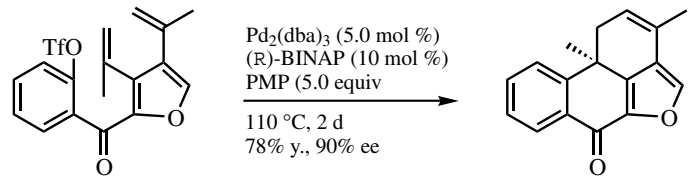
The move away from bulky BINAP ligands which Pfaltz's work may foreshadow, would certainly simplify library construction. The ready availability of chiral oxazolines from peptide residues may also be helpful in this respect.[107]–[109]

Microwave-promoted Heck reactions are another recent development. It was shown that Heck reactons 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.[110]

A very recent synthesis of the halenaquinol related natural product (+)-xestoquinone by Keay and co-workers[111] has provided confirmation of the suitability of the AHR for inclusion in Pd-mediated "cascade" polyene reactions.[112] The one-pot transformation of triflate **150** into the pentacycle **151** (Scheme 37) is achieved using conditions typical for the AHR, and gives (+)-**151** with a respectable 68% ee. Interestingly, the iodide analog of **152** gives little or no asymmetric induction, even in the presence of silver salts. To solve this interesting problem, Shibasaki and co-workers developed new conditions for the AHR of the iodide analog **152** of **150** giving the pentacycle **151** with



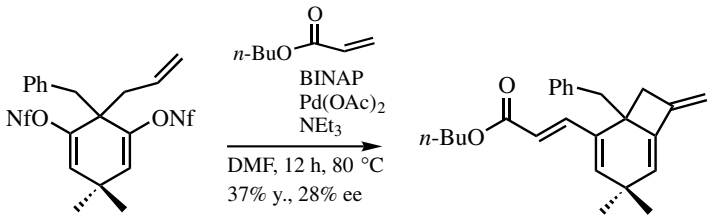
Scheme 37a



153 154

Scheme 37b

acceptable ee compared to Keay's results and showed again the efficiency of silver zeolite and also the importance of the amount of silver salts.[113] Moreover, Keay and coworkers reported the remote substituent effects on the enantioselectivity of intramolecular AHR and showed that the triflate **153** gave the tetracycle **154** in 78% yield and with 90% ee, which was the model compound for the catalytic asymmetric total synthesis of (+)-halenaquinone.[114]



155 **156**

Scheme 38

Quite recently, another Pd-catalyzed enantioselective desymmetrization has been also reported by Bräse, which constitutes the *exo*-methylenecycloalkanes containing the quarternary carbon center.[115] In this report, treatment of the bisnonaflate **155** with acrylate in the presence of BINAP and palladium catalyst gave the tetraene **156** in 37% yield and in up to 28% enantiomeric excess (**Scheme 38**).

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