The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis

Amy B. Dounay and Larry E. Overman*

Department of Chemistry, University of California, Irvine, California 92697-2025

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Contents

1. Introduction

The Pd(0)-catalyzed vinylation of aryl halides was first reported over 30 years ago in independent studies by Mizoroki and Heck.[1] The transformation that has come to be known as the Heck reaction is now broadly defined as the Pd(0)-mediated coupling of an aryl or vinyl halide or triflate with an alkene. Although the synthetic potential of this transformation was largely unappreciated for a number of years, the application of this powerful reaction in natural product synthesis has flourished recently.[2] The discovery and development of the asymmetric variant of the Heck reaction was inspired by a need in organic synthesis for catalytic asymmetric methods for constructing tertiary and quaternary stereocenters by carbon−carbon bond formation. During the past decade, the catalytic asymmetric variant of the Heck reaction has emerged as a reliable method for enantioselective carbon−carbon bond formation.[3] The focus of this article will be the application of catalytic asymmetric Heck cyclizations in natural product total synthesis. Some exploratory studies that preceded total synthesis applications are also described, as these studies provided insights that were critical for applying the asymmetric Heck cyclization in target-directed synthesis. Furthermore, an understanding of the mechanisms of catalytic reactions is necessary for the rational development of efficient asymmetric processes. Therefore, a brief discussion of the current mechanistic interpretation of the catalytic Heck reaction is provided. Diastereoselective Heck cyclizations and intermolecular Heck reactions have been reviewed previously[2] and are beyond the scope of this review.

2. Background

2.1. First Catalytic Asymmetric Heck Cyclizations

In 1989, Shibasaki and Overman independently reported the first examples of asymmetric Heck reactions. Shibasaki and co-workers described the use of a group-selective Heck cyclization of prochiral vinyl iodide **1** for formation of the *cis*-decalin **2** (Scheme 1). Under optimized conditions, which included use of (*R*)-BINAP as a chiral ligand, silver carbonate as a base, and NMP as solvent, **2** was obtained in good yield, albeit with rather modest enantioselectivity.[4] Of the various chiral diphosphine ligands surveyed in this preliminary study, BINAP provided the best

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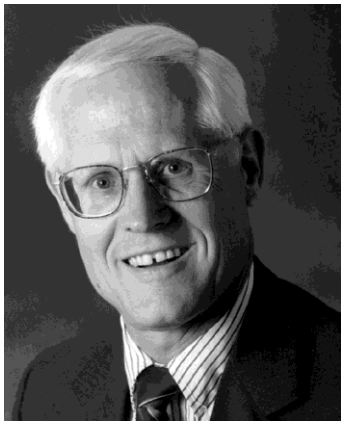
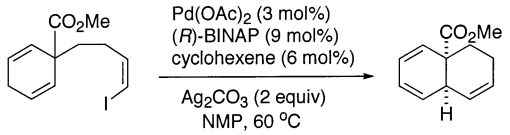
Amy Dounay was born in Englewood, Colorado, in 1974. She received her B.A. in chemistry from Colorado College in 1996, and completed her Ph.D. with Professor Craig J. Forsyth at the University of Minnesota in 2001. Dr. Dounay is currently an NIH Postdoctoral Fellow with Professor Larry Overman.



Larry Overman was born in Chicago, Illinois, in 1943 and raised in Hammond, Indiana. He obtained a B.A. degree from Earlham College in 1965, and completed his doctoral dissertation in 1969 with Professor Howard W. Whitlock, Jr., at the University of Wisconsin. After a NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine, in 1971, where he is now Distinguished Professor of Chemistry. Professor Overman's research interests center on the invention of new reactions and strategies in organic synthesis and the total synthesis of natural products and their congeners. Using synthesis strategies developed largely in his laboratory, Professor Overman's group has completed total syntheses of more than 80 structurally complex natural products.

Scheme 1

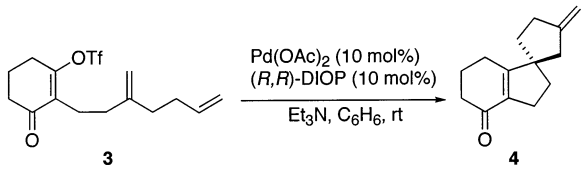


1 **2**

74% (46% ee)

enantioselectivity. To date, BINAP and closely related ligand systems remain the most generally reliable and effective ligands for asymmetric Heck reactions. Despite the modest enantioselectivity achieved in this preliminary study, Shibasaki's results demonstrated for the first time that an intramolecular Heck reaction could be employed for enantioselective construction of tertiary carbon stereocenters. Thus, this landmark report hinted at the potentially enormous synthetic power of the asymmetric variant of the intramolecular Heck reaction.

Scheme 2



3 **4**

90% (45% ee)

During the same year, Overman and co-workers reported the first case of using an asymmetric Heck cyclization for direct formation of a quaternary carbon stereocenter.[5] In this example, trienyl triflate **3** cleanly underwent two sequential Heck cyclizations at room temperature in the presence of $Pd(OAc)_2$, (*R*,*R*)-DIOP, and triethylamine in benzene to afford spirocycle **4** in 90% yield with 45% ee (Scheme 2). As in the Shibasaki report, enantioselectivities observed in this preliminary study were low. Nevertheless, this transformation represented a significant breakthrough in the development of catalytic asymmetric methods for the construction of synthetically demanding quaternary carbon stereocenters.[6]

Since the initial reports of the catalytic asymmetric Heck cyclization, this transformation has become the subject of intensive research efforts worldwide. The asymmetric intramolecular Heck reaction, which first provided low enantioselectivities in the cyclization of relatively simple substrates, has been developed into a powerful tool for the cyclization of complex, polyfunctional substrates, providing polycyclic products with excellent enantioselectivity. The discussion herein of the asymmetric Heck cyclization and its applications in natural product synthesis is intended to describe the evolution of the reaction to its current state. Furthermore, the detailed discussion of reaction conditions, mechanisms, and scope and limitations is designed to provide a practical guide for the synthetic chemist.

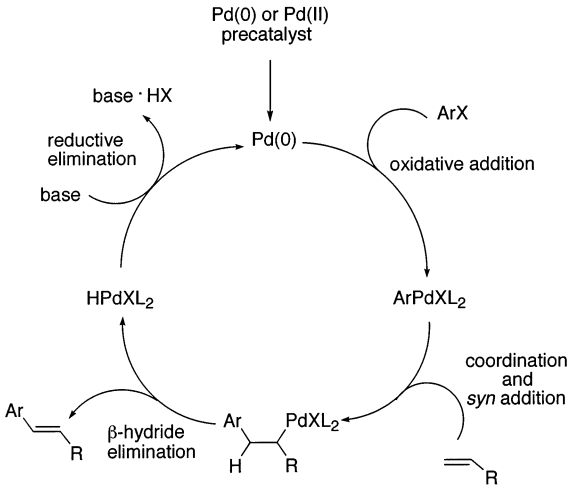
2.2. Heck Reaction Mechanism

The general mechanism for the Heck reaction has been widely accepted for many years; however, numerous recent and ongoing studies are revealing subtle mechanistic details of this transformation. Recent reviews on this topic provide a thorough discussion of mechanistic investigations of the Heck cyclization.[7] A brief overview of the Heck reaction mechanism is provided here.

The basic mechanism for the Heck reaction of aryl halides or perfluorosulfonates, as outlined in Scheme 3, involves initial oxidative addition of a Pd(0) catalyst to afford a σ-arylpalladium(II) complex. The order of reactivity for the oxidative addition step, and typically for the overall reaction, is X = I > OTf > Br $\gg$ Cl.[8] Coordination of an alkene and subsequent carbon−carbon bond formation by syn addition provide a σ-alkylpalladium(II) intermediate, which readily undergoes β-hydride elimination to release the alkene Heck product. A base is required for conversion of the hydridopalladium(II) complex to the active Pd(0) catalyst to complete the catalytic cycle.

The mechanism outlined in Scheme 3 provides a general description of the steps required for catalytic

Scheme 3



olefination; however, numerous studies of this transformation have suggested that this "textbook" diagram represents a vast oversimplification of the processes involved in the asymmetric Heck reaction. To account for the differences in reactivity and enantioselectivity observed in the Heck reactions of unsaturated triflates and halides, two distinct mechanistic pathways, termed "cationic" and "neutral", have been proposed. The names of these pathways describe the formal charge on the first-formed palladium(II)−alkene complex of each pathway.

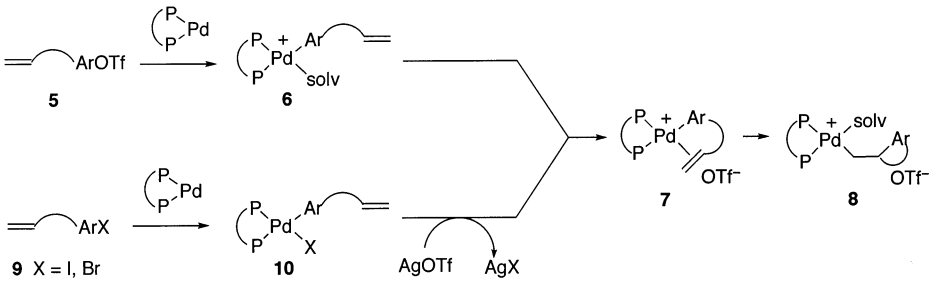
2.2.1. Cationic Pathway

The cationic reaction manifold was first proposed independently by Cabri[9] and Hayashi[10] to describe the Heck reactions of aryl triflates in the presence of palladium−diphosphine catalysts. This pathway is now generally invoked to describe asymmetric Heck reactions of unsaturated triflates, or halides in the presence of Ag(I) or Tl(I) additives; it is illustrated in Scheme 4 for the palladium−diphosphine-catalyzed intramolecular Heck cyclization of an unsaturated aromatic substrate. Oxidative addition of the Pd(0) catalyst is followed by either triflate dissociation or halide abstraction[11] by Ag(I) or Tl(I) salts to vacate a coordination site on the Pd(II) complex, thus permitting coordination of the pendant alkene (**7**).[12] In the cationic manifold, both phosphorus atoms of the chiral diphosphine ligand remain coordinated to the palladium center throughout the alkene coordination and migratory insertion steps. Either of these steps could be the enantiodifferentiating step of the asymmetric carbon−carbon bond formation.[13] Partial dissociation of the chiral ligand would diminish rigidity of the ligand and could lead to erosion of enantioselectivity. Thus, the cationic mechanism is consistent with the enhanced enantioselectivity typically achieved in the asymmetric Heck reactions of unsaturated halides by the addition of Ag(I) or Tl(I) salts.

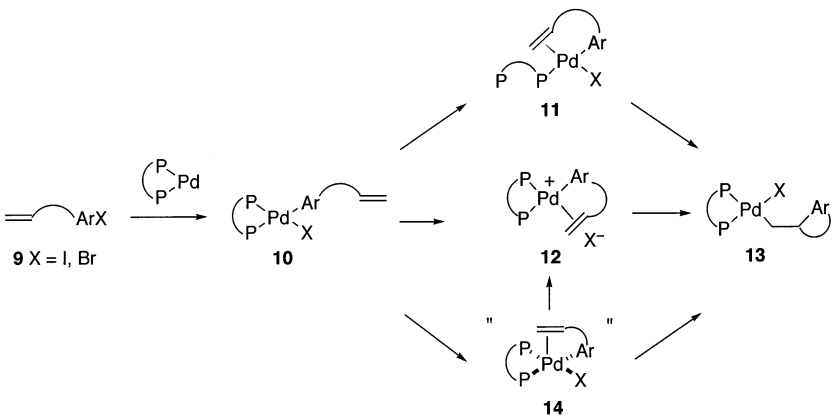
2.2.2. Neutral Pathway

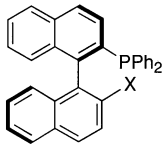
In the absence of additives such as Ag(I), the Heck reaction of unsaturated vinyl or aryl halides is expected to proceed through a neutral reaction manifold, as depicted for the intramolecular reaction of an aryl halide in Scheme 5. The modest enantioselectivity often observed in Heck reactions of this type has been attributed to the formation of a neutral palladium−alkene complex by partial ligand dissociation (**10** → **11**). However, as first reported by Overman and co-workers in 1992, the Pd/BINAP-catalyzed Heck cyclizations of certain aryl halide substrates proceed with high enantioselectivity *without halide scavengers* (vide infra, section 4.3.1).[14]

Scheme 4



Scheme 5





15 X = OTBS
16 X = O*i*-Pr
17 X = $OCHPh_2$
18 X = CO_2Me

Figure 1.

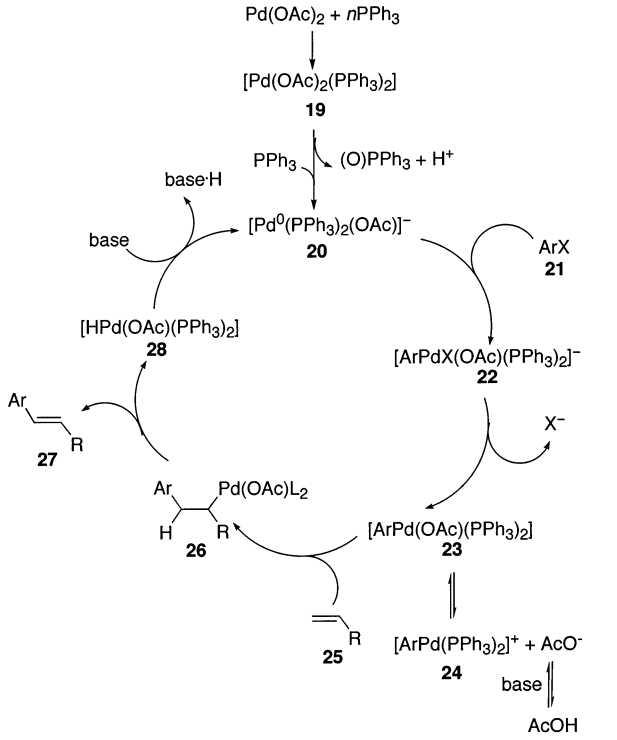
With these substrates, using monophosphine analogues of BINAP (**15**−**18**, Figure 1) to mimic the formation of the partially dissociated complex **11** led to the formation of Heck products in low enantiopurity. These results support the conclusion that, at least with some substrates, both phosphines remain bound to palladium during the enantioselective step in the neutral manifold Heck reactions with BINAP.[15]

To date, a complete understanding of the enantioselective Heck cyclization by a neutral reaction manifold remains elusive. Direct halide ionization and alkene coordination (**10** → **12**) has been excluded as a possible pathway for this transformation, as different results are obtained when the reaction is conducted under cationic and neutral conditions. Alternatively, because substitution on square planar Pd(II) complexes can occur by associative processes,[16] formation of complex **14** by initial axial coordination of the pendant alkene seems feasible. Reports of other isolated and characterized pentacoordinate Pd(II) complexes lend support to the proposed intermediacy of a complex such as **14**.[17] Both theoretical[18] and experimental data[19] suggest that direct migratory insertion by a pentacoordinate intermediate such as **14** is unlikely due to high activation energies. Therefore, for cases in which aryl halide substrates react with high enantioselectivity without halide scavengers, the proposed neutral pathway is **10** → **14** → **12** → **13**. The enantioselective step of the neutral pathway most likely occurs during formation of the cationic intermediate **12** by associative halide displacement (**10** → **14** → **12**).[15]

2.2.3. Anionic Pathway

Recent studies by Amatore and Jutand have shown that the ligand on the palladium precatalyst can profoundly influence the mechanism of Heck reactions.[20] Whereas the acetate anion derived from $Pd(OAc)_2$ precatalysts had been considered a bystander ligand, which does not participate directly in the catalytic reaction, experimental evidence now shows that the commonly used mixture of $Pd(OAc)_2$ and phosphine ligands initiates a catalytic cycle involving anionic Pd(0) and Pd(II) intermediates (Scheme 6). The Pd(0) catalyst generated in situ from $Pd(OAc)_2$ and PPh_3 is an anionic species, $[Pd(PPh_3)_2(OAc)]^-$ (**20**). Oxidative addition of this catalyst to PhI does not afford $[PhPdI(PPh_3)_2]$ as previously postulated, but instead gives a pentacoordinated complex, $[PhPdI(OAc)(PPh_3)_2]^-$ (**22**), in which both the acetate and iodide ions remain coordinated to the Pd(II) center.[21] This short-lived intermediate loses the halide ion to yield a new Pd(II) complex, *trans*-$[PhPd(OAc)(PPh_3)_2]$ (**23**). The increased reactivity of $[PhPd(OAc)(PPh_3)_2]$ compared to that of $[PhPdI(PPh_3)_2]$ has been attributed to the bidentate nature of the acetate ligand, which may assist in phosphine release to open a coordination site for the alkene substrate. Migratory insertion provides the σ-alkylpalladium complex **26**, which undergoes β-hydride elimination to yield alkene product **27** and hydridopalladium complex **28**. Deprotonation of **28** regenerates Pd(0) species **20**, thus completing the catalytic cycle. The proposed anionic mechanism illustrates the crucial role of acetate ions and provides an explanation for the observed effect of additives such as KOAc in Heck reactions.

Scheme 6

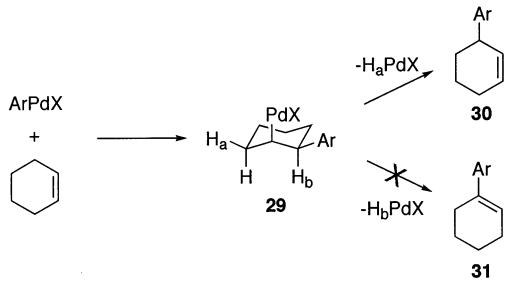


Related studies of the formation and reactivity of Pd(0) complexes derived from $Pd(OAc)_2$ and the bidentate phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) have also been reported.[22] A stable Pd(0) complex is formed from $Pd(OAc)_2$ in the presence of 2 equiv of dppp, water, and triethylamine. In this case, the oxidative addition of active catalyst to PhI generates the cationic complex $[PhPd(dppp)(dppp(O))]^+$, in which dppp(O) serves as a monodentate ligand. The Pd(II) complex bearing an acetate ligand, [PhPd(OAc)(dppp)], is formed only in the presence of added AcO^-. These latter results suggest that the anionic pathway could be relevant to asymmetric Heck reactions employing diphosphine ligands when acetate additives are employed.

2.3. Scope and Limitations

Control over regioselectivity in the formation of the new C−C σ-bond is required to utilize the Heck reaction effectively in complex molecule synthesis. For intramolecular Heck reactions, regiocontrol in the migratory insertion step is largely governed by the size of the ring being formed,[2] with 5-exo and 6-exo cyclizations being particularly favored. Poor regio-

Scheme 7



selectivity in the β-hydride elimination step limits the use of the asymmetric Heck reaction for construction of tertiary stereocenters. Whereas a mixture of regioisomeric products typically results from Heck insertions of acyclic alkenes, the use of cyclic alkenes as Heck substrates prevents the formation of the undesired substitution product during the β-hydride elimination step. As illustrated by the example in Scheme 7, stereospecific syn addition of an arylpalladium species to a cyclic alkene such as cyclohexene produces a σ-alkylpalladium(II) intermediate (**29**) bearing a single syn β-hydrogen (H_a). Syn elimination of this hydrogen provides **30**, preserving the newly formed tertiary center. An alternate approach, introduced by Tietze and co-workers, employs allyl silanes to control β-elimination in acyclic systems (see section 3.1.3).

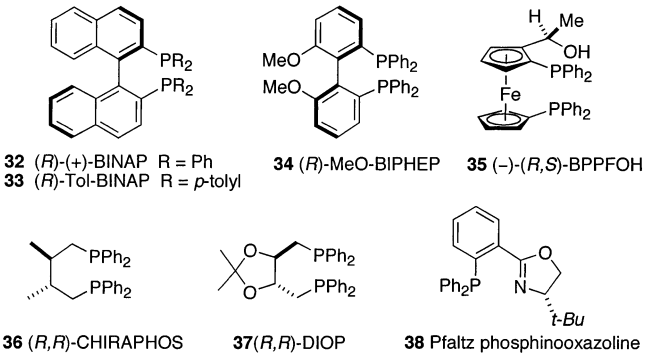
An additional concern arises from potential reversibility of the β-hydride elimination step, which introduces the possibility that the hydridopalladium(II) species produced initially upon β-hydride elimination could re-add across the initially generated double bond. Depending upon the regio- and stereochemistry of this hydropalladation step, subsequent β-hydride elimination could regenerate either the initial Heck product or a regioisomer. The use of low reaction temperatures[23] or additives such as silver salts has been shown to minimize this type of alkene isomerization in several cases.[24]

2.4. Experimental Conditions

The development of efficient, enantioselective Heck reaction conditions for a particular substrate generally requires optimization of a variety of reaction parameters. Asymmetric Heck reactions, which typically employ phosphine ligands, must be conducted under an inert atmosphere (nitrogen or argon) using degassed solvents, because phosphines are readily oxidized to phosphine oxides in the presence of oxygen and palladium.[25] Standard laboratory glassware can be used; however, as a convenient alternative, sealable Schlenk tubes are frequently used for heating reaction mixtures to elevated temperatures for prolonged reaction times with rigorous exclusion of oxygen.

2.4.1. Precatalysts

A variety of Pd(II) and Pd(0) complexes serve as effective precatalysts, or precursors to the active Pd(0) catalyst. The most commonly used precatalysts in asymmetric Heck chemistry are $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd_2(dba)_3{\cdot}CHCl_3$, all of which are commercially available and air stable. Typical catalyst loadings range from 5 to 10 mol % palladium. Recent studies by Amatore and Jutand have demonstrated that 2.0 equiv of diphosphine ligand is required per equivalent of Pd when $Pd(OAc)_2$ is used as a precatalyst, because 1 equiv of ligand is consumed in the reduction of the Pd(II) precatalyst to the Pd(0) catalyst species.[22]



32 (*R*)-(+)-BINAP R = Ph
33 (*R*)-Tol-BINAP R = *p*-tolyl
34 (*R*)-MeO-BIPHEP
35 (–)-(*R,S*)-BPPFOH
36 (*R,R*)-CHIRAPHOS
37(*R,R*)-DIOP
38 Pfaltz phosphinooxazoline

Figure 2.

Although most mechanisms written for the Heck reaction indicate the active Pd(0) diphosphine catalyst in a generic representation and omit altogether the ligands derived from the palladium precatalyst, these "spectator" ligands can play a significant role in the Heck reaction. The important role of acetate ions in Heck reactions that employ $Pd(OAc)_2$ as a precatalyst was discussed previously.[20] Dibenzylidene acetone (dba) can also play a role.[26] For example, Amatore and Jutand have shown that mixtures of $Pd(dba)_2$ and BINAP afford Pd(dba)(BINAP), which is sluggish in oxidative addition reactions with PhI.[26a] Likewise, Pregosin and co-workers have shown that Pd(dba)(MeO-BIPHEP) undergoes oxidative addition to aryl triflates and halides more sluggishly than the Pd(0) catalyst generated by reduction of $PdCl_2$(MeO-BIPHEP) with $NaBH_4$.[26c]

2.4.2. Ligands

A variety of chiral phosphine ligands have been used to effect asymmetric Heck reactions (Figure 2). BINAP (**32**) has been employed most widely to date. Oxidative addition is favored by basic ligands and by bidentate ligands having a small bite angle.[26a] Amatore and Jutand have demonstrated that the catalyst obtained from $Pd(dba)_2$ and DIOP (**37**) undergoes oxidative addition to PhI at a significantly higher rate than the corresponding catalyst having BINAP as a ligand.[26a] In transformations that require a catalyst more reactive than Pd(BINAP) and related systems, ligands such as **35** provide a useful alternative (vide infra, section 3.2.1).

2.4.3. Additives

Additives play a critical role in many asymmetric Heck reactions. Silver(I) additives have been used to increase the reaction rates in Heck reactions of unsaturated halides, prevent deactivation of the palladium catalyst, minimize alkene isomerization of the Heck products, and dramatically enhance enantioselectivity. Most of these changes are likely due to the fact that silver salts serve as efficient halide

scavengers, facilitating the formation of 16-electron, cationic palladium intermediates, thus diverting the Heck reaction from a neutral to a cationic pathway (vide supra). Although a variety of silver salts have been used as additives in Heck reactions of halide precursors, the most common and effective reagents are Ag_2CO_3, Ag_3PO_4, and silver-exchanged zeolite. Thallium salts (Tl_2CO_3, TlOAc, and $TlNO_3$) have also been used as halide scavengers in Heck reactions, but the high toxicity associated with these reagents makes them a less attractive alternative to silver salts. Recent reports suggest that the use of aqueous DMF−K_2CO_3 as a reaction medium for the Heck reactions of aryl bromides may provide an inexpensive and "green" alternative to the use of Ag and Th additives.[27] As part of a probe of the cationic and neutral reaction manifolds, Overman and Poon examined the use of halides as additives in the asymmetric Heck cyclizations of aryl triflates.[15] Their experiments demonstrated that addition of halide salts to the intramolecular Heck reactions of some unsaturated triflates directs the reactions of aryl triflates from the cationic to the neutral pathway, just as halide scavengers in the Heck reactions of vinyl and aryl halide substrates direct the reactions into the cationic manifold.

Shibasaki and co-workers have reported that the addition of tertiary alcohols such as pinacol or *tert*-butyl alcohol accelerated the Heck cyclizations of vinyl triflates in 1,2-dichloroethane (DCE); potassium acetate produced similar rate enhancements.[28,29] ^{31}P NMR studies suggest that these additives prevent the DCE-promoted oxidation of the catalytically active Pd(0) species to a Pd(II) species.

2.4.4. Bases

A base is required in Heck reactions to neutralize the acid (HX) that is produced when the hydridopalladium(II) species is reduced to regenerate the active Pd(0) catalyst. A stoichiometric amount of base is needed, but in practice, 3−5 molar equivalents are often used. A variety of inorganic bases have been used in asymmetric Heck reactions, with K_2CO_3 and $CaCO_3$ reported most frequently. Tertiary amine bases such as Et_3N, *i*-Pr_2NEt, Proton Sponge, and 1,2,2,6,6-pentamethylpiperidine (PMP) are also commonly employed. Among these, the extremely hindered base PMP has become a favorite choice for asymmetric Heck cyclizations.

2.4.5. Solvents and Temperature

Solvent polarity has been shown to affect enantioselectivity in many asymmetric Heck cyclization reactions. Polar aprotic solvents such as THF, CH_3CN, *N*,*N*-dimethylacetamide (DMA), *N*,*N*-dimethylformamide (DMF), and 1-methyl-2-pyrrolidinone (NMP) are typically used, although benzene, toluene, and DCE are preferred in some cases. Reaction temperatures range from room temperature to over 100 °C.

3. Natural Product Total Synthesis: Formation of Tertiary Stereocenters

3.1. Terpenoids

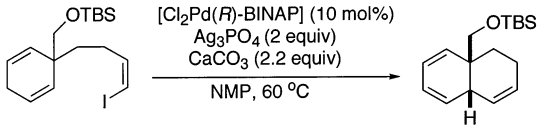
3.1.1. Vernolepin

In their initial report of the intramolecular asymmetric Heck reaction of terminal vinyl iodide **1**, Shibasaki and co-workers found that inorganic bases (e.g., NaOAc) or amine bases (e.g., *i*-Pr_2NH) provided enantioselectivities inferior to those realized with Ag_2CO_3.[4] In a later study of a closely related group-selective cyclization to produce **40**, these workers demonstrated that enantioselectivities observed in this reaction depended upon the counterion of the silver salt, with Ag_3PO_4 providing the best results (Scheme 8).[30] In general, polar solvents such as NMP provided enhancement in enantioselectivites over nonpolar solvents such as toluene. Analogous Heck cyclizations of trisubstituted vinyl iodides provided functionalized *cis*-decalin derivatives in up to 87% ee (Scheme 9).[31]

Ultimately, the greatest improvement in group-selective asymmetric Heck cyclizations to form substituted *cis*-decalins was achieved by the use of vinyl triflates rather than vinyl iodides as substrates (Scheme 10).[31] Treatment of prochiral triflates **43**−**46** with $Pd(OAc)_2$, (*R*)-BINAP, and K_2CO_3 in toluene gave *cis*-decalins **47**−**50** in moderate yields and with excellent enantioselectivities (89−92% ee). The synthesis of the decalin systems from vinyl triflates rather than vinyl iodides offers the two-fold advantage of improved enantioselectivity without the need for stoichiometric amounts of silver salts.

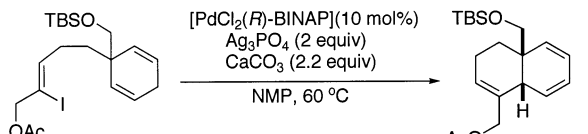
Further optimization of the cyclizations of prochiral vinyl triflates focused on improving the chemical yield by examining the effects of base, solvent, and additives.[28,29] The use of a tertiary amine base (*i*-Pr_2-

Scheme 8



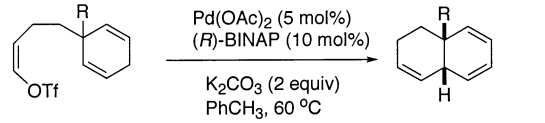
39 **40** 67% (80% ee)

Scheme 9



41 **42** 67% (87% ee)

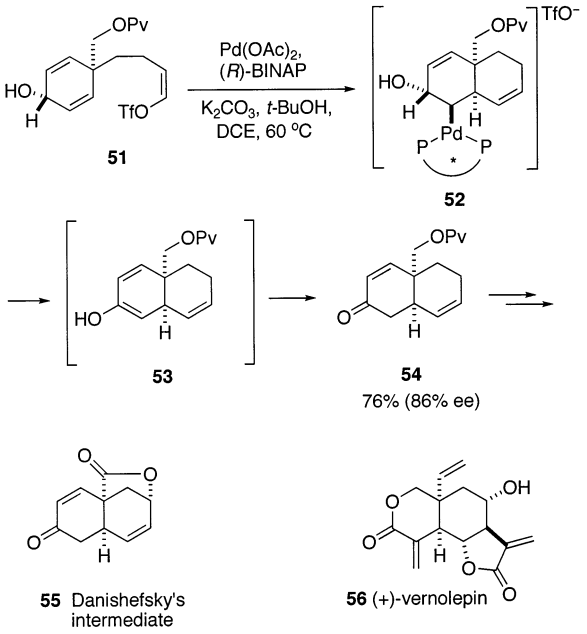
Scheme 10



43 R = CO_2Me
44 R = CH_2OPv
45 R = CH_2OTBS
46 R = CH_2OAc

47 54% (91% ee)
48 35% (92% ee)
49 44% (89% ee)
50 60% (91% ee)

Scheme 11

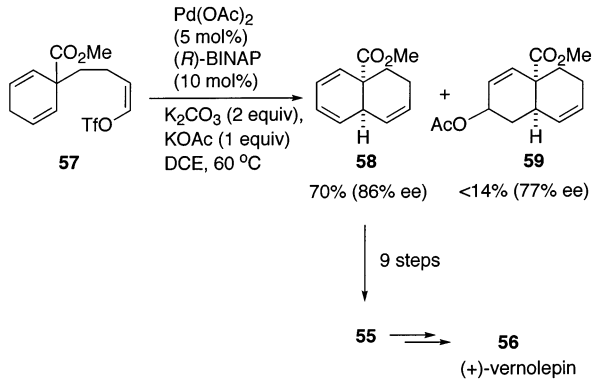


NEt) provided results inferior to those realized with K_2CO_3. In the absence of additives, reactions in toluene provided yields far superior to those obtained in reactions conducted in DCE or polar solvents. However, the addition of either tertiary alcohols (e.g., pinacol) or potassium acetate accelerated the reactions in DCE (vide supra). Use of $Pd(OAc)_2$, (*R*)-BINAP, K_2CO_3, and tertiary alcohol or potassium acetate in DCE for the Heck cyclization of terminal vinyl triflates provided *cis*-decalin products in high yield and up to 95% ee.[29]

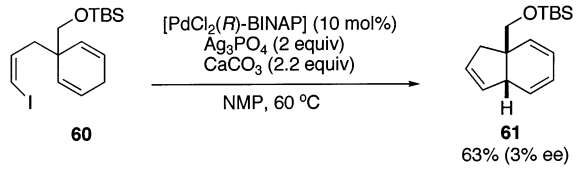
An asymmetric Heck cyclization was used by Shibasaki and co-workers to construct a substituted *cis*-decalin in synthetic efforts directed at (+)-vernolepin.[28,29] Specifically, asymmetric Heck cyclization of vinyl triflate **51** gave enone **54** in 76% yield and 86% ee under optimized conditions (Scheme 11).[28] The use of *tert*-butyl alcohol as an additive in this Heck cyclization was critical in suppressing byproduct formation attributed to the allylic alcohol functionality of triflate **51**. Nine additional steps were required for conversion of enone **54** to lactone **55**, an intermediate in Danishefsky's total synthesis of (±)-vernolepin (**56**).[32]

An alternative Heck cyclization strategy, which begins with a more readily accessible vinyl triflate starting material, was also developed by Shibasaki and co-workers to prepare (+)-vernolepin (Scheme 12).[29] Heck cyclization of prochiral vinyl triflate **57** provided *cis*-decalin **58** in 70% yield and 86% ee; allylic acetate **59**, which likely resulted from trapping of a palladium η^3-allyl intermediate with acetate anion, was formed also. The Heck cyclization product was again transformed in nine steps into Danishefsky's key intermediate (**55**).[32] From this point, lactone **55** was converted to (+)-vernolepin (**56**) according to the Danishefsky route in order to complete the first asymmetric total synthesis and determine the absolute stereochemistry of this natural product.

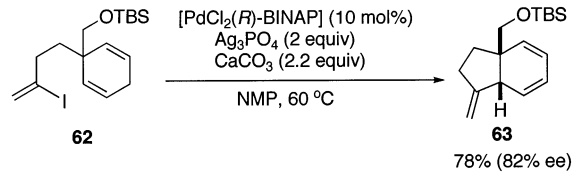
Scheme 12



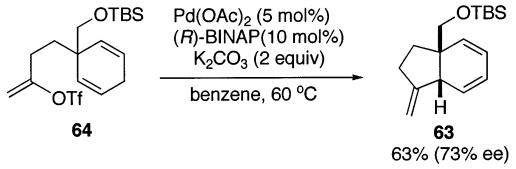
Scheme 13



Scheme 14



Scheme 15

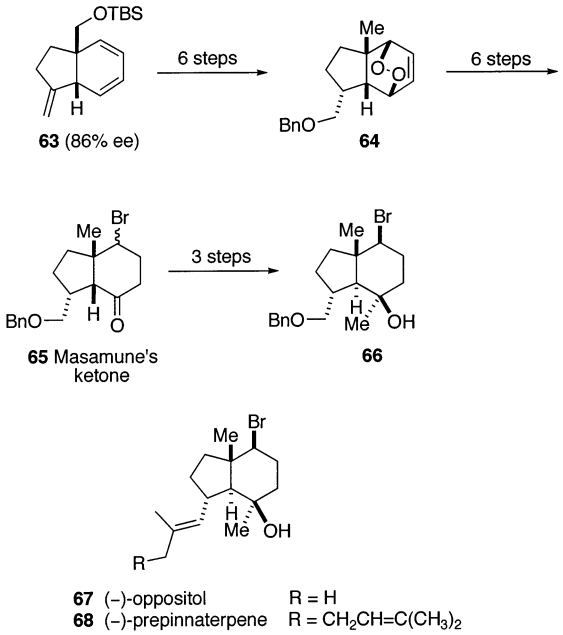


3.1.2. Oppositol and Prepinnaterpene

Extension of the methodology developed for preparing *cis*-decalins to the construction of hyndridane ring systems was accomplished by shortening the tether connecting a vinyl iodide or triflate to a cyclohexadiene.[33] As with the *cis*-decalins, the use of vinyl iodides was investigated first. Preliminary attempts to form bicyclo[4.3.0]nonanes by group-selective Heck cyclization of terminal vinyl iodide **60** delivered the desired product **61** in good yield, but with virtually no enantioselectivity (Scheme 13). Attempts to optimize this reaction proved unsuccessful. However, Heck cyclization of closely related vinyl iodide **62** provided *cis*-hydrindane **63** in 78% yield and 82% ee (Scheme 14), demonstrating that modest structural variation in Heck substrates can markedly affect enantioselectivity. Furthermore, use of a Pd(0) catalyst generated by in situ reduction of [Cl_2Pd(*R*)-BINAP] with cyclohexene provided hyndridane **63** with a slight improvement in enantioselectivity (86% ee vs 82% ee). Heck cyclization of the vinyl triflate analogue of **62** did not require the use of silver salts; however, this reaction delivered **63** in slightly lower yield and enantiopurity (Scheme 15).

This asymmetric route to *cis*-hydrindanes was employed in studies directed at the total syntheses

Scheme 16

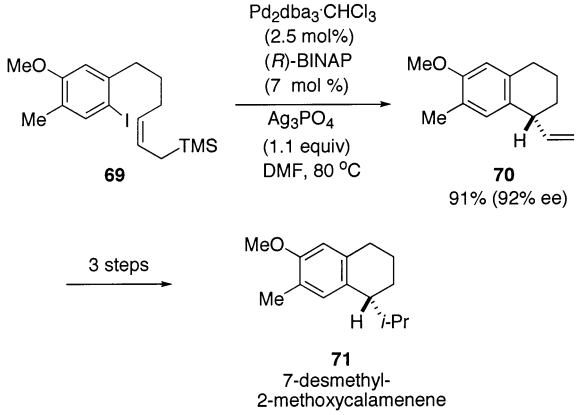


of the brominated terpenes (−)-oppositol and (−)-prepinnaterpene (Scheme 16).[34] To this end, the *cis*-hydrindane derivative **63** was converted to endo peroxide **64** in a six-step sequence that included photooxidation of the cyclohexadienyl moiety. Nine additional steps were required to convert peroxide **64** to alcohol **66**, a late intermediate in Masamune's total syntheses of (±)-oppositol and (±)-prepinnaterpene.[35]

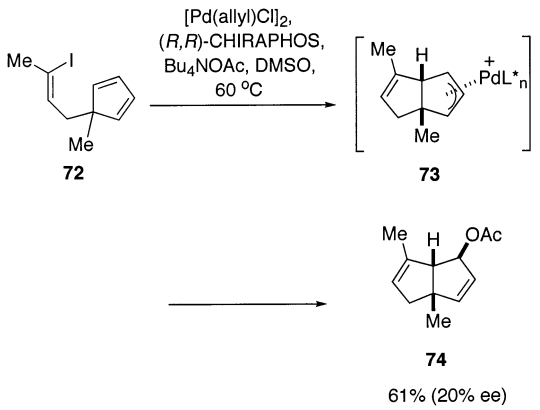
3.1.3. 7-Desmethyl-2-methoxycalamenene

As discussed earlier, one limitation of the Heck reaction is the lack of regioselectivity in the β-hydride elimination step in Heck reactions of acyclic alkenes. Thus, in most cases, the construction of tertiary centers by asymmetric Heck cyclizations has been restricted to the formation of endocyclic alkenes where syn β-hydride elimination is possible in only one direction. However, Tietze and co-workers have demonstrated that regioselective elimination to generate products with acyclic alkene side chains can be realized by using allylsilanes as terminating units in asymmetric Heck cyclizations.[36] For example, treatment of aryl iodide **69** with Pd_2dba_3·$CHCl_3$, (*R*)-BINAP, and Ag_3PO_4 in DMF at 80 °C gave vinyl tetralin **70** in 91% yield and 92% ee (Scheme 17). An analogous Heck precursor lacking the silyl substituent cyclized under identical reaction conditions to afford a mixture of alkene regioisomers. Early investigations of this methodology focused on the use of aryl iodides as Heck precursors; however, more recent investigations explored the use of vinyl iodides and triflates.[37] The applicability of this methodology in natural product synthesis was illustrated by the three-step conversion of **70** to 7-desmethyl-2-methoxycalamenene (**71**),[36b,c] a natural member of the cadinene sesquiterpenoids. Substituted tetrahydroisoquinolines and tetrahydrobenzo[*d*]azepines have also been synthesized in high enantiopurity using related asymmetric Heck cyclization reactions of allylsilanes.[36a]

Scheme 17



Scheme 18



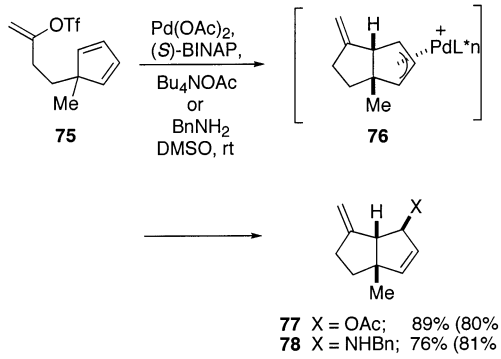
3.1.4. Capnellenols

Shibasaki and co-workers have investigated the utility of the asymmetric intramolecular Heck reaction in the construction of linear triquinanes. These studies led to the first reported tandem asymmetric Heck cyclization−η^3-allyl nucleophilic trapping sequence. The cascade process was initially explored with prochiral trienyl iodide **72** (Scheme 18).[38,39] Heck cyclization of **72** produced η^3-allylpalladium species **73**, which was trapped by an acetate anion at the least hindered terminus of the η^3-allyl system to provide *cis*-bicyclo[3.3.0]octadiene **74** in 60% yield, albeit with a modest 20% ee. Attempts to employ silver salts as halide scavengers in this reaction led to the decomposition of **72**, presumably due to the sensitivity of the cyclopentadienyl moiety. Heck cyclization of prochiral vinyl triflate **75** with $Pd(OAc)_2$, (*S*)-BINAP, and tetrabutylammonium acetate was more productive, giving **77** in excellent yield and 80% ee (Scheme 19). The corresponding allylic amine **78** was obtained in analogous fashion using benzylamine as the nucleophile.[40] Allylic acetate **77** was elaborated in seven steps to triquinane β-keto-ester **79** (Scheme 20), an intermediate in Shibasaki's previous syntheses of (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol (**80**) and (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetraol (**81**).[41]

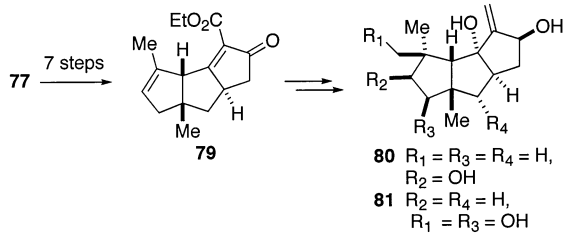
3.1.5. $\Delta^{9(12)}$-Capnellene

The use of soft carbanionic nucleophiles in tandem asymmetric Heck cyclization−η^3-allyl trapping se-

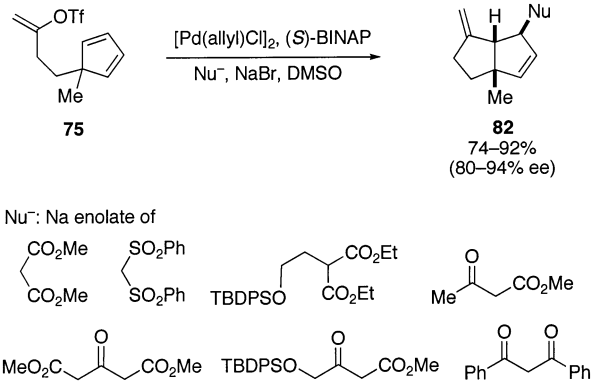
Scheme 19



Scheme 20



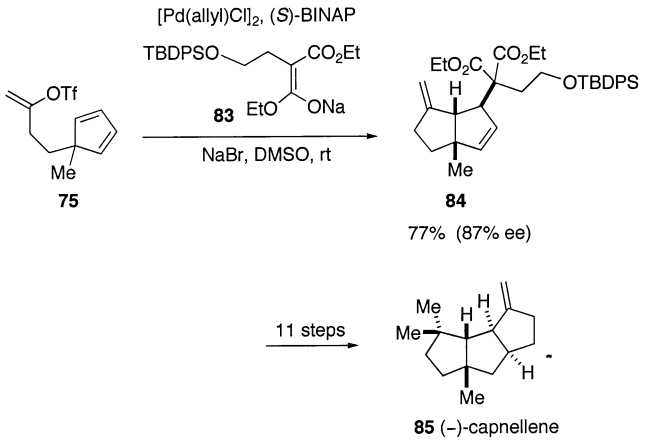
Scheme 21



quences has also been developed by Shibasaki and co-workers (Scheme 21).[42] The viability of this reaction was first demonstrated using the sodium anion of dimethyl malonate as a nucleophile. The generality of this approach was then explored using various soft carbanionic nucleophiles to provide the functionalized bicyclo[3.3.0]octane derivatives **82** in excellent yields (72−92%) and up to 94% ee. In the absence of NaBr, the enantioselectivity of the Heck reaction was significantly diminished. A speculative rationale to account for the effect of the NaBr additive has been advanced.[42]

The use of carbanionic nucleophiles in the Heck cyclization−η^3-allyl nucleophilic trapping sequence allows for streamlined access to the triquinane core common to various members of the capnellene family of natural products.[42] For example, Shibasaki and co-workers obtained **84** in 77% yield and 87% ee by Heck cyclization of **25** in the presence of malonate nucleophile **83** (Scheme 22). It is notable that two new carbon−carbon bonds and three stereocenters are elaborated in this single synthetic step. Only 11 additional steps were required to convert key intermediate **84** to (−)-$\Delta^{9(12)}$-capnellene (**85**). This first catalytic asymmetric total synthesis of (−)-$\Delta^{9(12)}$-

Scheme 22



capnellene was achieved in 19 steps and 20% overall yield from commercially available materials.

3.2. Alkaloids

3.2.1. Lentiginosine and Gephyrotoxin 209D

Catalytic asymmetric Heck cyclizations have been employed in numerous ways for asymmetric construction of chiral nitrogen heterocycles. For example, Shibasaki and co-workers have described the asymmetric Heck cyclization of *N*-allylpyridones to give simple unsaturated indolizidines in useful enantiopurity.[43] Initial attempts to effect enantioselective cyclization of dihydropyridone vinyl iodide **86** using Pd/BINAP in the presence of Ag_3PO_4 gave a mixture of unsaturated indolizidine isomers **87** and **88** (Scheme 23). The minor isomer **87** could be converted quantitatively to the major α,β-unsaturated lactam product **88** by subsequent reaction of the former with catalytic Pd/C in MeOH. Surprisingly, despite the demonstrated efficacy of BINAP ligands in related carbocyclic systems, the Pd/BINAP-catalyzed Heck cyclization of **86** proceeded slowly even at 90 °C, and indolizidine **88** was obtained in only 34% ee (Table 1, entry 1). A survey of other chiral diphosphine ligands demonstrated that the optimum ligand for

Scheme 23

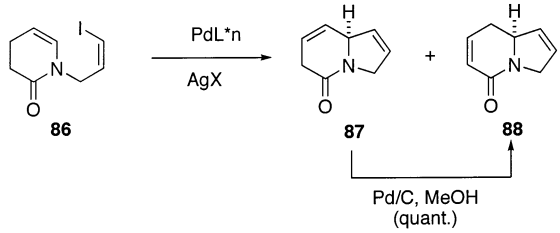
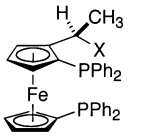


Table 1. Ligand Effects on the Cyclization of 86[a]

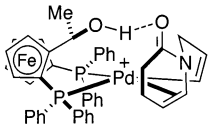
entry	ligand	temp (°C)	time (h)	ratio of **87**:**88**	yield (%)	ee of **88** (%)
1	(*R*)-BINAP	90	46	1:3.3	67	34 (*R*)
2	**35b**	50	8.5	1:5.5	79	45 (*S*)
3	**35a**	50	14	1:12	62	52 (*S*)
4	**35**	50	35	0:1	45	74 (*S*)

[a] Vinyl iodide **86** was treated with Pd_2dba_3·$CHCl_3$ (5 mol % Pd), ligand (12 mol %), Ag_3PO_4 (2 equiv), and $CaCO_3$ (2.2 equiv) in DMF.



35 (*R*)-(*S*)-BPPFOH (X = OH)
35a (*R*)-(*S*)-BPPFOAc (X = OAc)
35b (*R*)-(*S*)-BPPFA (X = NMe_2)

Figure 3.



89

Figure 4.

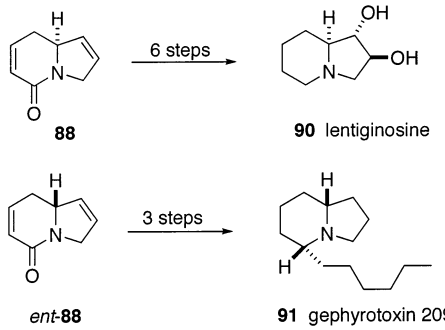
this transformation was (*R*)-(*S*)-BPPFOH (**35**),[44] which gave **88** as the only product in 45% yield and 74% ee (entry 4). The structurally similar BPPFA and BPPFOAc ligands (Figure 3) imparted somewhat lower enantiocontrol in this transformation. Hydrogen bonding of the hydroxyl group of ligand **35** with the pyridone carbonyl group was suggested to account for the higher enantioselection observed with this ligand (Figure 4); however, in energetic terms, the differences in enantioselectivities observed with the ligands depicted in Figure 3 are small. The vinyl triflate analogue of **86** was not examined, as it could not be prepared from an aldehyde precursor because of competitive reaction of the dihydropyridone.

Further optimization of the Heck cyclization of **86** focused on the effects of solvent, silver salt, and temperature on asymmetric induction. In contrast to the previously described results for assembly of carbocyclic systems, solvent polarity did not have a significant effect on enantioselectivity in the formation of indolizidine **88**. Whereas the use of DMSO as solvent led to diminished enantioselectivity in cyclizations to form decalins, it proved to be a good solvent for this indolizidine synthesis. Thus, Heck cyclization of **86** in DMSO using Ag_3PO_4 as a halide scavenger afforded **88** in high yield and up to 81% ee. A survey of silver salts demonstrated that silver-exchanged zeolite in 1:1 DMSO−DMF provided the best results, giving **88** in up to 94% yield and 86% ee at low temperatures (0 °C), although rather long reaction times (5 d) were required. The utility of indolizidine intermediate **88** in natural product synthesis was demonstrated by conversion of **88** to lentiginosine (**90**) and gephyrotoxin 209D (**91**) (Scheme 24).[45]

3.2.2. 5-Epiindolizidine 167B and 5E,9Z-indolizidine 223AB

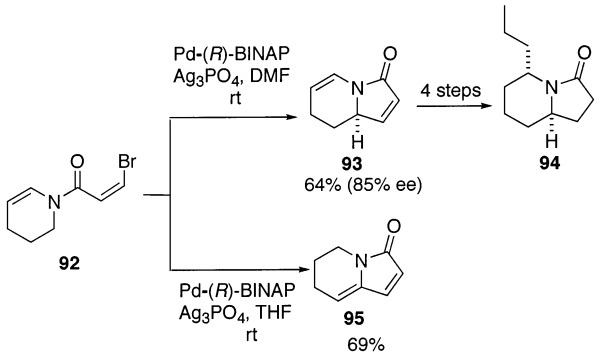
Sulikowski and co-workers have also reported enantioselective Heck cyclizations of enamides, in this case of acylated tetrahydropyridine precursors (Scheme 25).[46] In these studies, the selection of solvent proved to be critical for conversion of **92** to a chiral indolizidine derivative. Whereas Heck cyclization of vinyl bromide **92** using Pd/BINAP and Ag_3PO_4 in DMF at room temperature delivered enamide **93** in 85% ee, use of THF as solvent yielded only the

Scheme 24



88 **90** lentiginosine
ent-**88** **91** gephyrotoxin 209D

Scheme 25



92 **93** 64% (85% ee) **94** **95** 69%

achiral indolizidine **95**. In neither case was the initial Heck product observed. The role of the solvent in promoting isomerization of the initially formed Heck product to give either **93** or **95** is not clear. Unsaturated indolizidine **93** was converted in four steps to **94**, a common intermediate in total syntheses of two indolizidine alkaloids: 5-epiindolizidine 167B[47] and 5*E*,9*Z*-indolizidine 223AB.[48]

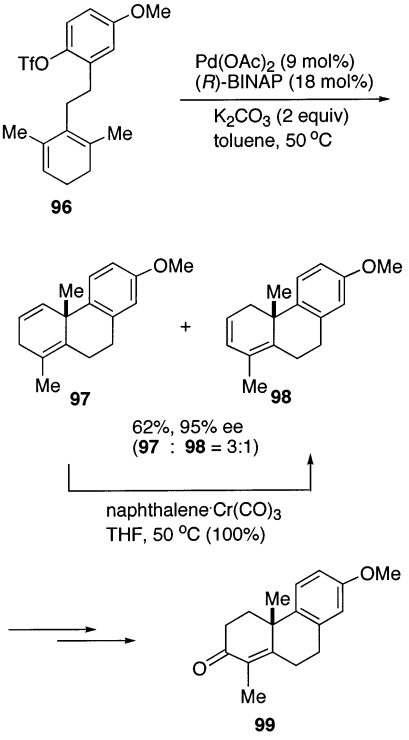
4. Natural Product Total Synthesis: Formation of Quaternary Stereocenters

4.1. Terpenoids

4.1.1. Kaurene and Abietic Acid

The initial report by Overman and co-workers on the use of asymmetric Heck cyclizations for the enantioselective construction of all-carbon quaternary stereocenters[5] has been followed by many additional examples of constructing rings and setting quaternary stereocenters in this fashion. Shibasaki and co-workers have studied the formation of quaternary benzylic stereocenters by asymmetric Heck cyclizations in the context of synthesis of tricyclic diterpenes.[49] In these studies, the readily available aryl triflate **96** underwent regio- and enantioselective Heck cyclization to provide a mixture of hydrophenanthrenes **97** and **98** in 62% yield and high enantiomeric purity (Scheme 26). Although both 5-exo and 6-exo cyclizations are generally favorable, only fused products resulting from 6-exo cyclization were observed. The authors propose that severe steric repulsion in the 5-exo transition state prevents formation of spirocyclic products; the reluctance of tetrasubstituted double bonds to coordinate to palladium(II) is an alternate rationale. Quantitative

Scheme 26



conversion of nonconjugated diene **97** to its conjugated isomer **98** was achieved by treating the isomeric mixture with catalytic amounts of naphthalene·CrO_3. Diene **98** then was transformed over several steps to enone **99**, an intermediate that previously had been employed in total syntheses of the tricyclic diterpenes (±)-kaurene (**100**)[50] and (±)-abietic acid (**101**)[51] (Figure 5).

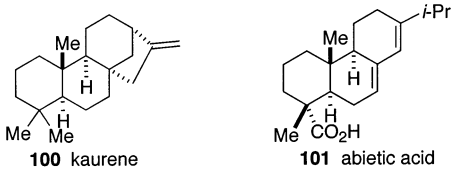
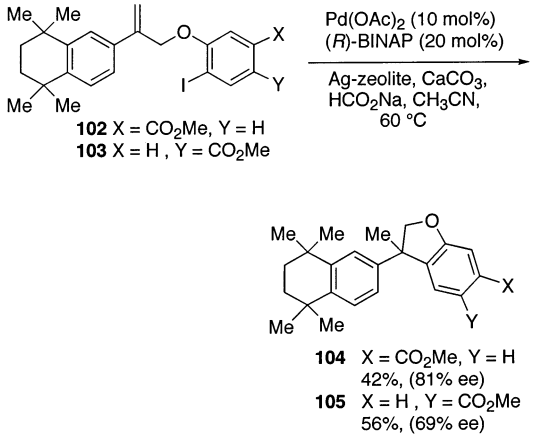


Figure 5.

4.1.2. Retinoids

Diaz and co-workers employed a tandem asymmetric Heck cyclization−hydride capture reaction in the synthesis of conformationally restricted retinoids bearing benzylic quaternary stereocenters (Scheme 27).[52] A variety of aryl iodides were surveyed for this transformation. For example, upon reaction with Pd(OAc)$_2$, (*R*)-BINAP, Ag-exchanged zeolite, $CaCO_3$, and sodium formate in acetonitrile, aryl iodide **102** produced **104** in moderate yield and good enantioselectivity. Modification of the substitution pattern about the aryl iodide resulted in a slight improvement in yield (**103** → **105**), albeit with a reduction of enantioselectivity. Poor stereoselectivities were observed when cyclizations of this type were conducted under "neutral" rather than "cationic" conditions. In these transformations, the σ-bonded palladium intermediate generated upon 5-exo cyclization cannot undergo β-hydride elimination; thus, a hydride source (e.g., HCO_2Na) is required to reduce this intermediate and regenerate the Pd(0) catalyst.

Scheme 27



4.2. Polyketides

4.2.1. Halenaquinone and Halenaquinol

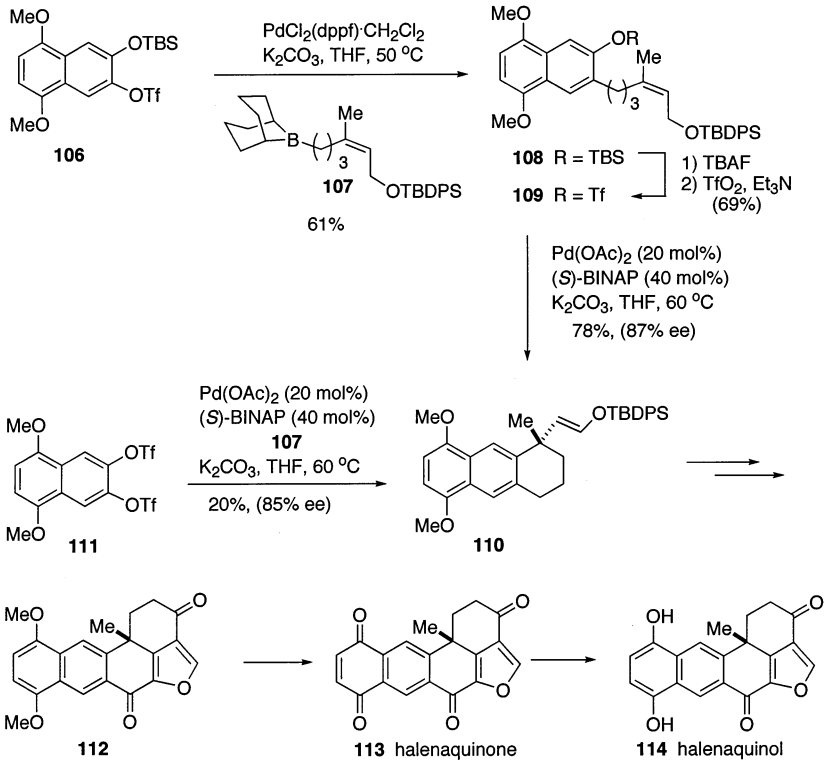
As an extension of their investigations of the utility of intramolecular Heck reactions for forming quaternary benzylic stereocenters, Shibasaki and co-workers studied cyclizations of alkenyl naphthyl triflates (Scheme 28). The products of intramolecular Heck transformations of this type represent useful intermediates for the syntheses of polyaromatic polyketide natural products such as halenaquinone (**113**) and halenaquinol (**114**).[53] Naphthyl triflate **109**, which was derived from Suzuki coupling of naphthalene derivative **106** with alkyl borane **107**, was cyclized using conditions that had become nearly standard for Heck reactions of aryl triflates [Pd(OAc)$_2$, (*S*)-BINAP, K_2CO_3, THF] to provide tetrahydroanthracene **110** in 78% yield and 87% ee.

Alternatively, **110** could be obtained directly from bis-triflate **111** by a cascade Suzuki cross-coupling and asymmetric Heck reaction. In this case, treatment of bis-triflate **111** with alkyl borane **107**, Pd(OAc)$_2$, (*S*)-BINAP, and K_2CO_3 in THF at 60 °C gave **110** in high enantiopurity, albeit in 20% yield. Although the yield for the one-pot transformation of **111** to **110** was poor, this conversion represents a novel application of the asymmetric Heck cyclization and remains the only reported example of tandem Suzuki cross-coupling−asymmetric Heck cyclization. A series of additional synthetic transformations was required to transform **110** to Harada's[54] pentacyclic intermediate **112**, which was readily converted to halenaquinone (**113**) and halenaquinol (**114**).

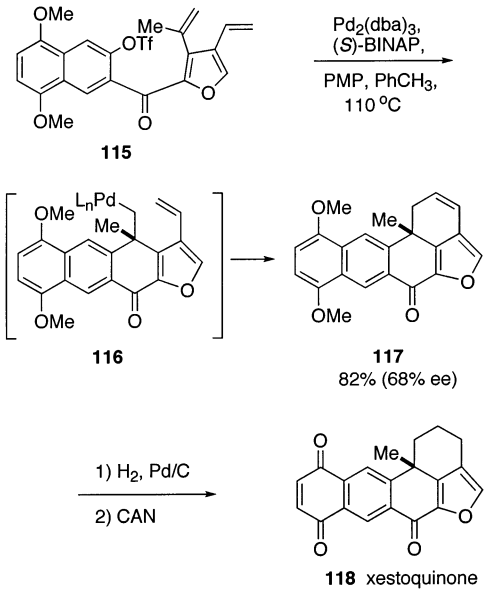
4.2.2. Xestoquinone

Keay and co-workers have reported the use of a cascade double Heck cyclization as the pivotal step in the asymmetric total synthesis of xestoquinone, a reduced congener of halenaquinone (Scheme 29).[55] In this step, naphthyl triflate **115** was cyclized with Pd$_2$(dba)$_3$, (*S*)-BINAP, and PMP in toluene at 110 °C to give the pentacyclic product **117** in excellent yield and 68% ee. This conversion proceeds by initial asymmetric 6-exo Heck cyclization to form the central

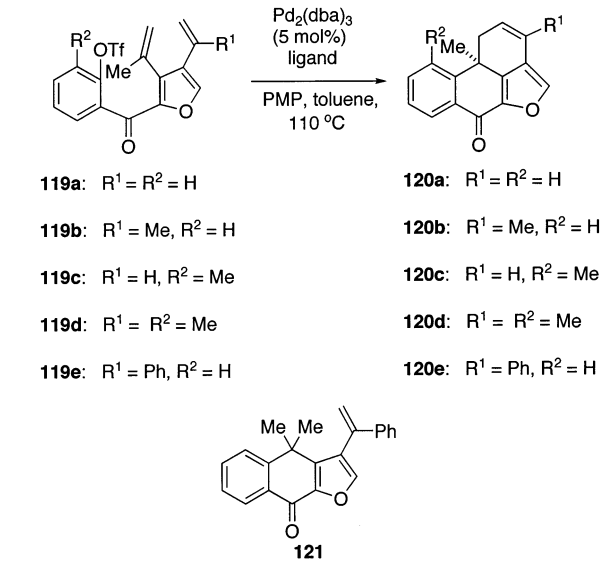
Scheme 28



Scheme 29



Scheme 30



six-membered carbocycle and install the benzylic quaternary stereocenter, followed by a second Heck cyclization, this time of neopentyl organopalladium intermediate **116**, to form the final ring of the pentacyclic product. The second insertion occurs in a 6-endo sense, because the typically favored 5-exo cyclization would be disfavored by developing ring strain. As has been seen in many other cases, the use of the aryl triflate derivative was critical to the success of this reaction. Attempts to effect the analogous Heck cyclization of the aryl bromide analogue met with little success, as the desired product was obtained in low enantiopurity (5−13% ee) under either neutral (PMP) or cationic (Ag_3PO_4) conditions. Following the asymmetric polyene cyclization of **115**, only reduction of the alkene and oxidation of the aromatic system were required to complete the first enantioselective synthesis of xestoquinone (**118**).

Efforts by Keay and co-workers to extend their cascade asymmetric Heck cyclization to the synthesis of halenaquinone led to an exploration of the effect of remote substituents on the enantioselectivity of the transformation.[56] These studies demonstrated that the presence of a methyl substituent on the distal alkene (R^1) improved enantioselectivity in forming the benzylic quaternary center (Scheme 30 and Table 2, entries 1 and 2). Likewise, the presence of a methyl group ortho to the triflate (R^2) resulted in enhanced

Table 2

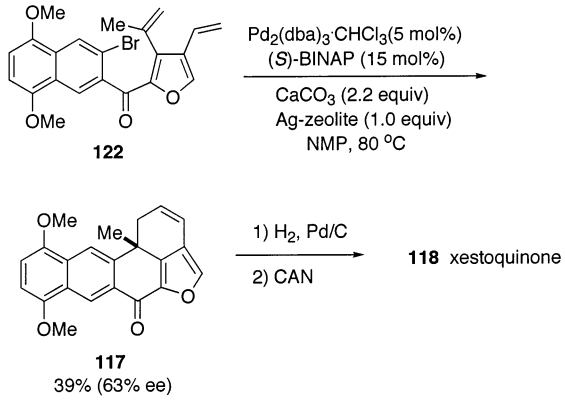
entry	substrate	ligand	product	yield (%)	ee (%)
1	**119a**	(*R*)-BINAP	**120a**	83	71 (*R*)
2	**119b**	(*R*)-BINAP	**120b**	78	90 (*R*)
3	**119b**	(*R*,*R*)-CHIRAPHOS	**120b**	61	24 (*S*)
4	**119c**	(*R*)-BINAP	**120c**	71	96 (*R*)
5	**119d**	(*R*)-BINAP	**120d**	68	71 (*R*)
6	**119e**	(*R*)-BINAP	**120e** + **121** (1:13)	91	
7	**119e**	(*R*,*R*)-CHIRAPHOS	**120e**	66	77 (*S*)

enantiocontrol (entry 4). Unfavorable steric interactions apparently exist when both R^1 and R^2 are methyl, as enantioselectivity is significantly lower in the cyclization of **119d** (entry 5). It is surprising that the desired reaction pathway is almost completely shut down when substrate **119e** having R^1 = phenyl is cyclized using (*R*)-BINAP as the ligand (entry 6), with the major product in this case being tricyclic ketone **121**. It is suggested that unfavorable interactions between the phenyl substituent and the BINAP ligand disfavor the intermediate neopentyl palladium alkyl from coordinating to the styrene side chain, allowing a competitive hydride-transfer process to dominate. Use of (*R*,*R*)-CHIRAPHOS as a chiral ligand for this transformation tips the balance to favor formation of the tetracyclic product **120e** (entry 7). More recent studies suggest that BINAPFu[57] may be a useful ligand for this cascade cyclization reaction.[58]

Recent investigations by Keay and co-workers examined in more detail the effects of various solvents and bases on Pd/BINAP-catalyzed polycyclizations to form tetracyclic products **120a** and **120e**.[58] These studies demonstrate that the use of dioxane as solvent or PMP as base promotes formation of the undesired tricyclic product because both reagents can serve as hydride donors. Further experiments showed that DABCO, which is an ineffective hydride donor due to its bridged structure, can be substituted for PMP to reduce formation of byproduct **121** without significant loss of enantioselectivity. Likewise, the use of toluene rather than dioxane as the solvent for these asymmetric polyene cyclization reactions maximizes the conversion to the desired tetrayclic products.

Following the report by Keay and co-workers that naphthyl bromides were poor substrates in the catalytic asymmetric polyene cyclization to form pentacycle **117**, Shibasaki and co-workers reported improved reaction conditions for this problematic transformation.[59] Treatment of naphthyl bromide **122** with $Pd_2(dba)_3{\cdot}CHCl_3$, (*S*)-BINAP, $CaCO_3$, and Ag-exchanged zeolite (1.0 equiv) in NMP at 80 °C afforded **117** with 63% ee, albeit in only 39% yield (Scheme 31). When 2 or 6 equiv of Ag-exchanged zeolite was used, both yield and enantioselectivities were diminished. Furthermore, as in previous examples, higher yields and superior enantioselectivies were achieved using Ag-exchanged zeolite as a halide scavenger rather than the more commonly used Ag_3PO_4. Following the conversion of **122** to **117** under

Scheme 31



the newly optimized reaction conditions, Shibasaki and co-workers were also able to convert this intermediate to xestoquinone (**118**) according to the Keay protocol.

4.2.3. Wortmannin

Shibasaki and co-workers have reported preliminary investigations toward a synthesis of the synthetically more formidable pentacyclic polyketide, wortmannin (**123**, Figure 6).[60,61] In a crucial step of the proposed synthesis of this natural product, an asymmetric Heck cyclization of a racemic dienyl hydrindane triflate would install the allylic quaternary carbon stereocenter and effect a kinetic resolution of this key intermediate (Scheme 32). Heck cyclization of **124** with catalysts having achiral ligands first demonstrated that a bidentate phosphine ligand such as 1,3-bis(diphenylphosphino)-propane (DPPP) could be used to achieve a high level of diastereoselectivity (**125**:**126** = 17:1, 90% yield) in this pivotal transformation. A series of chiral biden-

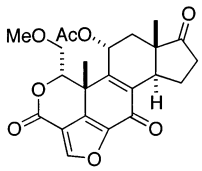


Figure 6.

Scheme 32

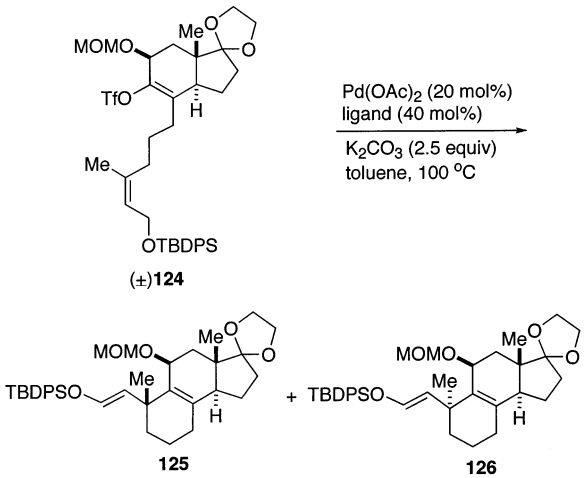


Table 3

ligand	time (h)	yield (%) (**125**:**126**)	ee of **125** (%)
(*R,R*)-CHIRAPHOS	20	14 (6:1)	4
(*R*)-BINAP	2	17 (5:1)	97
(*R*)-tol-BINAP	1.5	20 (11:1)	96

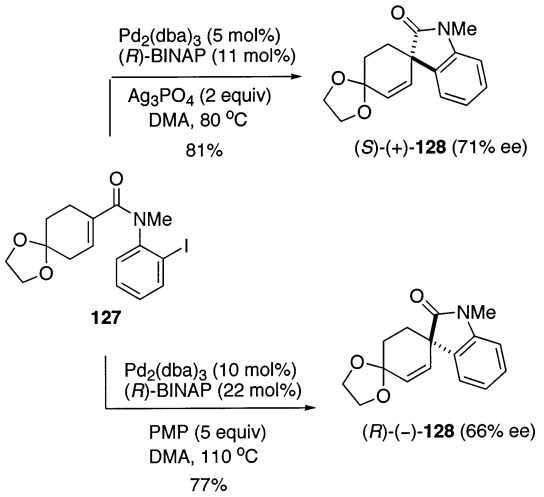
tate phosphine ligands were then surveyed (Table 3). The best results were obtained by treating **124** with $Pd(OAc)_2$, (*R*)-tol-BINAP, and K_2CO_3 in toluene at 100 °C to give **125** in a highly diastereoselective (11:1) and enantioselective (96% ee) fashion.

4.3. Alkaloids

4.3.1. Physostigmine and Physovenine

Following the initial report by Overman and co-workers of an asymmetric Heck polycyclization,[5] studies by this research group have focused on the synthesis of chiral nonracemic oxindoles that are potential precursors to a variety of alkaloid natural products.[62] Exploratory investigations of the intramolecular Heck reactions of (*E*)-α,*β*-unsaturated 2-iodoanilides demonstrated that treatment of iodoanilides such as **127** with $Pd_2(dba)_3$, (*R*)-BINAP, and either Ag_3PO_4 or PMP as an HI scavenger provided spirooxindoles in excellent chemical yield and with moderate enantioselectivity (Scheme 33).[62a,b] These studies led to the surprising discovery that either enantiomer of the cyclization product could be formed with good selectivity using a single enantiomer of the chiral diphosphine ligand. Thus, use of Ag_3PO_4 as an HI scavenger in the cyclization of **127** produced (*S*)-(+)-**128** in 71% ee, whereas use of the amine base PMP under otherwise identical reaction conditions yielded (*R*)-(−)-**128** in 66% ee. Similar results were realized in the Heck cyclizations of a variety of analogous (*E*)-α,*β*-unsaturated 2-iodoanilides. In these early studies, the scope of the amine-promoted asymmetric Heck cyclization was limited to anilides; little or no stereoinduction was observed in the asymmetric cyclizations of substrates that lacked the amide carbonyl group. However, more recent investigations show that this carbonyl group is not required for achieving high enantioselectivity in amine-promoted asymmetric Heck cyclizations.[63]

Scheme 33



Scheme 34

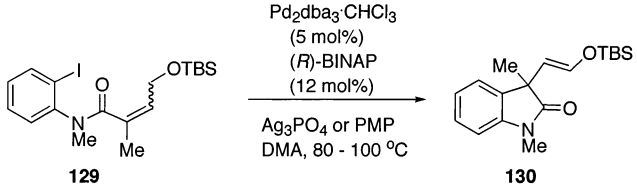


Table 4

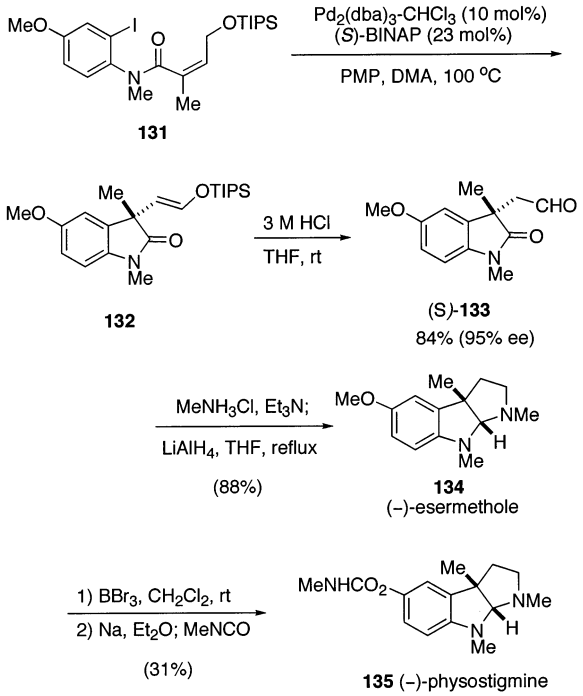
entry	substrate	additive	yield (%)	ee (%)
1	(*Z*)-**129**	Ag_3PO_4	53	78 (*R*)
2	(*Z*)-**129**	PMP	80	92 (*R*)
3	(*E*)-**130**	Ag_3PO_4	80	45 (*S*)
4	(*E*)-**130**	PMP	85	38 (*R*)

Overman and co-workers also investigated the intramolecular Heck reactions of several (*Z*)-α,*β*-unsaturated 2-iodoanilides.[62a,c] The Heck cyclizations of (*Z*)-iodoanilides such as (*Z*)-**129** were explored using the reaction conditions developed during the previous experiments: (1) silver-promoted cyclizations were conducted with 5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 12 mol % (*R*)-BINAP in the presence of 2 equiv of Ag_3PO_4 at 100 °C in DMA, and (2) base-promoted cyclizations were carried out identically in the presence of 4 equiv of PMP instead of Ag_3PO_4 (Scheme 34). Heck cyclization of (*Z*)-**129** under PMP-promoted conditions provided (*R*)-**130** in excellent yield and 92% ee, whereas the same transformation under silver-promoted conditions delivered (*R*)-**130** in lower yield and diminished enantioselectivity (Table 4). This result contrasts with analogous reactions of the (*E*)-iodoanilides, in which the sense of stereoinduction was reversed in cyclizations conducted under silver- or amine-promoted conditions.

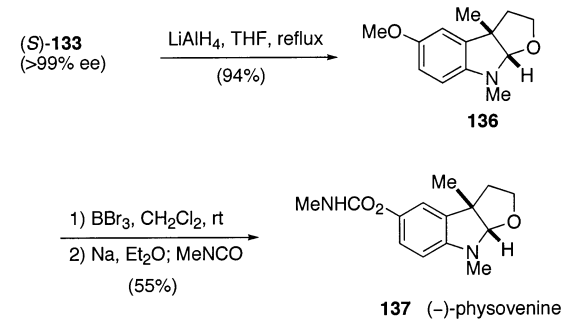
The detailed studies of the intramolecular Heck reaction of α,*β*-unsaturated iodoanilides by Overman and co-workers provided new insights into the effect of HI scavenger, alkene geometry, and substituents on the yield and enantioselectivity of this transformation. Perhaps most importantly, these studies unequivocally demonstrated that, with certain substrates, high enantioselection could be achieved with halide precursors in the absence of halide scavengers.

The synthetic utility of asymmetric Heck cyclizations to form 3,3-disubstituted oxindoles was first illustrated in an enantioselective total synthesis of the Calabar alkaloids (−)-physostigmine (**135**) and (−)-physovenine (**137**).[62a,d] Under the conditions discovered during exploratory investigations (see Scheme 34), Pd/BINAP-catalyzed reaction of (*Z*)-α,*β*-unsaturated iodoanilide **131** in the presence of PMP proceeded smoothly, and subsequent acid hydrolysis of the silyl enol ether intermediate delivered oxindole **133** in 84% overall yield and 95% ee (Scheme 35). A single recrystallization of this product provided enantiopure oxindole **133**, a central intermediate in the synthesis of both (−)-physostigmine (**135**) and (−)-physovenine (**137**). Condensation of **133** with methylamine followed by reduction of the resultant imine with $LiAlH_4$ gave (−)-esermethole (**134**), which was converted to (−)-physostigmine (**135**) following established procedures.[64] In a similar manner, **133** was also converted to (−)-physovenine (**137**) (Scheme 36).

Scheme 35



Scheme 36

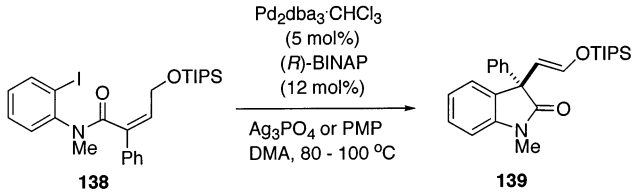


These syntheses constituted the first highly enantioselective catalytic asymmetric syntheses of physostigmine and congeners.

4.3.2. Quadrigemine C and Psycholeine

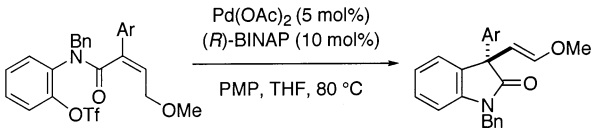
The initial reports by Overman and co-workers on the synthesis of oxindoles by the asymmetric intramolecular Heck reaction focused on constructing oxindoles bearing two alkyl substituents at the C3 quaternary stereocenter. These reports included only a cursory study of oxindoles bearing an aryl substituent at this site.[62] However, efficient access to the latter type of oxindoles was required for synthetic entry to a broad range of alkaloids and potential medicinal agents that contain diaryl-substituted quaternary stereocenters. Under the same reaction conditions that yielded 3,3-dialkyl-substituted oxindoles (e.g., **132** in Scheme 35) with high enantioselectivity, oxindole **139** was obtained with low to moderate stereoinduction (19% ee under neutral conditions and 65% ee under cationic conditions, Scheme 37).[62a,c] The observation that the cationic variant of the Heck cyclization of **138** was superior in this case prompted a detailed investigation of cyclizations of analogous aryl triflates.[65]

Scheme 37



Additive	ee(%)
PMP	19
Ag_3PO_4	65

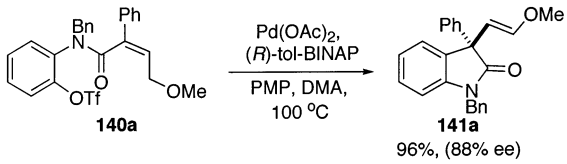
Scheme 38



140a Ar = Ph
140b Ar = 3-pyridyl
140c Ar = 4-MeO-C_6H_4
140d Ar = 1-naphthyl

141a 86% (84% ee)
141b 77% (88% ee)
141c 81% (79% ee)
141d 92% (92% ee)

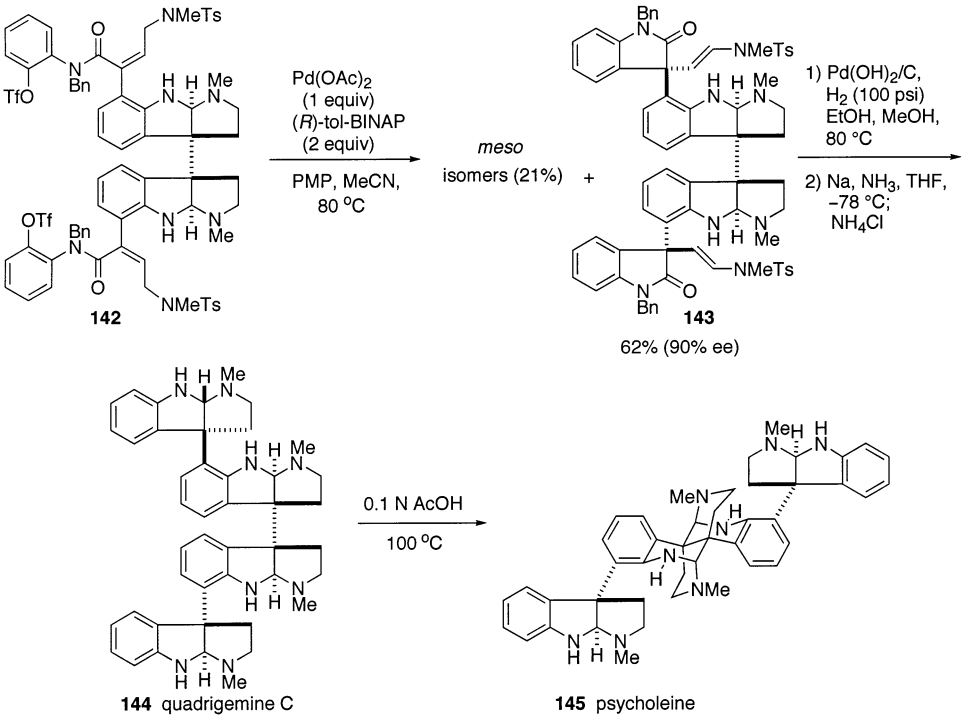
Scheme 39



The asymmetric Heck cyclization of aryl triflates such as **140a** was achieved using $Pd(OAc)_2$ as a precatalyst, (*R*)-BINAP as a chiral ligand, and PMP as a base to afford **141a** in 86% yield and with 84% ee (Scheme 38). Replacement of the α-phenyl group with other aryl or heteroaromatic substituents had little effect on the high chemical yield or enantioselectivity of related Heck cyclizations (**140b**−**d** → **141b**−**d**). Modest improvement in enantioselectivity was achieved using more polar solvents such as DMA or CH_3CN and employing (*R*)-tol-BINAP as the chiral ligand (Scheme 39).

These recent advances in the construction of 3-alkyl-3-aryloxindoles by the catalytic asymmetric Heck cyclization set the stage for the strategic implementation of this transformation in the total synthesis of several members of the polypyrrolidinoindoline family of alkaloids. The first example of a double asymmetric Heck cyclization was reported in the context of asymmetric total syntheses of quadrigemine C (**144**) and its isomer, psycholeine (**145**) (Scheme 40).[66] In this case, the asymmetric intramolecular Heck reaction was employed to desymmetrize the advanced meso intermediate **142** and simultaneously install the two peripheral biaryl quaternary stereocenters of **144** and **145**. The reaction conditions developed for the construction of relatively simple 3-aryl-3-alkyloxindoles proved to be directly applicable to this significantly more elaborate Heck precursor. Thus, a catalyst-controlled double Heck cyclization of **142** was achieved using $Pd(OAc)_2$, (*R*)-tol-BINAP, and PMP in CH_3CN at 80 °C to yield the C_1-symmetric bis-oxindole **143** as the major product

Scheme 40



in 62% yield and 90% ee. Stereoisomeric *meso*-bisoxindoles were also formed as minor side products in this reaction (21% combined yield). The use of (*R*)-BINAP as a ligand for this transformation resulted in reduced selectivity, providing **143** in lower yield and only 65% ee. Following the pivotal Heck cyclization, only two additional steps were required to complete the total synthesis of quadrigemine C (**144**), which constituted the first total synthesis of a higher-order member of the polypyrrolidinoindoline alkaloid family. This inaugural total synthesis of a tetrapyrrolidinoindoline alkaloid was accomplished in only 19 steps and proceeded in 2% overall yield. Subsequent acid-catalyzed isomerization of quadrigemine C provided psycholeine (**145**) as well.

This asymmetric total synthesis of the dodecacyclic alkaloids quadrigemine C and psycholeine provides a compelling illustration of the power of asymmetric Heck cyclization strategies in total synthesis. First, the key cyclization of **142** → **143** demonstrates the remarkable functional group tolerance of the Heck reaction, which in this case allows the enantioselective formation of two C−C bonds in a precursor containing a number of polar groups and sensitive functionalities. Second, this example illustrates the remarkable ability of intramolecular Heck reactions to form congested all-carbon quaternary centers.[67] Moreover, the strategy employed in this total synthesis differs considerably from almost all other applications of asymmetric catalysis in complex molecule construction, as catalytic asymmetric transformations typically are used at an early stage in a synthetic sequence to construct small chiral, enantioenriched building blocks. The late-stage implementation of the asymmetric Heck cyclization of **142** in the synthesis of quadrigemine C represents a significant departure from this conventional strategy.

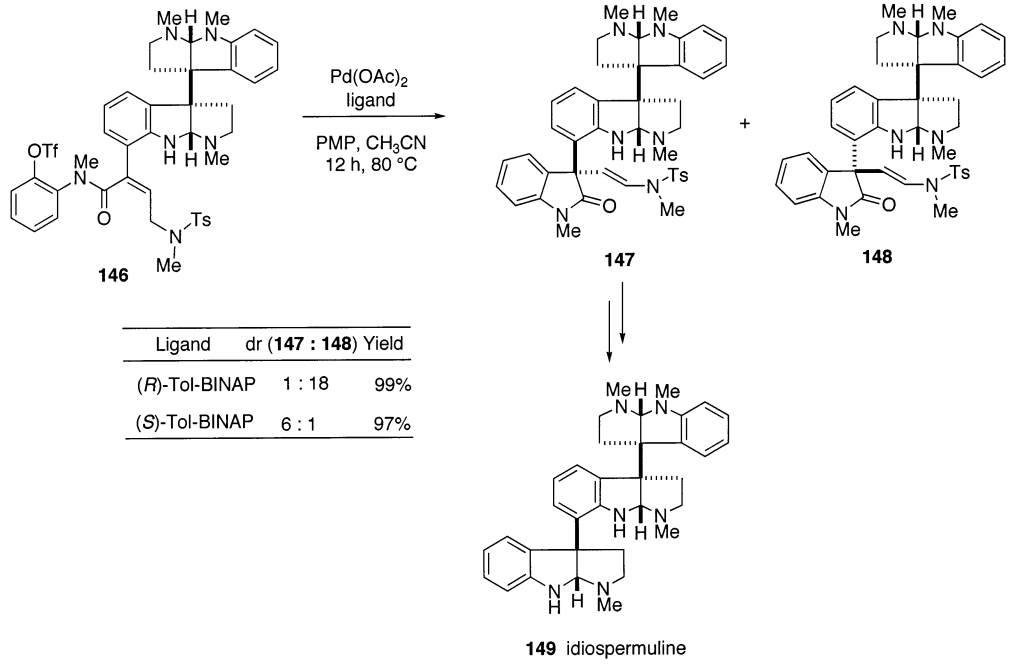
4.3.3. Idiospermuline

The recent enantioselective total synthesis of idiospermuline (**149**) by Overman and Peterson followed a strategy similar to that employed in the synthesis of quadrigemine C.[68] In the case of idiospermuline, the cyclization substrate was the chiral, enantiopure heptacyclic vinyl triflate **146** (Scheme 41). Heck cyclization of this intermediate using Pd(OAc)$_2$ and the achiral diphosphine ligand, dppf, proceeded with little diastereoselection to produce a mixture of oxindoles **147** and **148** in a 2:1 ratio. The ability to modulate this cyclization by ligand control was demonstrated by cyclizing **146** using palladium catalysts having tol-BINAP ligands. Employing (*R*)-tol-BINAP, diastereomer **148** was formed with high diastereoselectivity (dr = 18:1) in nearly quantitative yield. As expected, diastereoselection was reversed by using (*S*)-tol-BINAP, which provided **147** and **148** in a 6:1 ratio. The diminished diastereoselectivity achieved with the *S* enantiomeric catalyst reflects a mismatch in this case between substrate and ligand control. The asymmetric total synthesis of idiospermuline (**149**) was completed from **147** in only two additional steps by hydrogenation of the enamide and a one-pot reductive deprotection and cyclization process.

4.3.4. Spirotryprostatin

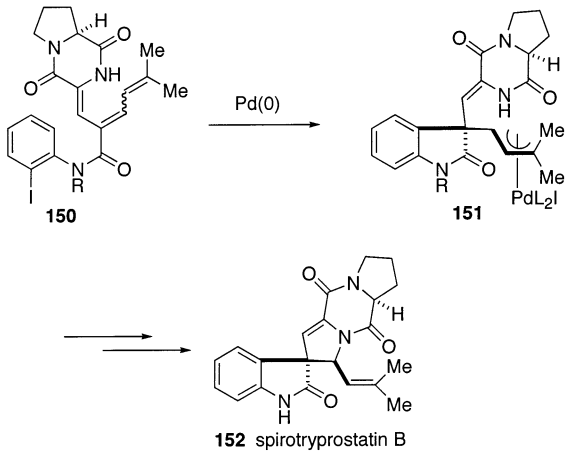
A tandem asymmetric Heck cyclization−η^3-allylpalladium capture process was employed by Overman and Rosen in efforts toward the synthesis of (−)-spirotryprostatin B (**152**).[69] The strategy underlying this synthetic approach was to correlate the relative configurations of the quaternary stereocenter and the adjacent tertiary stereocenter in the natural product to the geometry of the internal alkene in the Heck cyclization substrate (Scheme 42). A favored 5-exo

Scheme 41

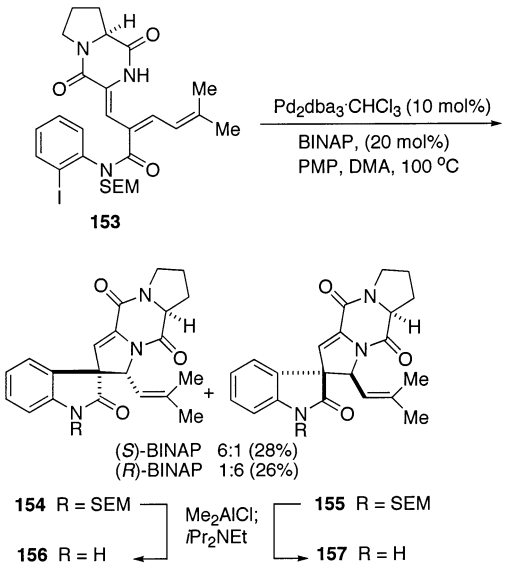


Ligand	dr (**147 : 148**)	Yield
(*R*)-Tol-BINAP	1 : 18	99%
(*S*)-Tol-BINAP	6 : 1	97%

Scheme 42



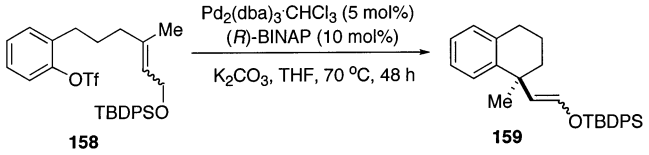
Scheme 43



intramolecular Heck cyclization of chiral, enantiopure triene precursor **150** would generate an η^3-allylpalladium intermediate (**151**), which would be trapped by the proximal nitrogen of the tethered diketopiperazine. Use of a chiral palladium catalyst was expected to control the stereochemical outcome of the first carbon−carbon bond formed in this sequence. The viability of this approach was first investigated with triene **153**, in which the internal alkene possesses a *Z* configuration (Scheme 43). Cyclization of **153** with Pd_2dba_3·$CHCl_3$, (*S*)-BINAP, and PMP in DMA at 100 °C delivered a 6:1 mixture of spirocycles **154** and **155** in 28% yield. Likewise, cyclization of **153** using (*R*)-BINAP under otherwise identical conditions provided a 1:6 mixture of **154** and **155**. Cleavage of the SEM protecting groups from these products produced 18-*epi*-spirotryprostatin B (**156**) and 3-*epi*-spirotryprostatin B (**157**).

This application of cascade palladium-mediated cyclizations to the synthesis of **156** and **157** verified that the catalytic asymmetric Heck cyclization of conjugated triene **153** could be achieved with excellent regioselectivity and with a reasonable degree of catalyst control in the formation of the quaternary stereocenter. Furthermore, these transformations demonstrated that the η^3-allylpalladium intermediate is generated and trapped without loss of stereochemical integrity. Moreover, the relative configurations of the quaternary stereocenter and the adjacent tertiary stereocenter in **154** and **155** confirm that the nitrogen of the tethered diketopiperazine attacks the allylpalladium complex anti to the metal center. These preliminary studies suggested that the required configuration of natural spirotryprostatin B (**152**) would be obtained by Pd/(*S*)-BINAP-catalyzed cyclization of a triene analogous to **153**, in which the internal alkene possesses the *E* configuration. However, all attempts to access spirotryprostatin B by this catalytic asymmetric approach were thwarted by isomerization of the internal double bond of such

Scheme 44



Substrate	Yield (%)	ee (%)
(*E*)-**158**	95	51 (*R*)
(*Z*)-**158**	97	80 (*S*)

triene substrates under asymmetric Heck reaction conditions.[69]

4.3.5. Eptazocine

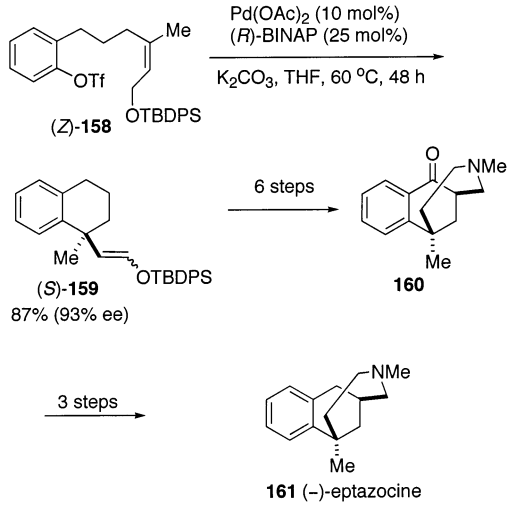
One additional example of using a catalytic asymmetric Heck cyclization to form a quaternary stereocenter in the context of an alkaloid total synthesis, in this case the structurally simple alkaloid (−)-eptazocine, was reported by Shibasaki and co-workers.[70] In model studies, the role of alkene geometry was investigated in cyclizations of the *E* and *Z* isomers of alkene **158** (Scheme 44). Treatment of (*E*)-**158** with Pd_2dba_3·$CHCl_3$, (*R*)-BINAP, and K_2CO_3 in THF at 70 °C afforded tetralin (*R*)-**159** as a mixture of alkene geometrical stereoisomers (trans:cis = 84:11) in 95% yield and 51% ee. Subjection of (*Z*)-**158** to identical reaction conditions produced (*S*)-**159** as a mixture of alkene isomers (trans:cis = 92:5) in 97% yield and 80% ee. Furthermore, cyclization of **158** at slightly lower temperature (50 °C) using $Pd(OAc)_2$ as a precatalyst provided (*S*)-**158** in higher geometrical purity (trans:cis = 98:2), albeit in slightly reduced yield and enantiopurity. As is typically observed in catalytic Heck cyclizations proceeding by a "cationic" pathway, the absolute configuration of the product obtained using the Pd/(*R*)-BINAP system was dependent upon the geometry of the starting alkene, and high enantioselection was realized only with the *Z* precursor. The choice of $Pd(OAc)_2$ as a palladium precatalyst also provided some improvement in enantioselectivity over that achieved using a catalyst generated from Pd_2dba_3·$CHCl_3$.

Applying the previously optimized conditions toward the total synthesis of (−)-eptazocine (**161**), aryl triflate **158** bearing a *Z*-alkene side chain was cyclized to give (*S*)-**159** in 87% yield and 93% ee (Scheme 45). Six additional steps transformed this product to tricyclic amine **160**, which was forwarded to (−)-eptazocine (**161**) according to a previously reported procedure.[71]

5. Conclusions and Future Prospects

In the intervening years since the first reports in 1989,[4,5] catalytic asymmetric Heck cyclizations have been employed as central strategic steps in total syntheses of a wide variety of polycyclic natural products. No other catalytic asymmetric C−C bond-forming reaction has yet found comparably wide application. Three major factors contribute to the broad utility of catalytic asymmetric Heck cyclizations in the construction of complex structures: the high functional group tolerance of palladium(0)-catalyzed reactions, the remarkable capacity of this transformation to forge C−C bonds in situations of considerable steric congestion, and the ability to orchestrate this reaction in cascade processes that form multiple rings.

Scheme 45



It is certain that many more applications of catalytic asymmetric intramolecular Heck reactions will be described in the future. Apparent in this survey is the small number of ligands that thus far have found use, with Noyori's BINAP ligand being the most widely employed.[72] Two future trends are easy to predict: a larger variety of chiral ligands[57,73] will be available for asymmetric Heck processes, and a larger variety of cascade processes involving intramolecular Heck reactions will be developed.

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