Asymmetric Heck Reaction

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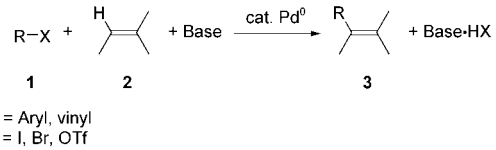
Abstract: The asymmetric Heck reaction is a powerful method for the synthesis of both tertiary and quaternary chiral carbon centers, with an enantiomeric excess often greater than 80%, and in some cases much higher (up to 99% ee). A variety of carbocyclic and heterocyclic systems can be constructed, including spirocyclic systems. The scope of the reaction with respect to the product alkene isomerization is somewhat limited by problems of regioselectivity, however, these problems are surmountable, and a new generation of ligands that dissociate more rapidly from the products, might improve both enantio- and regiocontrol. A variety of chiral compounds prepared by the asymmetric Heck reaction were successfully utilized in the enantioselective syntheses of complex natural products.

Keywords: asymmetric catalysis; carbon-carbon bond-forming reaction; chiral ligand; Heck reaction; homogeneous catalysis; natural product synthesis

1 Introduction

The palladium-mediated coupling of aryl or alkenyl iodides, bromides, or triflates with alkenes in the presence of base, i.e., Pd-catalyzed arylation or alkenylation of alkenes, was first independently discovered in the 1970s by Mizoroki et al.[1] and Heck et al.[2] (Scheme 1). This methodology is generally referred to as the Heck reaction.[3] A great advantage of the Heck reaction is that the substrate is not limited to activated alkenes, but can be a simple olefin. Moreover, there are many benefits associated with Pd-mediated reactions,[4] particularly ease of scale-up and tolerance to water and/or other functional groups, such as ketones, esters, amides, ethers, or heterocyclic rings, which supply polyfunctional molecules. Thus, the Heck reaction is one of the most important carbon-carbon bond-forming reactions and has been applied to a variety of complex natural product syntheses.

Interest in the Heck reaction has recently increased dramatically. Perhaps the most significant progress to date is the development of an enantioselective variant.[5]



Scheme 1. The Heck reaction.

Given the many reports of chiral phosphine ligands dating from the early 1970s,[6] it is somewhat surprising that the phosphine-mediated Heck reaction was not subjected to asymmetrization attempts until the late 1980s, even though the reaction is not usually used to generate stereogenic centers,[7] and that for many years chelating diphosphines in general were thought to be unsuitable ligands.[8] Reports of successful examples of the asymmetric Heck reaction were independently published in 1989 by Shibasaki et al.[9] and Overman et al.[10] and the reaction has since been successfully developed to the point where both tertiary and quaternary centers can be generated (Scheme 2). Although the enantioselectivity achieved in these preliminary studies was mod-

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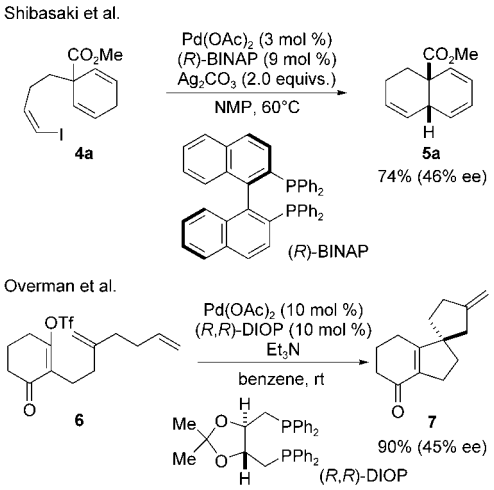
Erasmus Vogl studied chemistry in Düsseldorf, Cambridge, Bangalore and Mülheim/Ruhr from 1990 and received his PhD in 1997. After a postdoctoral fellowship in the Shibasaki group at the University of Tokyo, he joined Central Research of Bayer AG in 1999. He was a Visiting Scientist at MIT and is currently developing new products for the biocides division of Bayer Chemicals AG.

Takashi Ohshima received his PhD. from the University of Tokyo in 1996 under the direction of Professor Masakatsu Shibasaki. In the following year, he joined Otsuka Pharmaceutical Co., Ltd. for one year. After two years as a postdoctoral fellow at The Scripps Research Institute with Professor K. C. Nicolaou (1997–1999), he returned to Japan and joined Professor Shibasaki's group in The University of Tokyo as an assistant professor. He has received the Fujisawa Award in Synthetic Organic Chemistry (2001) and Pharmaceutical Society of Japan Award for Young scientists (2004).

est, the great potential of the asymmetric variants of the intramolecular Heck reaction was demonstrated, leading to later success in this field. The majority of the reported examples involve intramolecular reactions, which allow for relatively easy control of alkene regiochemistry and geometry of the product and tolerate less reactive alkene substrates. In contrast, successful intermolecular reactions have until recently been limited to quite reactive substrates, principally O- and N-heterocycles, and to the formation of tertiary centers on ring carbon atoms, which simplifies the control of alkene regiochemistry.

The present article provides a survey of the relevant literature, beginning with a discussion of the mechanistic aspects of stereoselection in the asymmetric Heck reaction. The sections are organized according to the various types of underlying carbon skeletons, or natural product fragments, of the resulting compounds. Diastereoselective variations, which are frequently utilized for the con-



Scheme 2. First examples of an asymmetric Heck reaction.

struction of natural products, are generally not included.[3]

2 Mechanism

Comprehensive overviews of the current state of mechanistic theory regarding the Heck reaction have been provided.[3,5] Therefore, the following discussion selectively focuses on the factors that impart the regio- and enantiocontrol necessary for a successful asymmetric Heck reaction.

2.1 Regioselectivity

The mechanism of the Heck reaction with bidentate phosphine ligands is generally thought to follow the four-step catalytic cycle shown in Scheme 3, with the following steps: (**A**) oxidative addition of **1** to the Pd^0 species **8** bearing a bidentate phosphine ligand to give the Pd^{II} species **9**, (**B**) coordination and *syn*-insertion of the alkene substrate **2** into the Pd–R^1 bond of **9** to give **10**, (**C**) β- or β′-hydride elimination from **10** to give either **3a** or **3b**, and finally (**D**) regeneration of **8** by reductive elimination of HX from **11**.

The three major factors governing regioselectivity are:

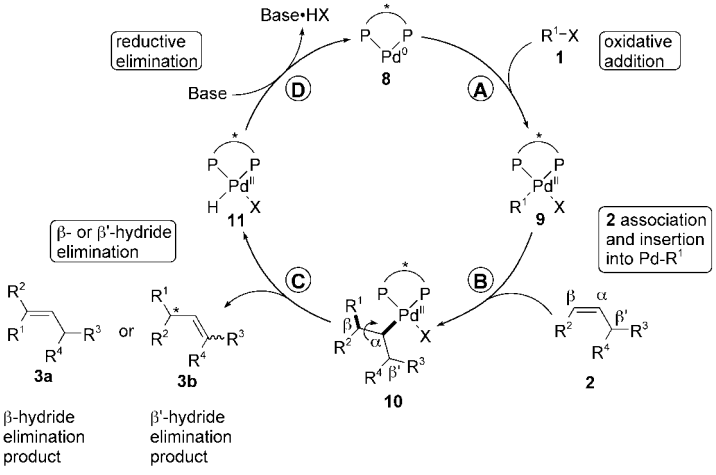
(1) The regioselectivity of the insertion into Pd–R^1 is heavily dependent upon the nature of the steric and electronic environment provided by R^2, R^3, and R^4 for unsymmetrical alkenes. This lack of selectivity, which tends to somewhat limit the scope of the reaction, can be overcome by selecting appropriate chiral ligands and reaction conditions.

(2) The problem of competing β- and β′-hydride elimination in **10** further complicates the regioselectivity issue. In fact, the majority of reported Heck reactions avoid the problem by using a simple acrylate ester as a substrate (CH_2=$CHCO_2R$, monosubstituted alkene, which gives (*E*)-R^1CH=$CHCO_2R$ as a product). Because of its highly unsymmetrical steric and electronic environment, the use of a simple acrylate ester also avoids problems with regioselectivity in step **B**. While this constitutes a mild and quite powerful method for the synthesis of β-substituted acrylates, the opportunity to form a tertiary chiral center is lost by removing β′-hydride elimination.

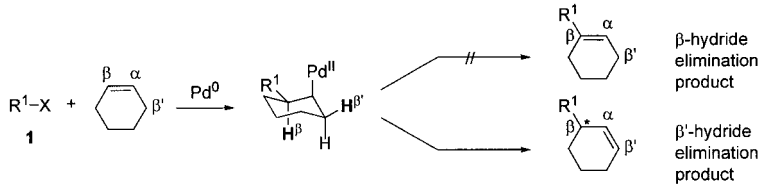
(3) Even if the regioselectivity of step **C** can be controlled, another problem lies in its reversibility, which can result in re-insertion of the **3b** alkene into the Pd–H bond in **11** either to regenerate **10** or to form a regioisomer of **10** with the Pd atom attached to the same carbon atom as R^3 and R^4. If either of these substituents contains a suitably positioned hydrogen atom, then the α,β′-alkene can isomerizes into a β′,γ′-position, a problem that is especially prone to occur with endocyclic alkene products (see Section 4).

Fortunately, methods to suppress this isomerization have been developed, involving the addition of thallium[11] or silver[12] salts to the reaction mixture. The use of silver salts is usually preferred due to their lower toxicity and fortuitous double role as enhancers of enantioselectivity (*vide infra*).

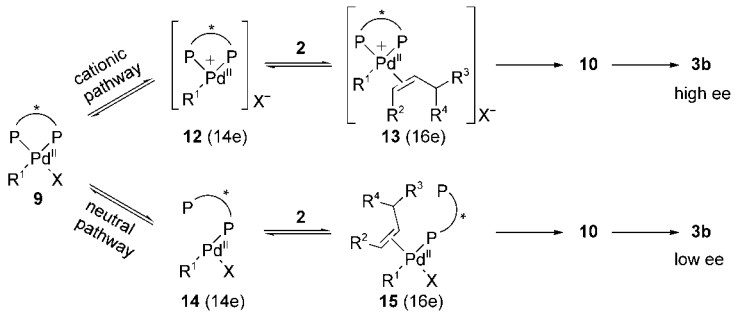
The preferential formation of **3b** rather than **3a** is essential for the asymmetric reaction to occur. Therefore, it is necessary to examine the factors that control the competing elimination processes in step **C** and the consequent prerequisites to ensure the predominance of the desired pathway. As both insertion into **9** and elimination from **10** are *syn*-processes, rotation about the C^{α}–C^{β} 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 (Scheme 4). It is primarily for this reason that all the reported asymmetric Heck reactions forming tertiary centers involve endocyclic alkene substrates with the exception of the allylsilane work of Tietze et al. (see Section 3.1.5). Other methods to direct the selectivity of step **C** involve choosing suitable R groups to influence the relative thermodynamic stabilities of the possible products. The most common tactic is to make R^3 or R^4 = OH or OR, resulting in the formation of an enol, which subsequently tautomerizes to the aldehyde or ketone, or enol ether, with the interesting exception of Overman's work,[13] in which preferential β-methoxide elimination occurs. A similar strategy commonly employed in asymmetric Heck reactions is to choose R^3 or 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



Scheme 3. Heck reaction with disubstituted alkenes bearing β- and β′-hydrogens.



Scheme 4. Heck reaction with endocyclic alkene.



Scheme 5. Cationic and neutral pathways for the asymmetric Heck mechanism.

this occurs in many of the published asymmetric Heck reactions.

2.2 Enantioselectivity

The key step in the catalytic cycle with regard to enantioselectivity is step **B**, association of the alkene **2** and its insertion into the Pd–R^1 bond (Scheme 3). As with the Heck reaction, the mechanism for this process remains a matter for conjecture, with the currently favored rationale having been proposed in 1991 by Hayashi et al.[14] and independently by Cabri et al.,[15a] although the cationic pathway *via* **12** and **13** had been proposed as early as 1990 (Scheme 5).[16] Its development and subsequent evolution was reviewed by Cabri et al.[15c]

Two possible routes are proposed:

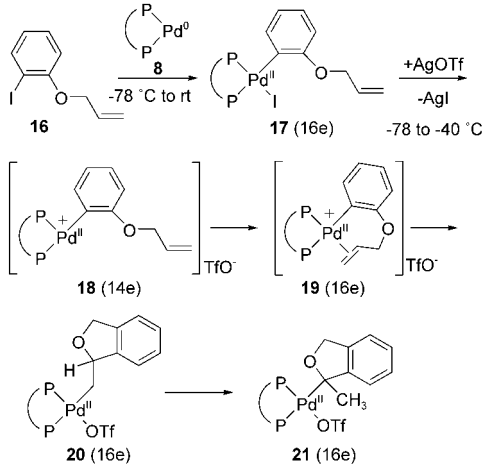
1) The former "cationic" pathway begins with the dissociation of X from **9** to generate the tricoordinate 14e cationic complex **12** with the accompanying counterion X^-. Complexation of alkene **2** into the vacant site then gives the 16e species **13**, and insertion of **2** into the Pd–R^1 bond followed by reformation of the Pd–X bond gives **10** as desired, with the chiral bidentate ligand remaining fully chelated throughout and thus maximizing the asymmetric induction.

2) The alternative "neutral" pathway starts with the dissociation of one arm of the bidentate ligand resulting in the 14e neutral species **14**; association and complexation into the vacant site of **2** gives the 16e neutral species **15**, which, by alkene insertion into Pd–R^1 and re-complexation of the previously displaced phosphine moiety, also gives **10**.

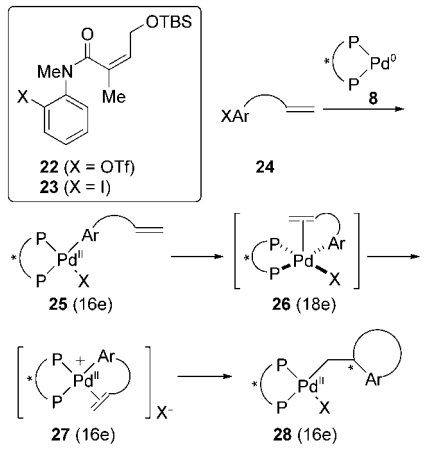
The nature of X in R^1–X **1** (and thus the strength of the Pd–X bond in **9**) is clearly an important factor. Aryl and alkenyl triflates are generally assumed to follow the cationic pathway (the Pd–OTf bond being weak[17]), with either route being available to reactions using aryl/alkenyl halides. In practice, it is possible to influence which pathway is 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 **9** and replacing it with its own anionic component[5]), or by adding excess halide anions to reactions using triflates, resulting in nucleophilic displacement of the triflate anion from **9**.[15b] The nature of the alkene substrate is also important, with electron-rich olefins favoring the cationic pathway and therefore being the most suitable for the asymmetric Heck reaction, while the neutral pathway makes for a faster reaction with electron-poor substrates[15a].

The first detailed study of the individual steps in the cationic pathway of the intramolecular Heck reaction was described by Brown et al.[18a] Oxidative addition of aryl iodide **16** to Pd^0 generated the very stable neutral 16e intermediate **17**, which was characterized by X-ray crystallography (Scheme 6). After removal of the iodide from the neutral intermediate by treatment with AgOTf at $-78\,^\circ C$, a rapid alkene coordination to the cationic 14e species **18** and subsequent insertion proceeded at $-40\,^\circ C$ to form the cyclic Pd intermediate **21** as the next detectable complex. In addition, characterization of reactive intermediates and mechanistic studies of the intermolecular Heck reaction were also performed (see Section 4.1).[18b, c]

Partial dissociation of the chiral ligand in this neutral pathway would seem to make it less well suited to asymmetric induction. In fact, the evidence from most of the asymmetric Heck reactions reported so far suggests that conditions that favor the cationic route also give the best



Scheme 6. Detailed study of the individual steps of the cationic pathway.



Scheme 7. Proposed neutral pathway for an intramolecular asymmetric Heck reaction including the formation of a pentacoordinate intermediate (**26**).

enantiomeric excess. There is, however, a significant exception to this rule (see also Section 3.2.1). Overman et al. observed that for a special aryl *triflate* **22** the addition of halide salts to the reaction mixture dramatically increased the enantiomeric excess of the intramolecular Heck reaction product (Scheme 7).[19] On the other hand, if the corresponding aryl *iodide* **23** was used as a starting material, high enantiomeric excess 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, when the bidentate diphosphine ligand (*R*)-BINAP was substituted by potentially monodentate analogues of (*R*)-BINAP, only low enantioselectivity was obtained, providing evidence that both phosphines of the diphosphine ligand remain coordinated to the Pd center during the enantioselective step. A "refined" neutral pathway for the asymmetric Heck reaction involving a pentacoordinate intermediate such as **26** without partial dissociation of the diphosphine was suggested to account for these findings mechanistically.

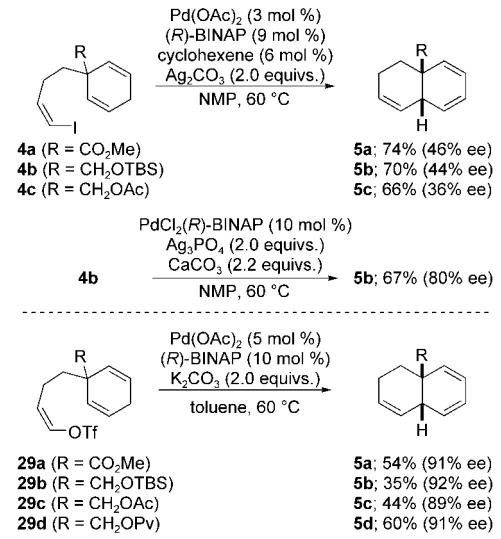
Consideration of the geometry of the palladium center during the catalytic cycle is fundamental for the further development of more detailed descriptions of the stereoinduction. Explicit three-dimensional models of how the chirality is transferred from the ligand to the substrate are beginning to emerge.

3 Intramolecular Reaction

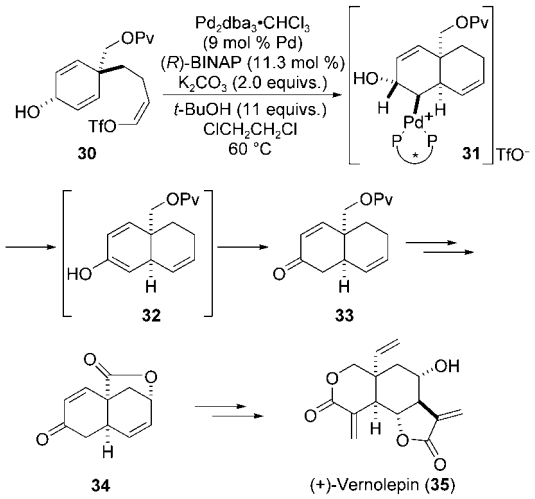
3.1 Formation of Tertiary Carbon Centers

3.1.1 Decalins

The asymmetric Heck reaction of the prochiral alkenyl iodides **4** into the chiral decalin system **5** was reported in 1989 by Shibasaki et al. (Scheme 8).[9] The reaction conditions (dipolar aprotic solvent and presence of silver salts), while similar to those of a previously reported non-enantioselective method,[12a] differ crucially in the choice of the chiral ligand and solvent. For example, very low or negligible enantiomeric excess was obtained using THF, MeCN, or DMSO, and the preferred solvent was *N*-methyl-2-pyrrolidinone (NMP). Similarly, the widely used chiral phosphine ligands BPPM [1-*t*-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)azolidine] and BPPFA {*N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine} failed to give significant asymmetric induction, with (*R*)-BINAP proving to be the ligand of choice, which is a consistent pattern in most of the reported examples of the asymmetric Heck reaction. Using a prochiral substrate, two stereocenters can be set in one step, a tactic that is used repeatedly in the tertiary center-generating asymmetric reactions reported by Shibasaki et al.[5] The modest enantiomeric excess reported (33–46% ee) for the conversion of **4** to **5** was greatly improved as a result of a study of the effects of varying the anionic component of both the Pd source and more particularly the silver salt.[16] The use of a Pd^0 catalyst complex pre-formed *in situ* from $PdCl_2$(*R*)-BINAP[20] and cyclohexene gave an improved enantiomeric excess relative to the 1:3 $Pd(OAc)_2$/(*R*)-BINAP pre-reduced catalyst used in the original work. The use of AgOAc as the Ag^+ source reduced the enantiomeric excess to almost zero, indicating that the nucleophilic acetate counterion is undesirable, 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 enantiomeric excess was 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, **5b** was obtained in 80% ee and 67%



Scheme 8. Enantioselective syntheses of *cis*-decalins using the asymmetric Heck reaction of alkenyl iodide or alkenyl triflate.



Scheme 9. Enantioselective synthesis of (+)-vernolepin (**35**).

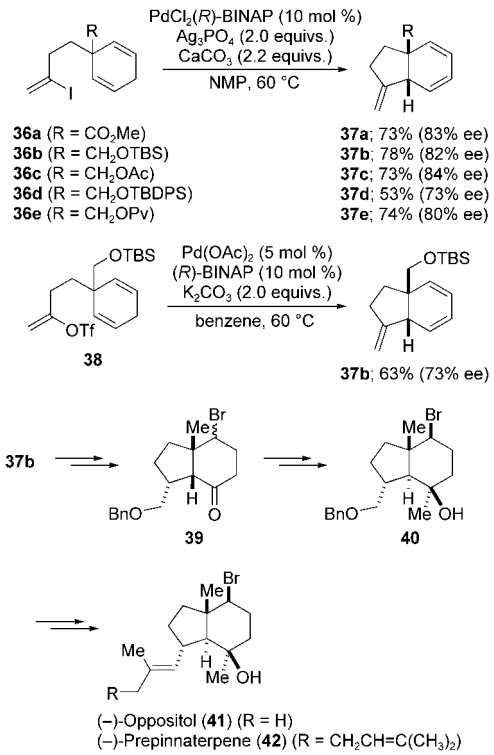
yield.[16] The introduction of the new ligand 2,2′-bis(diphenylarsino)-1,1′-binaphthyl (BINAs),[21] the diarsine equivalent of BINAP, considerably increased the yield for the conversion of **4b** to **5b**. After optimization, the product **5b** was obtained in 90% yield with 82% ee (see also Section 5.3).

The use of alkenyl triflates **29** in place of iodides **4** gave better enantioselectivity[22] and allowed for the omission of expensive silver salts and the use of hydrocarbon solvents (toluene or benzene). In addition, use of the alkenyl triflates eliminates the deleterious effects of $Pd(OAc)_2$ on the enantiomeric excess observed in NMP. Thus, products **5a**–**d** were obtained in 35–60% yield with uniformly excellent enantiomeric excess (89–92%) under the conditions indicated.

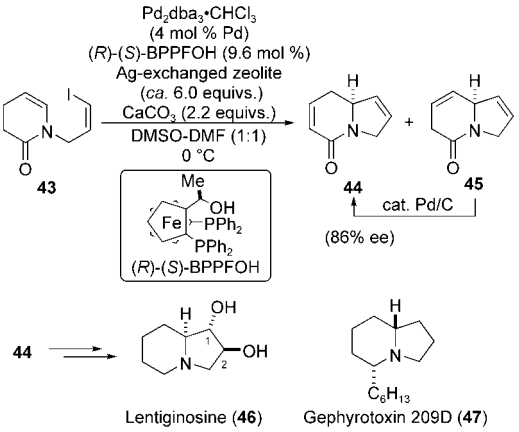
A significant extension in scope of the reaction was highlighted in the synthesis of a range of bicyclic enones and dienones, including a key intermediate **34** in Danishefsky's synthesis[23] of (+)-vernolepin (**35**) (Scheme 9).[24a] The asymmetric Heck reaction was initially the conversion of **30** to the chiral decalin system **33**, *via* the intermediate **31**. The best solvent for this reaction was 1,2-dichloroethane (DCE), with the addition of *t*-BuOH positively affecting the reaction rate and chemical yield without reducing the enantiomeric excess.[24b] Compound **33** was converted to **34** *via* a 9-step process; there was also an alternative approach starting from the more readily available **5a**.[24c] Use of the DCE/tertiary alcohol solvent system for the conversion of **29a** to **5a** improved the yield relative to that previously reported; a study of the various tertiary alcohols revealed that pinacol was the most effective, giving **5a** in 78% yield with 95% ee. The authors successfully synthesized (+)-vernolepin (**35**), and were thereby able to determine its absolute configuration.

3.1.2 Hydrindans

The general method described above for decalin synthesis has also been applied to the synthesis of 6,5-ring systems through the formation of hydrindans (Scheme 10).[25a] Both iodides **36** and triflate **38** were converted to the corresponding *cis*-hydrindans by methods similar to those used for decalins; Ag_3PO_4 was again the most effective silver salt in this conversion. Small increases (=



Scheme 10. Enantioselective syntheses of *cis*-hydrindans.



Scheme 11. Enantioselective syntheses of indolizidines.

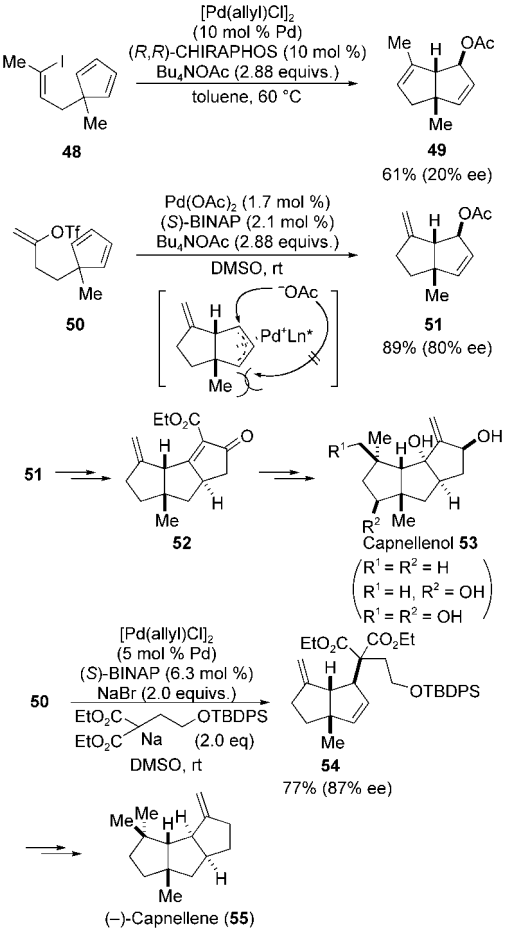
5%) in enantiomeric excess were obtained for **36** by pre-reducing the palladium catalyst *in situ*. The triflate **38** gave **37b** in slightly lower enantiomeric excess than observed for the corresponding conversion of **36b**, with potassium carbonate being the most effective base. The hydrindan **37b** was later converted by the same group into **40**,[25b] which is a key intermediate in the syntheses of (−)-oppositol (**41**) and (−)-prepinnaterpene (**42**).[26] 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 (**39** to **40**), which demonstrates that both *cis*- and *trans*-junctions can be obtained from the asymmetric Heck reaction products.

3.1.3 Indolizidines

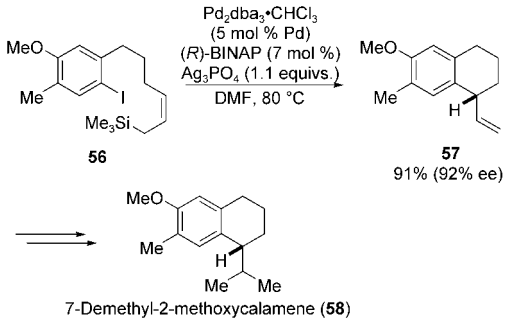
The 6,5-bicyclic synthesis outlined above was extended to indolizidines, formed by an asymmetric Heck reaction of a suitable prochiral alkenyl iodide such as **43**, which can be easily prepared by allylation of the lactam. In contrast to purely carbogenic systems, the most effective ligand is BPPFOH {(*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol},[27] which gives results clearly superior to those obtained with BINAP (Scheme 11).[28] The use of an Ag-exchanged zeolite also gives somewhat better results than the usual Ag_3PO_4 silver source. The indolizidine is obtained as a mixture of **44** and **45** (94% yield, 86% ee) and treatment of the mixture with catalytic Pd/C in MeOH at room temperature gives clean isomerization of **45** to **44** in essentially quantitative yield. Compound **44** was converted to the natural products lentiginosine (**46**), 1,2-diepilentiginosine, and gephyrotoxin 209D (**47**).[28c]

3.1.4 Diquinanes

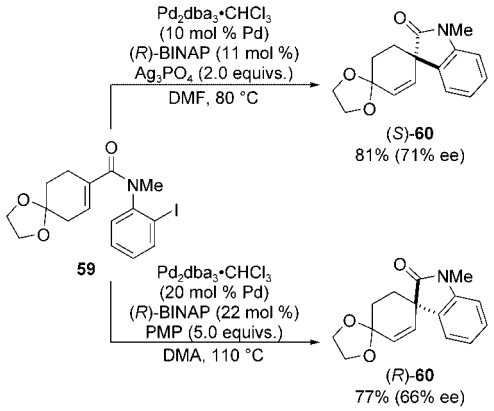
The successful execution of asymmetric Heck reactions for the formation of 6,6- and 6,5-ring systems from prochiral substrates led to an extension of the method to form 5,5-systems, which are the backbone of a large number of natural products. The use of prochiral cyclopentadienyl systems, however, involves the generation of a π-allylpalladium species, which must then be trapped by a suitable nucleophile.[29] 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 considered. The former problem figures prominently in the first example to be published of asymmetric Heck reaction-based diquinane synthesis (Scheme 9).[30a, b] Although cyclization of iodide **48** gave the bicyclo[3.3.0]octane **49** in reasonable yield, the observed enantiomeric excess was low (*ca.* 20%). The authors attribute this failing in large part to the instability of **48** in the presence of silver salts, necessitating their omission from the reaction medium and so forfeiting the beneficial effects noted in earlier work.[16] The presence of tetrabutylammonium acetate, a source of nucleophilic acetate, is essential, as the reaction does not proceed in its absence. This was the first example of a domino-type asymmetric Heck reaction (see also Section 6). The problem of low enantiomeric excess was circumvented



Scheme 12. Enantioselective syntheses of diquinanes.



Scheme 13. Asymmetric Heck reaction using an allylsilane.



Scheme 14. Enantioselective synthesis of spiroindol.

by using the triflate **50**, which gave the diquinane **51** with 80% ee and 89% yield. The authors converted this to the triquinane **52**, an intermediate in a previously described synthesis of $\Delta^{9(12)}$-capnellenols **53**.[31] Later, this domino process was further extended to other nucleophiles, such as amines[30b] and carbanions.[30c] Using the carbanion capture process, the first catalytic asymmetric synthesis of (−)-$\Delta^{9(12)}$-capnellene (**55**) was achieved.[30c] In this case, BINAP was the most effective ligand, and the addition of sodium bromide significantly improved the enantiomeric excess in all cases studied.

3.1.5 Tetralins

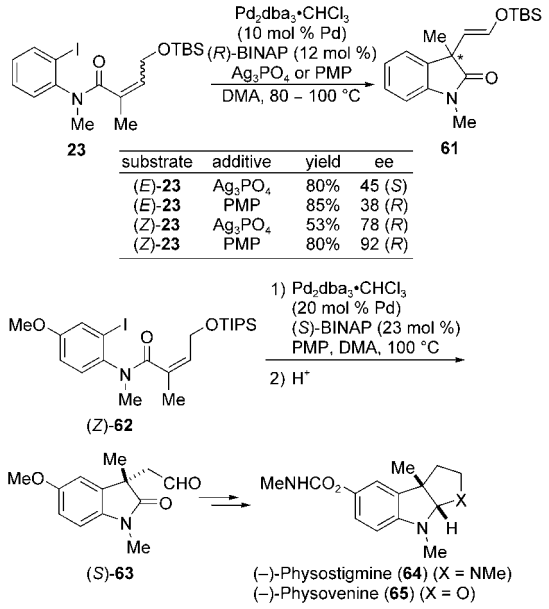
All of the examples discussed so far rely on the use of an endocyclic alkene substrate to resolve the β- vs. β′-hydride elimination regiocontrol problem discussed in Section 2.1. A more general approach to the problem was described by Tietze et al., and involves the use of allylsilanes as the alkene component (Scheme 13).[32a, b] By carefully choosing reaction conditions, either a vinyl- or a trimethylsilylvinyl-substituted carbocycle can be produced in the non-enantioselective reaction. Under conditions suitable for the asymmetric Heck reaction, however, the former product predominates. Yields and enantiomeric excesses are good, and the method has been successfully applied to the synthesis of the norsesquiterpene 7-demethyl-2-methoxycalamene (**58**) *via* the key cyclization of **56** to **57**.[32c, d]

3.2 Formation of Quaternary Carbon Centers

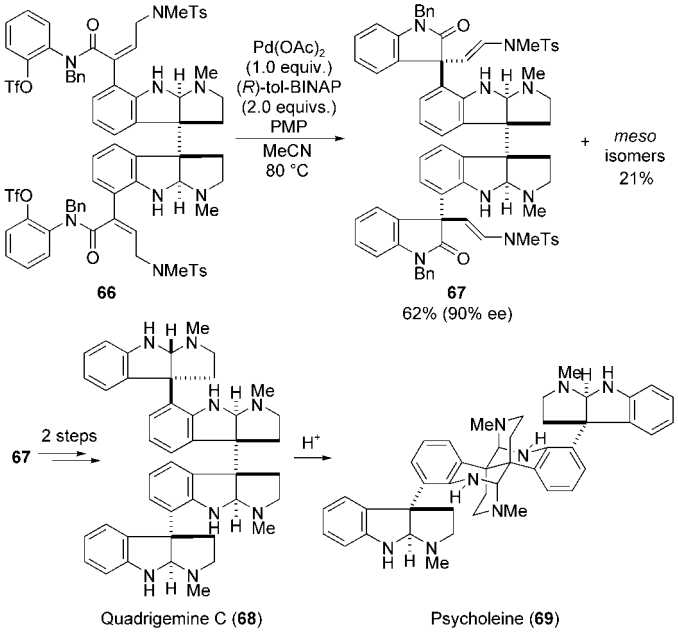
3.2.1 Spirocyclizations and Alkaloid Synthesis

The enantioselective formation of quaternary carbon centers remains a significant challenge to synthetic chemists.[33] The obvious attraction of the asymmetric Heck reaction in this role is the elimination of the competing pathways in step C (Scheme 3), as no β-hydrogen is present to compete with the desired β′-hydride elimination step. Thus, there is no need to use endocyclic alkene substrates. The first successful case was reported by Overman et al. in 1989 (Scheme 2),[10] a pioneering strategy that opened the way for the development of asymmetric Heck reactions leading to quaternary carbon centers. Furthermore, polycyclizations are well within the scope of the Heck reaction. Contrary to the case of polycyclizations of carbocations and free radicals, cyclizations resulting from sequential intramolecular insertions of palladium metal alkyls are most effective when the transition metal propagates at the least substituted terminus of the participating alkene units. As with the work creating tertiary centers reported by Shibasaki et al., the enantiomeric excesses of the cyclizations obtained at the outset were modest, with the spirocyclic compound **7** being obtained in good yield and moderate enantiomeric excess when (*S*,*S*)-DIOP was substituted for triphenylphosphine (Scheme 2). Although this work clearly demonstrated the viability of such a process, the full potential of the approach did not become apparent until the publication of a remarkable study concerning the synthesis of spiroindoles (Scheme 14).[34] Performing the asymmetric Heck cyclization of iodoanilide **59** in DMA in the presence of Ag_3PO_4 gave (*S*)-**60** in 81% yield with 71% ee. This result was very similar to those achieved by other workers for tertiary centers under similar conditions. By performing the reaction in the absence of Ag salts and using 1,2,2,6,6-pentamethylpiperidine (PMP) as the base, however, the opposite (*R*)-**60** isomer was obtained *using the same enantiomer* of BINAP.

Similar studies of the cyclization of alkene **23** revealed that the effect is reproduced when (*E*)-**23** is used, although the enantiomeric excess of the enantiomer obtained when using PMP was low (30–40%). In contrast, when (*Z*)-**23** was used in conjunction with (*R*)-BINAP both sets of conditions gave the expected (*R*)-enantiomer of **61** with good yield and excellent enantiomeric excess (>90% ee) (Scheme 15).[35] These results suggest that the observed "geometry effects" (identical to that observed by Shibasaki et al. for carbocycle formation, *vide infra*) are more powerful than the "base/additive ef-

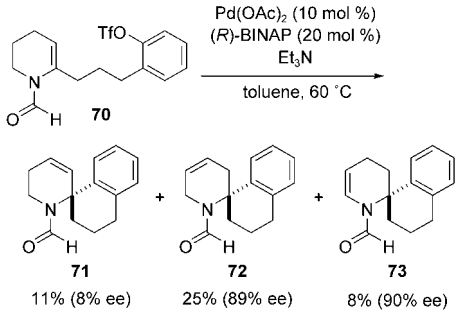


Scheme 15. Enantioselective synthesis of spiroindol; base/additive effects and geometry effects.



Scheme 16. Double asymmetric Heck reaction.

fects" in determining the sense of chiral induction. The reaction using (*Z*)-**62** and (*S*)-BINAP under identical conditions gave (*S*)-**63**, which was converted to the natural products (−)-physostigmine (**64**) and (−)-physovenine (**65**).[36] These surprising results spurred mechanistic investigation of the asymmetric Heck reaction, as they effectively rebutted the prevailing view that the "cationic pathway" is the only mechanism capable of producing high enantiomeric excess, by demonstrating



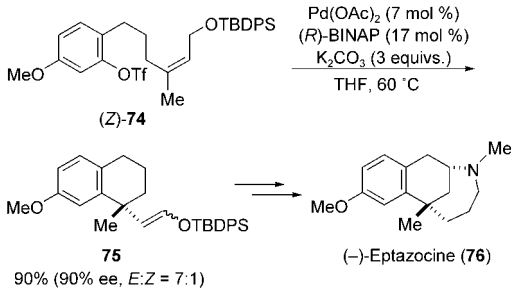
Scheme 17. Enantioselective synthesis of spirocyclic tetrahydropyridine.

that the alternative "neutral pathway" is also likely to do so with certain substrates (see Section 2.2).

As an extension of this strategy, a double asymmetric Heck cyclization was achieved by Overman et al. in the context of enantioselective syntheses of quadrigemine C (**68**) and its isomer, psycholeine (**69**) (Scheme 16).[37] In this case, the catalyst-controlled double asymmetric Heck reaction was employed to desymmetrize the advanced *meso* substrate **66** and simultaneously create the two peripheral biaryl quaternary stereocenters in **68** and **69**. When the reaction was performed using $Pd(OAc)_2$, (*R*)-tol-BINAP, and PMP in acetonitrile at 80 °C, the C_1-symmetrical bis-oxindole **67** was obtained as the major product in 62% yield and 90% ee with a 21% combined yield of *meso* isomers.

An asymmetric Heck reaction with 1,2,3,4-tetrahydropyridines also provided access to spirocyclic systems. Using *N*-formyl-1,2,3,4-tetrahydropyridines, Ripa and Hallberg succeeded in preparing various spirocyclic derivatives of tetrahydropyridines in moderate yield (Scheme 17).[38b] The asymmetric cyclization of **70** using (*R*)-BINAP as a chiral ligand resulted in the formation of three isomers **71**, **72**, and **73** with a rather long reaction time being required. Good enantiomeric excesses were obtained for **72** and **73** (89% and 90%, respectively). The migration of the double bond could not be controlled effectively by varying the reaction conditions. Interestingly, the introduction of the chiral phosphanyldihydrooxazole (first reported by Pfaltz et al.; see Section 5.1) as a ligand helped to suppress the formation of the double bond isomer **73**.[38b] At the same time, the regioselectivity could be considerably changed in favor of the formation of **71** to yield a 6:1 mixture of (*R*)-**71** (87% ee) and (*R*)-**72** (>99% ee) after 48 h at 110 °C, using *i*-Pr_2NEt as the base. If the corresponding iodide was used instead of the triflate **70**, only low to moderate enantiomeric excess was observed. The role of the *N*-formyl moiety could be important for chiral induction and this might provide further information about the mechanism.

The synthesis of benzylic quaternary centers by an asymmetric Heck reaction was also developed by Shibasaki et al. in the synthesis of (−)-eptazocine (**76**)



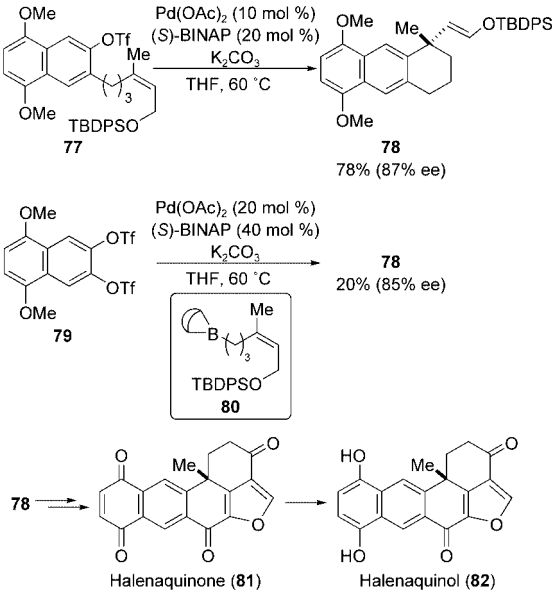
Scheme 18. Enantioselective synthesis of (−)-eptazocine (**76**).

(Scheme 18).[39] The key step involves the formation of a quaternary carbon center by asymmetric Heck arylation of a trisubstituted alkene **74**, with BINAP being the preferred ligand. The "geometry effect" reported by Overman for spiroxindoles (*vide supra*) is clearly present, with (*Z*)-**74** giving much better enantioselectivity and the opposite enantiomer to that obtained when using (*E*)-**74**. The conversion of (*Z*)-**74** to **75** was achieved with excellent yield and enantiomeric excess: desilylation gave the corresponding aldehyde,[40] which was converted to (−)-eptazocine (**76**) *via* a 5-step sequence.

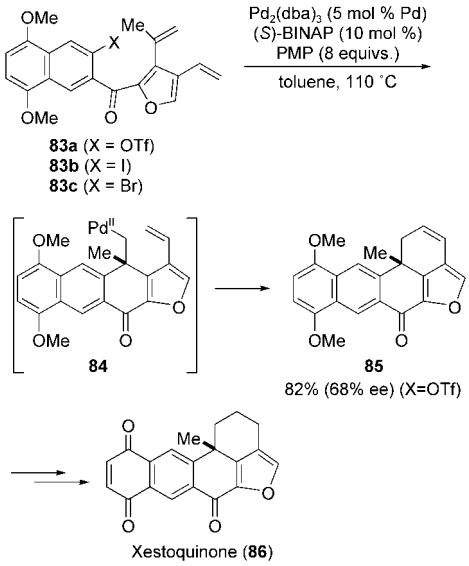
3.2.2 Polyketides

The synthesis of halenaquinone (**81**) and halenaquinol (**82**) initially featured the conversion of **77** to **78** as a key step, which gave the desired product in 78% yield and 87% ee (Scheme 19)[41] under very similar conditions used in the eptazocine synthesis described above. Consistent with the current trend towards sequential or "one-pot" transformations (*vide infra*) the authors were able to combine the asymmetric Heck reaction with a Suzuki-type coupling reaction of the trialkylborane **80**, which was pre-generated *in situ* by hydroboration, with the C_2-symmetrical ditriflate **79**, to obtain **78** more directly.[41] Although the chemical yield of this sequence was still low (20%) and the catalyst loading rather high (20 mol %), the obtained enantiomeric excess was excellent (85%), suggesting that further development of the method is feasible.

The synthesis of the halenaquinone-related natural product (+)-xestoquinone (**86**) by Keay et al.[42] confirmed the suitability of the asymmetric Heck reaction for inclusion in Pd-mediated "domino" polyene cyclizations (see also Section 6). A one-pot transformation of aryl triflate **83a** into the pentacyclic product **85** was achieved under conditions typical for the asymmetric Heck reaction, and gave (+)-**85** with a respectable 68% ee (Scheme 20). This conversion proceeded by an initial asymmetric Heck cyclization (6-*exo*) to form the intermediate **84** followed by a second Heck cyclization (6-*endo*). The typically favored 5-*exo* cyclization would



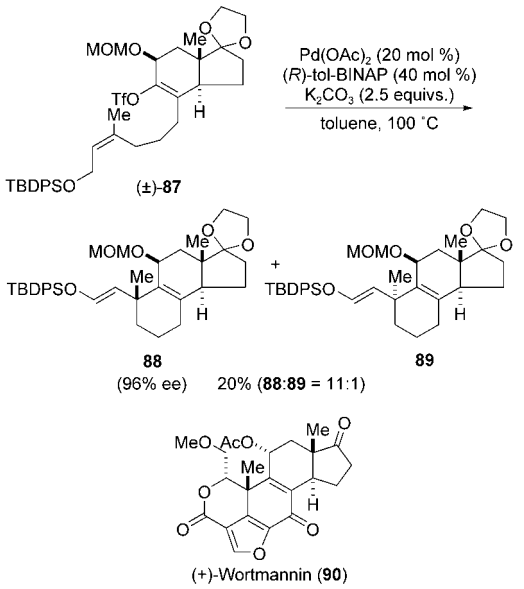
Scheme 19. Enantioselective synthesis of halenaquinone (**81**) and halenaquinol (**82**).



Scheme 20. Domino polyene cyclization and enantioselective synthesis of xestoquinone (**86**).

not be favored in this case because of increasing ring strain. Interestingly, the aryl iodide **83b** gave little or no asymmetric induction, even in the presence of silver salts. As aryl halides were prepared more readily than the corresponding triflates, the domino asymmetric Heck reaction of aryl bromide **83c** was further improved (in up to 63% ee) by adjustment of the silver source (Ag-exchanged zeolite) and the amount of the silver salt (1.0 equiv.).[43]

Kinetic resolution using the asymmetric Heck reaction was achieved by Shibasaki et al.[44] In a preliminary



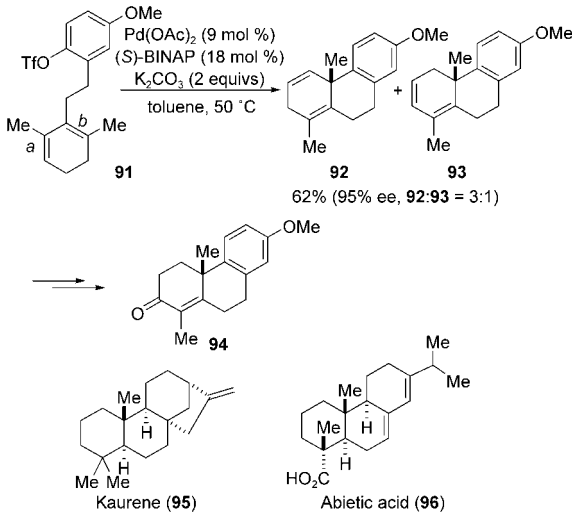
Scheme 21. Kinetic resolution using the asymmetric Heck reaction.

study, the Heck cyclization of racemic **87** with catalysts with achiral ligands was first demonstrated and the desired cyclic product **88** was obtained in high yield with high diastereoselectivity (90% yield, **88**:**89** = 17:1). The asymmetric variant of this process through kinetic resolution was achieved using the Pd-(*R*)-tol-BINAP complex, providing the desired **88**, a potential synthetic intermediate for (+)-wortmannin (**90**),[45] in a highly diastereo- (**88**:**89** = 11:1) and enantioselective (96% ee) manner, albeit in moderate yield (20%) (Scheme 21).

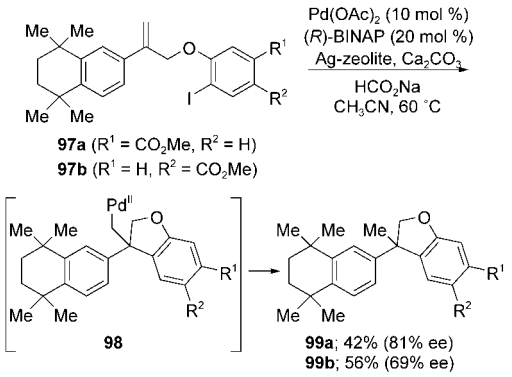
3.2.3 Terpenoids

There is another report of quaternary center formation by asymmetric Heck reaction: the conversion of the aryl triflate **91** to a 3:1 mixture of the tricyclic **92** and its isomer **93**, both of which were converted to the enone **94**, a key intermediate in the syntheses of kaurene (**95**) and abietic acid (**96**) (Scheme 22).[46] Compound **92** was also quantitatively isomerized to **93**. The essentially complete selectivity towards 6-*exo* cyclization (insertion to *a*) rather than 5-*exo* cyclization (insertion to *b*) is noteworthy. The authors explained this on the basis of unfavorable steric interactions in the alternative intermediates.

Another type of domino process involving an asymmetric Heck reaction was utilized by Diaz et al. for the enantioselective synthesis of retinoid derivatives.[47] A domino asymmetric Heck cyclization-hydride capture process, i.e., asymmetric hydroarylation, of aryl iodide **97** (see also Section 4.4) was catalyzed by the Pd-(*R*)-BINAP complex with sodium formate to produce the cyclic compound **99** *via* the intermediate **98** in moderate yield and good enantioselectivity.



Scheme 22. Enantioselective synthesis of a key intermediate of kaurene (**95**) and abietic acid (**96**).



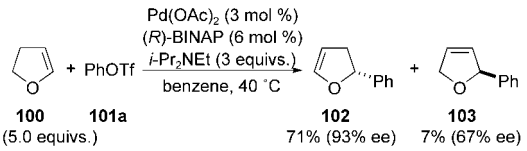
Scheme 23. Domino asymmetric Heck cyclization-hydride capture process.

4 Intermolecular Reaction

4.1 Dihydrofurans and Cyclic Enol Ethers

The first example of the intermolecular asymmetric Heck reaction was reported in 1991 by Hayashi et al. and involved the asymmetric arylation of 2,3-dihydrofuran (**100**) using aryl triflates such as **101a** (Scheme 24).[14] 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 **102**, together with minor amounts of the 2,5-dihydrofuran isomer **103**.

The rationale proposed by the authors for this outcome is shown in Scheme 25; it is hypothesized that the catalytic complex can be added to either face of the substrate, ultimately producing the complexes (*R*)-**106** and (*S*)-**106**, but that in the case of the (*S*)-**106**, unfavorable steric factors cause an immediate dissociation

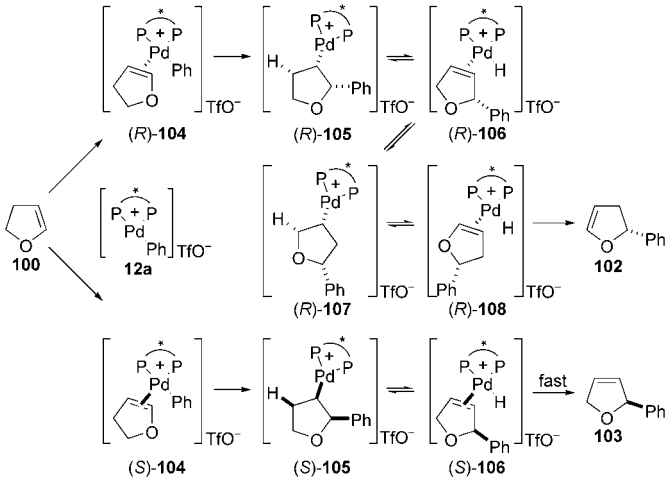


Scheme 24. First example of intermolecular asymmetric Heck reaction.

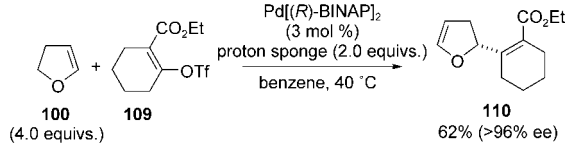
of the Pd species, producing the minor product **103**. In contrast, (*R*)-**106** is able to undergo a re-insertion of the alkene into the Pd–H bond followed by a second β-hydride elimination to produce **102**. The overall effect is a kinetic resolution of (*R*)- and (*S*)-**106**, effectively enhancing the facial selectivity shown in the initial transformation of **100** to **104** by selectively removing the **106** enantiomer produced by complexation to the undesired face of **100**. Recently, the proposed mechanism depicted in Scheme 25 was further reinforced and refined by Brown et al.[18c] The reactive intermediate in the asymmetric Heck reaction that was produced by two Pd–H-mediated isomerization steps, was identified by NMR and mass spectrometry. In addition, molecular orbital calculations on the reaction pathway between $[CH_2(PH_2)_2]PdPh^+$ and **100** revealed several structurally interesting intermediates and elucidated the isomerization pathway. As might be expected from the above argument, reaction conditions which gave proportionally larger amounts of **103** also afforded the best enantiomeric excess for the major product **102**; thus, when a proton sponge was used as the base, product **102** was obtained with >96% ee, at the cost of a 71:29 ratio of **102**:**103** whereas, in contrast, the use of Na_2CO_3 gave a lower enantiomeric excess (75%), but much better regioselectivity (97:3).[48a, b] The authors noted that the presence of the nucleophilic acetate anion in the reaction medium assisted the dissociation of (*S*)-**106**, and presumably (*R*)-**106** as well, making possible the formation of **103**.[49]

Even more impressive results were obtained using alkenyl triflates. For example, the asymmetric Heck reaction between **100** and alkenyl triflate **109** gave the expected major product **110** with >96% ee, without formation of the undesired regioisomer (Scheme 26).[48c] The use of 2,2-dialkyl-2,3-dihydrofurans for the intermolecular Heck reaction was reported by Guiry et al., in which 2,5-dihydrofuran isomers were obtained in up to 98% ee using the P-N ligand (see Section 5.1).[50]

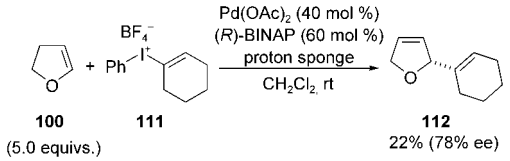
An interesting corollary to this work was reported by Reiser et al., who found that at high pressure the enantiomeric excess of the major product in the conversion of **100** to **102**/**103** was dramatically increased, suggesting that such conditions enhanced the kinetic resolution process.[51] Shibasaki et al. demonstrated that the reaction can be performed using hypervalent alkenyliodonium salts instead of alkenyl triflates (transformation of **111** to **112**, Scheme 27), although yields are lower due to the highly reactive nature of the salts, which leads to



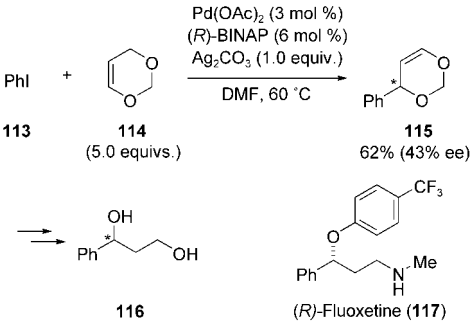
Scheme 25. Mechanism for intermolecular asymmetric Heck reaction of dihydrofuran **100**.



Scheme 26. Intermolecular asymmetric Heck reaction of alkenyl triflate.



Scheme 27. Intermolecular asymmetric Heck reaction of hypervalent alkenyliodonium salt.



Scheme 28. Intermolecular asymmetric Heck reaction of 4*H*-1,3-dioxin (**114**).

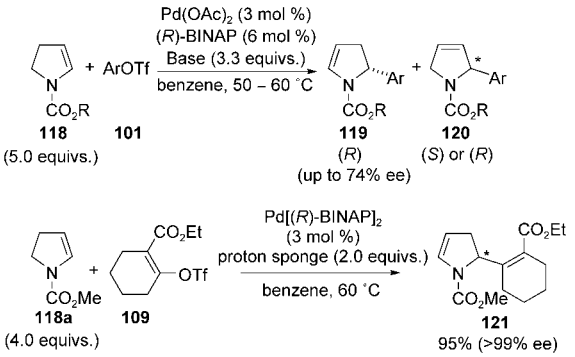
competition from uncatalyzed and/or non-phosphine mediated processes.[52] In this case, only the 2-alkenyl-2,5-dihydrofuran **112** is obtained, suggesting that dissociation from the Pd complex formed after the first β-hydride elimination is more rapid than when using triflates.

Asymmetric arylation of 4*H*-1,3-dioxin (**114**) was also reported by Yamanaka et al., although the yield and enantiomeric excess are more modest (Scheme 28).[53] Hydrolysis of the product **115** conveniently gave the corresponding 1,3-diol **116**, an intermediate in the Sharpless' synthesis of fluoxetine (**117**).[54]

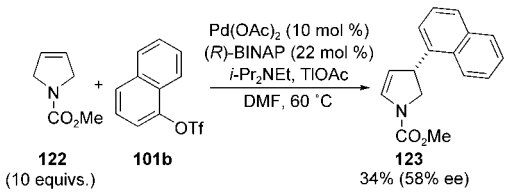
4.2 Dihydropyrroles

The methods described for the arylation of dihydrofurans (see above) can also be applied to 2,3-dihydropyrroles **118**,[55] with similar patterns of regio- and enantioselectivity. Little or no enantiomeric excess was obtained when using aryl iodides. The aryl triflates **101**, however, gave mixtures of 2-aryl-2,3-dihydropyrroles **119** and 2-aryl-2,5-dihydropyrroles **120**, with the former predominating and the kinetic resolution process again being in effect, as evidenced by the inverse relationship between the enantiomeric excess of **119** and the **119**:**120** ratio (Scheme 29). The reaction was successfully extended to alkenyl triflates **109**, which gave even better enantiomeric excess (>99% ee) than that obtained for the dihydrofurans.[48c]

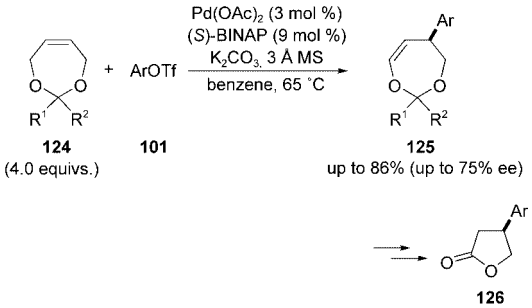
An example of a reaction with 2,5-dihydropyrroles **122** was reported by Sonesson and Hallberg et al.[56] Arylation of **122** using 1-naphthyl triflate (**101b**) and an (*R*)-BINAP/$Pd(OAc)_2$/*i*-Pr_2NEt system in DMF gave the 3-arylation product **123** (Scheme 30) with moderate yield and enantiomeric excess. The addition of excess



Scheme 29. Intermolecular asymmetric Heck reaction of 2,3-dihydropyrrole **118**.



Scheme 30. Intermolecular asymmetric Heck reaction of 2,5-dihydropyrrole **122**.



Scheme 31. Intermolecular asymmetric Heck reaction of 4,7-dihydro-1,3-dioxepin **124**.

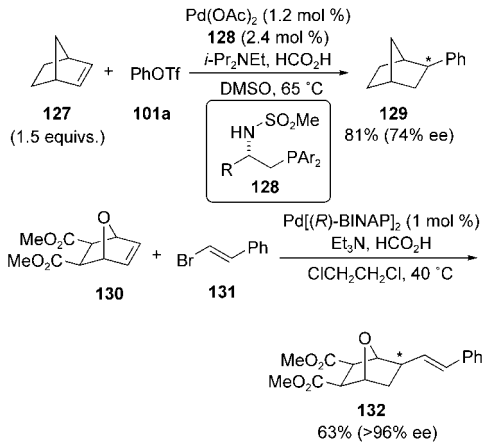
acetate suppressed formation of the undesired 2-arylation product, which was formed after initial isomerization of the double bond in **122**, and this was conveniently achieved by adding TlOAc, with the thallium cation acting as a co-catalyst. Unfortunately, attempts to perform this reaction with other aryl triflates or with aryl iodides were unsuccessful.

4.3 Dihydrodioxepins

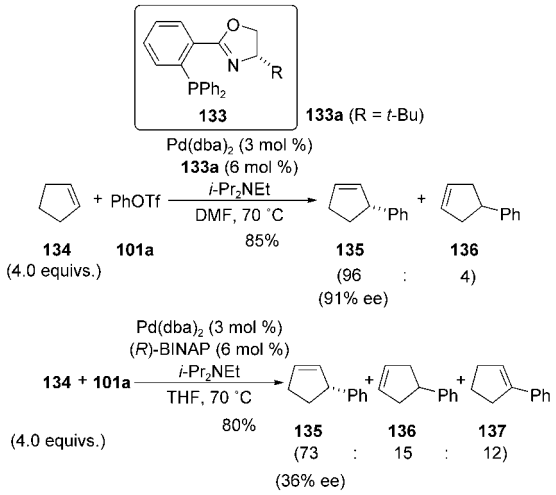
Arylation of the 4,7-dihydro-1,3-dioxepin **124** (easily derived from *cis*-2-butene-1,4-diol), using the aryl triflate **101**, was reported by Shibasaki et al. (Scheme 31).[57] The reaction is significant in that the resulting enol ethers **125** are easily converted (by hydrolysis and then oxidation of the intermediate lactol) to chiral β-aryl-γ-butyrolactones **126**, which are themselves useful synthetic intermediates.[58] Also noteworthy is the important role of added molecular sieves, which enhance both chemical yield and enantiomeric excess. A combination of 3 Å MS and potassium carbonate base was most effective, with the best auxiliary system ($R^1 = R^2 = H$) giving **125** with a satisfactory 75% ee. Gratifyingly, these figures showed only minor perturbations when the Ar ring substituents were varied. Significantly improved enantiomeric excess (92% ee) was reported for this process using a new P,N-ligand system (see Section 5.1).

4.4 Hydroarylations of [2.2.1]Bicyclics

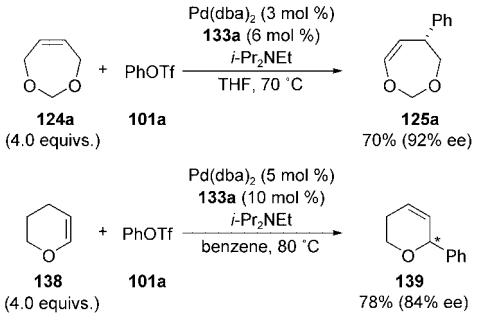
Asymmetric hydroarylation/hydroalkenylation, although not strictly a Heck reaction as the β-hydride elimination step is replaced by reductive elimination, nevertheless shares a common mechanistic pathway with regard to the enantioselective step and is thus briefly discussed. In 1991, Brunner et al. reported hydrophenylations of norbornene (**127**) and norbornadiene using aryl iodides, although the enantiomeric excess obtained was low (<40%).[59] The preferred ligand was (−)-NORPHOS; BINAP does not appear to have been test-



Scheme 32. Intermolecular asymmetric hydroarylation/hydroalkenylation.



Scheme 33. Intermolecular asymmetric Heck reaction of cyclopentene using P,N-ligand **133**.



Scheme 34. Other examples of intermolecular asymmetric Heck reaction using P,N-ligand.

ed. The system was revisited by Achiwa et al. as a means of testing novel phosphine ligands of the general structure **128**.[60] Using **128** as a chiral ligand, the conversion of **127** to **129** was performed in 81% yield and 74% ee (Scheme 32). Hayashi et al. have performed the reaction using alkenyl halides and triflates both on norbornene (**127**) and on hetero-analogues such as **130**; excellent enantiomeric excess and satisfactory yield were obtained.[61] Hydrophenylation of a similar system was also reported by Moinet and Fiaud.[62]

5 New Chiral Ligands

5.1 P,N Ligands

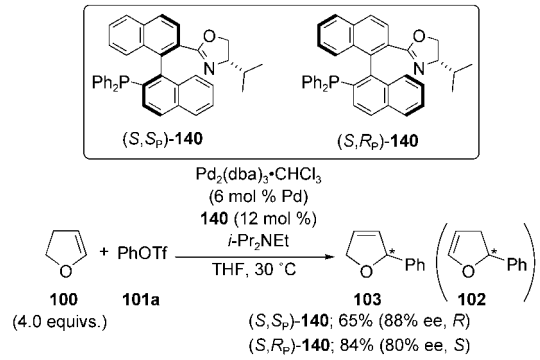
The great majority of asymmetric Heck reactions reported utilized the BINAP ligand system, which was most effective in most of the cases in which the performances of different ligands were assessed. The significant number of exceptions to this rule, however, suggests that experimentation with alternatives will prove worthwhile. The most dramatic recent development has been the introduction by Pfaltz et al. of the oxazoline-based P,N ligands such as **133**,[63] which produced a distinctly improved enantiomeric excess with several previously reported asymmetric Heck reactions.[64] For example, the Hayashi-type intermolecular reaction of dihydrofuran (**100**) with cyclohexenyl triflate catalyzed by $Pd(dba)_2$ and **133a** with *i*-Pr_2NEt as the base gives the 2-cyclohexenyl-2,5-dihydrofuran (**112**) in 92% yield and > 99% ee, a major improvement over the enantiomeric excess obtained with BINAP (58% yield, 87% ee).[65] Similar to the alkenylation of **100** using hypervalent iodonium salt **111** (see Scheme 27), no trace of the isomeric 2-alkenyl-2,3-dihydrofuran product is formed, indicating rapid dissociation of the catalyst from the initial product of β′-hydride elimination. 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 (**134**), giving region-defined products **135** with high yields, excellent enantiomeric excess, and only small amounts (< 5%) of the unwanted regioisomers **136** (Scheme 33). This catalyst system is also interesting in terms of reaction rates and decreased catalyst loading, indicating a higher catalyst turnover compared to BINAP. The conversions outlined here are noteworthy in that they constitute examples of intermolecular asymmetric Heck reactions 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.

Two further examples of arylation reactions catalyzed by phosphanyldihydrooxazole-palladium complexes are shown in Scheme 34 with the formation of **125a** and **139** in high yield and excellent enantiomeric excess.[66] Interestingly, phosphanyldihydrooxazoles **133** with smaller substituents (R) on the oxazole ring than *t*-Bu produce less reactive catalysts. This finding was

very unusual; because *t*-Bu is a very bulky group, the steric hindrance near the metal center could be expected to slow down the metal-catalyzed process.

Given the success and popularity of ligands **133**, many types of P,N ligands, which contain an oxazole unit such as an N ligand in most cases, were synthesized and applied to the asymmetric Heck reaction. New chiral P,N ligands: (S,S_P)- and (S,R_P)-2-[4-(isopropyl)oxazole-2-yl]-2′-diphenylphosphino-1,1′-binaphthyls **140** were independently synthesized by Ikeda et al.[67] and Hayashi et al.[68a] One of their structural characteristics is that **140** has two independent chiral elements, the binaphthyl axial chirality and the carbon central chirality, on the oxazoline ring. Hayashi et al. demonstrated the asymmetric Heck reaction of **100** with **101a** using (S,S_P)-**140** or (S,R_P)-**140** as a chiral ligand to afford **103** in a highly enantio- and regioselective manner (Scheme 35). The regioisomer **102**, which was a major product in the reaction catalyzed by Pd-BINAP, was not detected at all. This regioselectivity is similar to that in Pfaltz's report. As shown, ligands (S,S_P)- and (S,R_P)-**140** induced opposite configurations in product **103**. This observation indicates that the axial chirality has a more important role in the enantiocontrol than the carbon central chirality on the oxazolines. X-ray crystallography studies supported this argument.[68b] The same tendency was also observed at the palladium-catalyzed asymmetric allylic alkylation.[67,68b]

Recently, several new types of P,N ligands, which present up to three chiral centers in the molecule, were synthesized by Kündig et al. (**141**[69]), Hashimoto et al. (**142**[70]), Hou et al. (**143**[71]), Gilbertson et al. (**144**[72a], **145**[72b], **146**[72c, d]), Busacca et al. (**147**[73]), and Pfaltz et al. (**148**[74]). The results of the Hayashi-type intermolecular asymmetric Heck reaction (except ligand **147**) using these ligands are summarized in Figure 1. For ligands **144** and **145**, the absolute configuration of the products was controlled by the chirality of the 4-position on the oxazolines, that is (4*S*)-ligands gave (*R*)-products. These results are consistent with that using **133**. On the other hand, when ligands **143** and **146** were used, the absolute configuration of the products was controlled by changing the additional chirality and/or the size of the substituents. Ligand **147** catalyzed a spiroindole cyclization similar to **59** (Scheme 14) in up to 88% ee. The advantage of the P,N-ligand as compared with BINAP in intramolecular asymmetric Heck reactions was also reported by Guiry et al.[75]



Scheme 35. Intermolecular asymmetric Heck reaction using the chiral P,N-phosphinooxazoline ligand **140**.

5.2 N,N Ligands

The use of a chiral bisoxazoline ligand **149** for the enantioselective palladium-catalyzed annelation of allenes was reported by Larock and Zenner (an example is given in Scheme 36).[76] The alkene insertion step here is followed by an intramolecular nucleophilic attack of the amine functionality, which could be described as

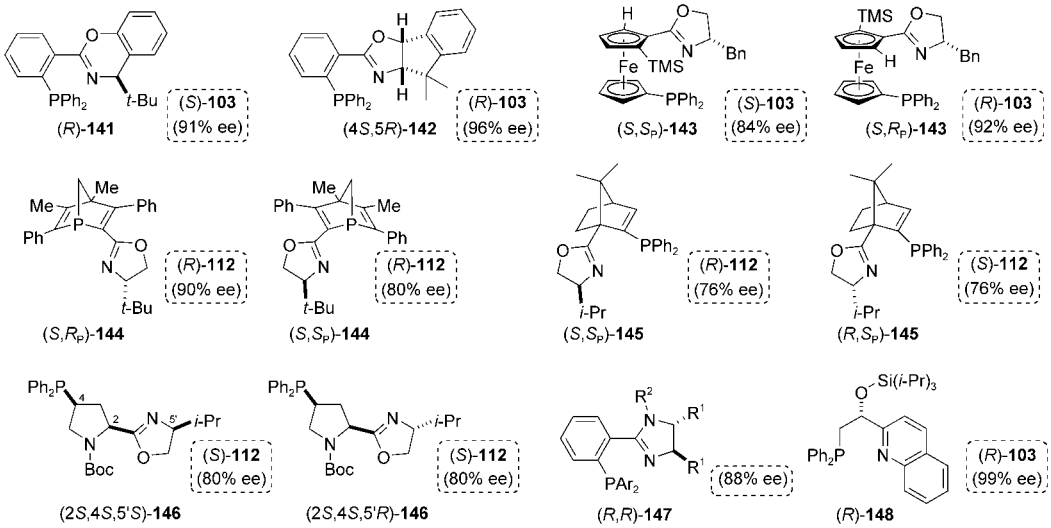
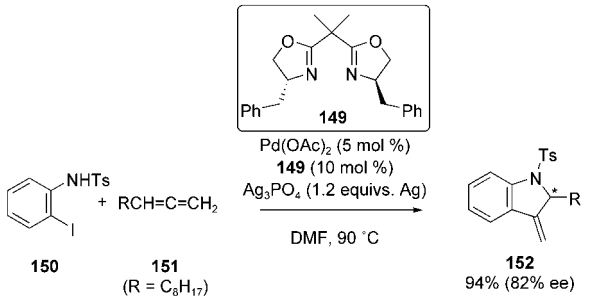


Figure 1. Structure of other chiral P,N-type ligands.



Scheme 36. Asymmetric reaction of allenes using chiral N,N-type ligand.

an "intramolecular anion capture process". Whereas the reaction is not strictly a Heck reaction, the high yields and enantiomeric excess obtained for various substrates are remarkable.

5.3 P,P Ligands and Derivatives

Many BINAP-type bidentate phosphine ligands have been applied to a variety of transition metal-catalyzed asymmetric transformations with a remarkable degree of success. Although the great majority of them are electron-rich phosphine ligands, less electron-rich ligands, such as tri-2-furylphosphine (TFP) and triphenylarsine, are advantageous for some transition metal-mediated organic reactions. As mentioned in Section 3.1.1, the new diarsine ligand (BINAs[21]) was a very effective ligand for the asymmetric Heck reaction of **4**. In this direction, several new biaryl bidentate ligands were developed (Figure 2). 2-Diphenylarsino-2′-diphenylphosphino-1,1′-binaphthyl (BINAPAs)[77] was synthesized and successfully applied in asymmetric Heck reactions of a compound similar to **77** (see Scheme 19) with superior reactivity compared to BINAP. Thienyl-type ligands (TMBTP and BITIANP[78]) and furyl-type ligands (BINAPFu and TetFuBINAP[79]) also have several advantages in some asymmetric Heck reactions when compared with BINAP.

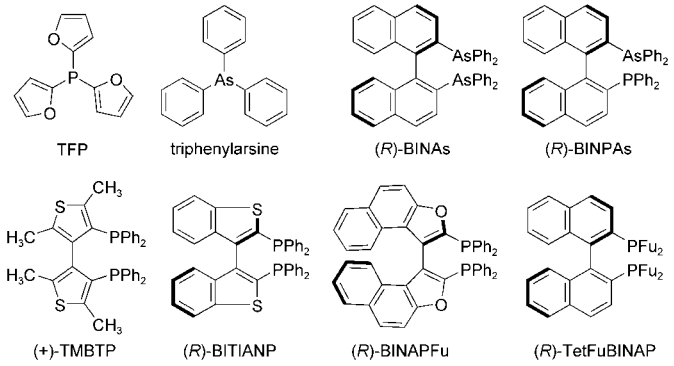
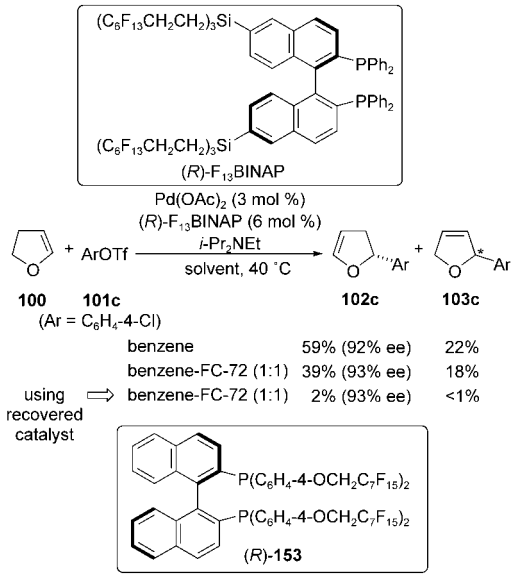


Figure 2. Structure of other chiral phosphine and arsine ligands.

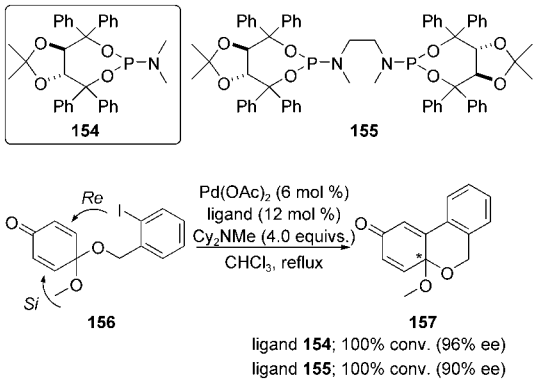


Scheme 37. Intermolecular asymmetric Heck reaction using chiral fluorous BINAP-type ligand.

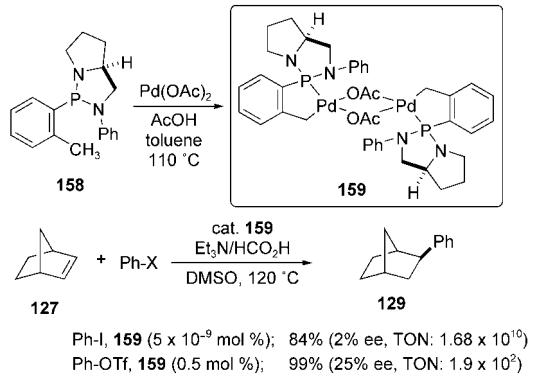
Recovery of the catalyst, even that of the chiral ligand, is not usually practical in the asymmetric Heck process. Recently, a chiral fluorous BINAP-type ligand (F_{13}BINAP), which is expected to be recyclable in an organic-fluorous biphasic system, was synthesized and applied to the asymmetric Heck reaction by Nakamura et al.[80] F_{13}BINAP had good solubility in fluorinated solvents. F_{13}BINAP was easily oxidized, however, by trace amounts of oxygen in the fluorous phase during the reaction; as a result, recycling of the catalyst was not successful. Another fluorous BINAP-type ligand **153** was synthesized by Pozzi and Sinou et al.[81] It is interesting to compare **153** and F_{13}BINAP: although (*R*)-**153** catalyzed the same reaction in α,α,α-trifluorotoluene to afford (*R*)-**102c** (100% yield, **102c**: **103c** = 97:3, 68% ee), the reaction did not proceed in a toluene/FC-72 biphasic system.

5.4 Other Types of Ligands and Diastereoselective Reactions

Recently, an efficient intramolecular asymmetric Heck reaction of cyclohexadienones **156** using *monodentate* phosphoramidite ligand **154** was developed by Feringa et al.[82] In this reaction system, the monodentate ligand **154** gave a higher enantiomeric excess than the bidentate ligand **155** (Scheme 38). For comparison, BINAP was also examined in this system and **157** was obtained in 0–50% yield and 0–5% ee. Preliminary mechanistic studies of this reaction indicated a possible "neutral" pathway.



Scheme 38. Asymmetric Heck reaction using monodentate phosphoramidite ligand.



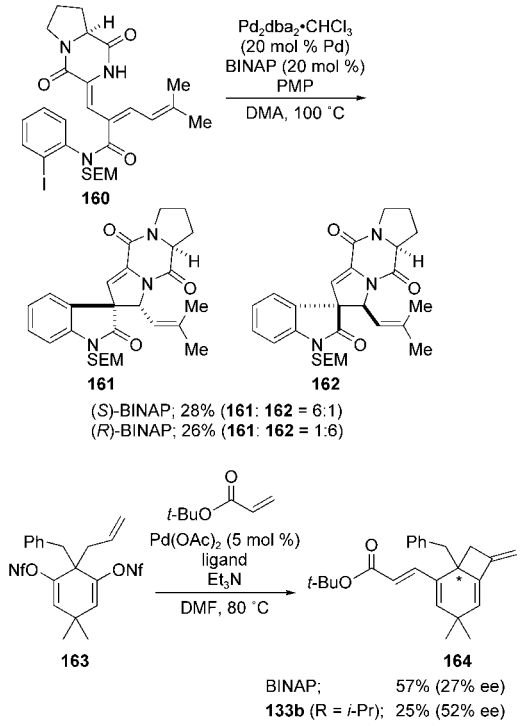
Scheme 39. Intermolecular asymmetric hydroarylation using a chiral palladacycle catalyst.

In 1995, Herrmann discovered highly efficient palladacycle catalysts in Heck and related reactions of aryl halides with catalyst turnover numbers (TONs) up to 5×10^5.[83] Later, the TON of the intermolecular Heck reaction reached up to 8.9×10^6.[84] On the other hand, a few syntheses of a chiral palladacycle catalyst were tried and most of the attempts failed. Recently, the asymmetric Heck reaction using a chiral phosphapalladacycle catalyst was reported by Buono et al.[85] The chiral phosphapalladacycle catalyst **159**, which was prepared from $Pd(OAc)_2$ and the chiral *o*-tolyldiazaphospholidine ligand **158**, promoted the asymmetric Heck reaction of norbornene (**127**) with phenyl triflate (**101a**) or iodobenzene (**113**) to afford *exo*-phenylnorbornane **129** (Scheme 39). Although the enantiomeric excesses are low (up to 25% ee), excellent TONs (up to 1.68×10^{10}) were achieved. Isolation of the Pd^{IV} intermediate suggests a mechanism for the Heck reaction involving the $Pd^{II}-Pd^{IV}$ catalytic cycle.

6 Methodological Developments

Following a general trend in organic chemistry, the asymmetric Heck reaction can also be integrated in domino reaction sequences.[86] This methodology allows the formation of complex compounds starting from a simple substrate in very few steps. As described in Section 3.2.2, Keay et al. reported an elegant enantioselective total synthesis of (+)-xestoquinone (**86**), in which a highly efficient domino-type asymmetric Heck reaction was developed. A double asymmetric reaction by Overman et al. (Scheme 16) and the sequential Suzuki-type coupling-asymmetric Heck reaction process by Shibasaki et al. (Scheme 19) were also successful. Another instructive method in this issue is the domino-type asymmetric Heck reaction, which was first demonstrated by Shibasaki et al. (Scheme 12), and the Pd-catalyzed annelation of allenes shown in Scheme 36 is also classified into this category. Recently, this type of domino process was successfully employed by Overman and Rosen in efforts toward the synthesis of (−)-spirotryprostatin B, in which the reaction of triene **160** using a chiral palladium catalyst proceeded with excellent regioselectivity and with a reasonable degree of catalyst control of the first carbon-carbon bond formation (Scheme 40).[87] Bräse reported a domino intramolecular asymmetric Heck-intermolecular Heck reaction of 1,3-bis(enol nonaflates) **163** to the highly congested bicyclic compound **164**.[88] Although the level of asymmetric induction is low (up to 52% ee), this result indicates that the concept of two leaving groups in the desymmetrization reaction is desirable.

The increase of the catalyst turnover numbers is indeed another major area where further improvements



Scheme 40. Other examples of domino processes involving asymmetric Heck reactions.

could be made. Such improvements were recently achieved for the standard Heck reaction by the use of high pressure conditions,[89] the use of preformed palladacycles as catalysts (see Section 5.4), or by using a macrocyclic tetraphole as the ligand.[90] Dendritic diphosphine-palladium complexes as catalysts for Heck reactions also possess superior stability compared to the monomeric parent compounds.[91] Transferring such innovations to the asymmetric Heck reaction remains an important goal. The current surge of interest in combinatorial chemistry[92] might also be highly significant to the development of new ligands, as both Heck reactions on solid support[93] and the generation and screening of chiral phosphine ligand libraries[94] have been demonstrated, potentially opening the way to combinatorial screening of asymmetric Heck reaction catalyst systems. The move away from bulky BINAP ligands, which Pfaltz's work might foreshadow, would certainly simplify library construction. The ready availability of chiral oxazolines from peptide residues might also be helpful in this respect.[95] Microwave-promoted Heck reactions are another recent development. Heck reactions of common substrates like *p*-iodoanisole and methyl acrylate, which under standard conditions need several hours for reasonable conversions, can be performed in just a few minutes if DMF is used as a solvent and microwave irradiation is applied.[96]

7 Summary and Conclusions

From its modest beginnings in the late 1980s, the asymmetric Heck reaction has developed into a powerful method for the synthesis of both tertiary and quaternary chiral carbon centers, with enantiomeric excesses typically in excess of 80% and in some cases much higher. A variety of carbocyclic and heterocyclic systems can be constructed including spirocyclic systems. Problems of regioselectivity with respect to product alkene isomerization that somewhat limit the scope of the reaction might be surmountable, and a new generation of ligands that dissociate more rapidly from the products might improve both enantio- and regiocontrol. It should be possible to increase the efficiency of the catalysts. Furthermore, the search for improved ligand systems will be greatly assisted by combinatorial screening methods, to which the mild and functionality-tolerant asymmetric Heck reaction might be well suited. Certainly the reaction is useful for one-pot multi-step processes. The development of the Heck reaction, as a transition metal-catalyzed process is an attractive in terms of atom economy.[97] It remains to be determined, however, if industrial applications of the asymmetric process will follow.

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