1. Introduction

The Pd(0)-catalyzed vinylation of aryl halides was first reported over 30 years ago in independent studies by Mizoroki and Heck. 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. 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. 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 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 for formation of the cis-decalin (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. Of the various chiral diphosphine ligands surveyed in this preliminary study, BINAP provided the best...
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.

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. In this example, trienyl triflate 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.

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. 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 $\alpha$-aryl palladium(II) complex. The order of reactivity for the oxidative addition step, and typically for the overall reaction, is $X = I > OTf > Br > Cl$. Coordination of an alkene and subsequent carbon-carbon bond formation by syn addition provide a $\alpha$-alkyl palladium(II) intermediate, which readily undergoes $\beta$-hydride elimination to release the alkene Heck product. A base is required for conversion of the hydrodopalladium(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
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(II)–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 enantiomeric excess 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).\(^14\)
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 enantio-purity. 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 theoretical18 and experimental data19 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 PPh3 is an anionic species, [Pd(PPh3)2(OAc)].20 Oxidative addition of this catalyst to PhI does not afford [PhPd(l[PPh3])2] as previously postulated, but instead gives a pentacoordinate complex, [PhPd(OAc)(PPh3)]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)(PPh3)]2 (23). The increased reactivity of [PhPd(OAc)(PPh3)]2 compared to that of [PhPd(l[PPh3])2] has been attributed to the bidentate nature of the acetate ligand, which may assist in phosphate release to open a coordination site for the alkene substrate. Migratory insertion provides the α-alkylpalladium complex 26, which undergoes β-hydride elimination to yield alkene product 27 and hydridod palladium 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.

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 monoden-
tate 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 α-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-

Figure 1.

Scheme 6
selectivity in the $\beta$-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 $\beta$-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 $\sigma$-alkylpalladium(II) intermediate (29) bearing a single syn $\beta$-hydrogen ($H_β$). 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 $\beta$-elimination in acyclic systems (see section 3.1.3).

An additional concern arises from potential reversibility of the $\beta$-hydride elimination step, which introduces the possibility that the hydropalladation step follows the $\beta$-hydride elimination could re-add across the initially generated double bond. Depending upon the regio- and stereochemistry of this hydropalladation step, subsequent $\beta$-hydride elimination could regenerate either the initial Heck product or a regiosomer. The use of low reaction temperatures or additives such as silver salts has been shown to minimize this type of alkene isomerization in several cases.

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. 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)$_3$-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 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.

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. Dibenzylidene acetone (dba) can also play a role. 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 Ph$I$. 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$_4$.

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. Amatore and Jutand have demonstrated that the catalyst obtained from Pd(dba)$_2$ and DIOP (37) undergoes oxidative addition to Ph$I$ at a significantly higher rate than the corresponding catalyst having BINAP as a ligand. In transformations that require a catalyst more reactive than Pd(BINAP) and related systems, ligands such as 35 provide a useful alternative.

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 Ag₂CO₃, Ag₃PO₄, and silver-exchanged zeolite. Thallium salts (Tl₂CO₃, TlOAc, and TINO₃) 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-K₂CO₃ 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 ³¹P 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 K₂CO₃ and CaCO₃ reported most frequently. Tertiary amine bases such as Et₃N, i-Pr₂NEt, 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, CH₃CN, 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-Pr₂NH) provided enantioselectivities inferior to those realized with Ag₂CO₃.⁴ 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 Ag₃PO₄ providing the best results (Scheme 8).³⁰ In general, polar solvents such as NMP provided enhancement in enantioselectivities 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 K₂CO₃ 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$_₂$-
NET provided results inferior to those realized with K$_2$CO$_3$. 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$_2$CO$_3$, 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.

An asymmetric Heck cyclization was used by Shibasaki and co-workers to construct a substituted cis-decalin in synthetic efforts directed at (+)-vernolepin. Specifically, asymmetric Heck cyclization of vinyl triflate 51 gave enone 54 in 76% yield and 86% ee under optimized conditions (Scheme 11). 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).

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). Heck cyclization of prochiral vinyl triflate 57 provided cis-decalin 58 in 70% yield and 82% ee; allylic acetate 59, which likely resulted from trapping of a palladium allyl intermediate with acetate anion, was formed also. The Heck cyclization product was again transformed in nine steps into Danishefsky's key intermediate (55). 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.

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. 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-hyndridane 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$_2$Pd(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-hyndridanes was employed in studies directed at the total syntheses
of the brominated terpenes (–)-oppositol and (–)-prepinnaterpene (Scheme 16). 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 Pd2dba3·CHCl3, (R)-BINAP, and Ag2PO4 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), a natural member of the cadinene sesquiterpenoids. Substituted tetrahydroisoquinolines and tetrahydrobenzodiazepines have also been synthesized in high enantiopurity using related asymmetric Heck cyclization reactions of allylsilanes.36a

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–η3-allyl nucleophilic trapping sequence. The cascade process was initially explored with prochiral trienyl iodide 72 (Scheme 18).38,39 Heck cyclization of 72 produced η3-allylpalladium species 73, which was trapped by an acetate anion at the least hindered terminus of the η3-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 (±)-Δ9(12)-capnellene-3β,8β,10α-triol (80) and (±)-Δ9(12)-capnellene-3β,8β,10α,14-tetraol (81).41

3.1.5. Δ9(12)-Capnellene

The use of soft carbanionic nucleophiles in tandem asymmetric Heck cyclization–η3-allyl trapping se-
sequences has also been developed by Shibasaki and co-workers (Scheme 21). 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.

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. 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 (−)-Δ^{9(12)}-capnellene (85). This first catalytic asymmetric total synthesis of (−)-Δ^{9(12)}-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 enantioselectivity. 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

#### Table 1. Ligand Effects on the Cyclization of 86

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>ratio of 87:88</th>
<th>yield (%)</th>
<th>ee of 88 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP</td>
<td>90</td>
<td>46</td>
<td>1:3.3</td>
<td>67</td>
<td>34 (R)</td>
</tr>
<tr>
<td>2</td>
<td>35b</td>
<td>50</td>
<td>8.5</td>
<td>1:5.5</td>
<td>79</td>
<td>45 (S)</td>
</tr>
<tr>
<td>3</td>
<td>35a</td>
<td>50</td>
<td>14</td>
<td>1:1.2</td>
<td>62</td>
<td>52 (S)</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>50</td>
<td>35</td>
<td>0.1</td>
<td>45</td>
<td>74 (S)</td>
</tr>
</tbody>
</table>

a Vinyl iodide 86 was treated with Pd_{2}(dba)$_3$·CHCl$_3$ (5 mol % Pd), ligand (12 mol %), Ag$_3$PO$_4$ (2 equiv), and CaCO$_3$ (2.2 equiv) in DMF.
this transformation was \((R)\)-(S)-BPFOH (35),\textsuperscript{44} which gave 88 as the only product in 45% yield and 74% ee (entry 4). The structurally similar BPPFA and BPPOAc 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).\textsuperscript{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).\textsuperscript{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 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\textsuperscript{47} and 5E,9Z-indolizidine 223AB.\textsuperscript{48}
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).

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). A variety of aryl iodides were surveyed for this transformation. For example, upon reaction with \(\text{Pd(OAc)}_2\), \((R)-\text{BINAP}\), \(\text{Ag-exchanged zeolite}, \text{CaCO}_3\), 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 \(103 \rightarrow 105\), 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 \(\sigma\)-bonded palladium intermediate generated upon 5-exo cyclization cannot undergo \(\beta\)-hydride elimination; thus, a hydride source (e.g., \(\text{HCO}_2\text{Na}\)) is required to reduce this intermediate and regenerate the \(\text{Pd}(0)\) catalyst.

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). 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 \([\text{Pd(OAc)}_2, (S)-\text{BINAP}, \text{K}_2\text{CO}_3, \text{THF}]\) 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, \(\text{Pd}(\text{OAc})_2\), \((S)-\text{BINAP}, \text{K}_2\text{CO}_3, \text{THF})\] to give tetrahydroanthracene 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). In this step, naphthyl triflate 115 was cyclized with \(\text{Pd}_2(\text{dba})_3\), (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...
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$_2$PO$_4$) 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...
enantiocontrol (entry 4). Unfavorable steric interactions apparently exist when both R\textsubscript{1} and R\textsubscript{2} are methyl, as enantioselectivity is significantly lower in the cyclization of \textit{119d} (entry 5). It is surprising that the desired reaction pathway is almost completely shut down when substrate \textit{119e} having R\textsubscript{1} = phenyl is cyclized using (R)-BINAP as the ligand (entry 6), with the major product in this case being tricyclic ketone \textit{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 \textit{120e} (entry 7). More recent studies suggest that BINAPFu\textsuperscript{57} may be a useful ligand for this cascade cyclization reaction.\textsuperscript{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 \textit{120a} and \textit{120e}.\textsuperscript{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 \textit{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 tetracyclic products.

Following the report by Keay and co-workers that naphthyl bromides were poor substrates in the catalytic asymmetric polyene cyclization to form pentacyle \textit{117}, Shibasaki and co-workers reported improved reaction conditions for this problematic transformation.\textsuperscript{55} Treatment of naphthyl bromide \textit{122} with Pd\textsubscript{2}(dba)\textsubscript{3}-CH\textsubscript{Cl}\textsubscript{2}, (S)-BINAP, CaCO\textsubscript{3}, and Ag-exchanged zeolite (1.0 equiv) in NMP at 80 °C afforded \textit{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 enantioselectivities were achieved using Ag-exchanged zeolite as a halide scavenger rather than the more commonly used Ag\textsubscript{3}PO\textsubscript{4}. Following the conversion of \textit{122} to \textit{117} under 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).\textsuperscript{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 \textit{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-
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$_2$CO$_3$ in toluene at 100 °C to give 125 in a highly diastereoselective (11:1) and enantiomeric (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, 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. 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$_3$PO$_4$ or PMP as an HI scavenger provided spirooxindoles in excellent chemical yield and with moderate enantioselectivity (Scheme 33). 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$_3$PO$_4$ 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.

### Scheme 33

![Scheme 33](image)

### Table 3

<table>
<thead>
<tr>
<th>ligand</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>(R,R)-CHIRAPHOS</td>
<td>20</td>
<td>14 (6:1)</td>
<td>4</td>
</tr>
<tr>
<td>(R)-BINAP</td>
<td>2</td>
<td>17 (5:1)</td>
<td>97</td>
</tr>
<tr>
<td>(R)-tol-BINAP</td>
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<td>20 (11:1)</td>
<td>96</td>
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</table>

### Table 4

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>additive</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)-129</td>
<td>Ag$_3$PO$_4$</td>
<td>53</td>
<td>78 (R)</td>
</tr>
<tr>
<td>2</td>
<td>(Z)-129</td>
<td>PMP</td>
<td>80</td>
<td>92 (R)</td>
</tr>
<tr>
<td>3</td>
<td>(E)-130</td>
<td>Ag$_3$PO$_4$</td>
<td>80</td>
<td>45 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(E)-130</td>
<td>PMP</td>
<td>85</td>
<td>38 (R)</td>
</tr>
</tbody>
</table>

Overman and co-workers also investigated the intramolecular Heck reactions of several (Z)-α,β-unsaturated 2-iodoanilides. The Heck cyclizations of (Z)-idoanilides 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$_3$PO$_4$ 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$_3$PO$_4$ (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)-idoanilides, 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 enantioselectivity 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). 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 (−)-eser methione (134), which was converted to (−)-physostigmine (135) following established procedures. In a similar manner, 133 was also converted to (−)-physovenine (137) (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. 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

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 CH3CN 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 CH3CN at 80 °C to yield the C3-symmetric bis-oxindole 143 as the major product.
in 62% yield and 90% ee. Stereoisomeric meso-bis-oxindoles 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. 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. Idiospermine

The recent enantioselective total synthesis of idiospermine (149) by Overman and Peterson followed a strategy similar to that employed in the synthesis of quadrigemine C.68 In the case of idiospermine, 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 idiospermine (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–η3-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
intramolecular Heck cyclization of chiral, enantiopure triene precursor 150 would generate an $\eta^2$-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$_2$(dba)$_3$·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 $\eta^2$-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
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 Pd2dba3·CHCl3, (R)-BINAP, and K2CO3 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 precatall catalyst provided (S)-158 in higher geometrical purity (trans:cis = 98:2), albeit in slightly reduced yield and enantioselectivity. 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 Pd2dba3·CHCl3.

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 poly cyclic 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.

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 ligands73,74 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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