C–H FUNCTIONALIZATION: A NEW STRATEGY FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

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1.1. INTRODUCTION

The advent of transition metal-catalyzed transformations at C–H bonds has enabled the efficient formation of a wide range of carbon–carbon and carbon–heteroatom bonds from simple C–H bonds [1]. As a strategy, these transformations use unactivated C–H bonds as functional groups to generate molecular complexity. While these processes represent a chemical ideal from the standpoint of atom economy and synthetic efficiency, the ubiquitous nature of C–H bonds and their relative strength [2] pose a significant challenge for selectivity and reactivity, which has been the focus of research efforts over the past decade. The current knowledge in the field has enabled the use of C–H functionalization as a reliable tool for natural product synthesis, even as a late-stage manipulation in complex targets [3].

Synthetic approaches toward transition metal-catalyzed transformations at C–H bonds are divided between two distinct mechanisms [4]. Outer sphere mechanisms (*coordination chemistry*) proceed via the direct interaction of the C–H bond being functionalized with a ligand coordinated to the transition metal. This mechanism has been exploited both in metal-catalyzed carbene/nitrene insertions into C–H bonds and in metal-oxo-catalyzed C–H oxidations [5,6]. On the other hand, inner sphere mechanisms (*organometallic chemistry*) involve the formation of a carbon–metal bond as a result of C–H bond cleavage [7]. This chapter will discuss the application of the latter form of reactivity, also known as C–H activation or C–H functionalization, to the synthesis of biologically active molecules. While many of the
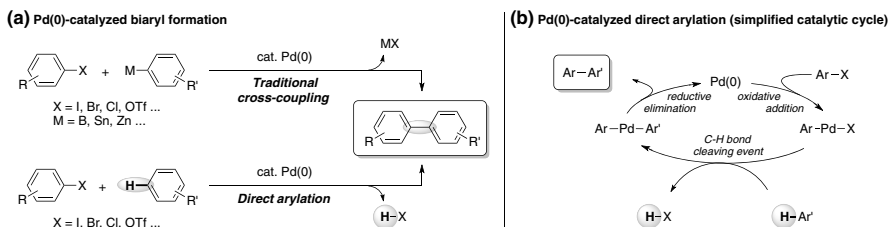
contributions made in the field will be highlighted, an exhaustive list of syntheses relying on this strategy will not be made. Instead, the examples described in the following sections have been chosen to give the reader a broad perspective of the different strategies of C–H bond functionalization that have been applied to natural product synthesis.

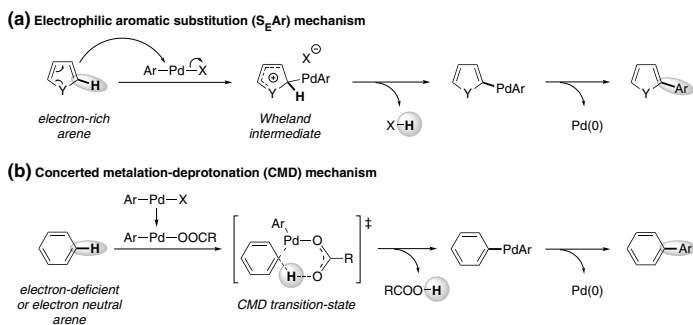## 1.2. PALLADIUM(0)-CATALYZED INTRAMOLECULAR DIRECT ARYLATION

Direct arylation constitutes an important alternative to traditional cross-coupling reactions for the formation of biaryl bonds [8], a prevalent motif in biologically active and medicinally relevant molecules. In direct arylation reactions, one of the preactivated coupling partners, often the organometallic component, is replaced by a simple (hetero)arene C–H bond, streamlining the overall biaryl bond forming process (Scheme 1.1a) [9]. Several transition metals have been used to harness this reactivity, including ruthenium, rhodium, palladium, and copper to name a few. Pd(0)-based catalyst systems have been extensively investigated in this area due to their functional group tolerance. Moreover, they provide the ability to use commercially available (or easily prepared) aryl halides as the sole preactivated coupling partner in these processes.

The general catalytic cycle for this transformation consists of three steps (Scheme 1.1b): (i) oxidative addition of the aryl (pseudo)halide to a Pd(0) catalyst generates a Pd(II) intermediate, (ii) interaction of the Pd(II) species with the (hetero) arene C–H bond leads to C–H bond cleavage and elimination of HX, and (iii) reductive elimination produces the biaryl product while regenerating the Pd(0) catalyst.

The selective functionalization of an sp^2 C–H bond in (hetero)arenes containing several potential reaction sites poses a significant challenge to direct arylation reactions. When the electronic and/or steric properties of the substrate do not lead to regioselective C–H bond cleavage, strategies have been developed to overcome this hurdle. The installation of a Lewis basic directing group on the unactivated coupling partner, which acts as a ligand for the metal, can be used to guide site-specific arene metalation [10]. On the other hand, intramolecular reactions also eliminate some of the problems of regioselectivity. In these cases, C–H bond functionalization is generally governed by the size of the metalacyclic intermediate formed during the catalytic cycle.

(a) Pd(0)-catalyzed biaryl formation

X = I, Br, Cl, OTf ...
M = B, Sn, Zn ...

Traditional cross-coupling

X = I, Br, Cl, OTf ...

Direct arylation

(b) Pd(0)-catalyzed direct arylation (simplified catalytic cycle)

reductive elimination

oxidative addition

C–H bond cleaving event

SCHEME 1.1 Palladium(0)-catalyzed direct arylation.

(a) Electrophilic aromatic substitution (S$_E$Ar) mechanism

electrophilic arene · Wheland intermediate · Pd(0)

(b) Concerted metalation-deprotonation (CMD) mechanism

electron-deficient or electron neutral arene · CMD transition-state · Pd(0)

SCHEME 1.2   Proposed mechanisms for direct arylation.

The mechanism of C–H bond cleavage in these processes has been extensively debated in the literature, with two pathways having received significant attention. In direct arylation reactions featuring electron-rich (hetero)aromatic substrates, an electrophilic aromatic substitution (S$_E$Ar) mechanism is typically proposed involving a Friedel–Crafts process, where the nucleophilic (hetero)arene reacts with the electrophilic metal center (Scheme 1.2a) [11]. On the other hand, electron-deficient and electron-neutral arenes have been proposed to react through a concerted metalation–deprotonation (CMD) mechanism, involving C–H deprotonation with concomitant (hetero)arene metalation (Scheme 1.2b) [12]. It should also be noted that recent studies have demonstrated that this CMD pathway may also be operative in direct arylation reactions featuring electron-rich arenes [13].

With the advances made in the field of direct arylation over the last decade, several groups have used this strategy to complete the syntheses of natural product targets [14]. Selected examples will be discussed to highlight different synthetic strategies and the resulting developments that have been made in this area.
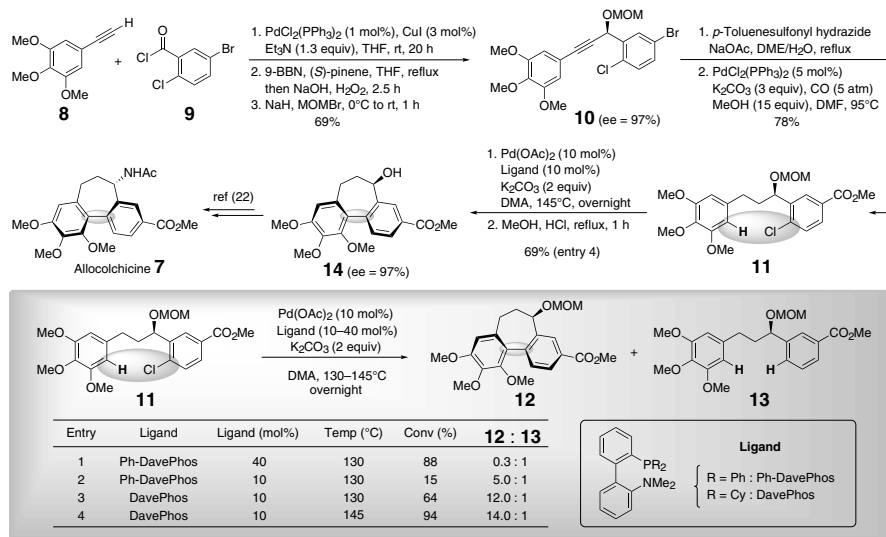
Owing to its significant antifungal and anti-HIV properties, the pradimicin–benanomicin class of antibiotics has sparked the interest of the synthetic community [15]. Members of this class of compounds contain a benzo[a]naphthacenequinone core, an amino acid, and a disaccharide moiety. In 1999, Suzuki and coworkers used a clever direct arylation strategy to access pradimicinone **1**, the common aglycone to this class of antibiotics (Scheme 1.3) [16]. Thus, by temporarily tethering arene **2** and aryl iodide **3** through an esterification, the sterically hindered biaryl bond was formed using an intramolecular direct arylation reaction. Optimization studies led to the use of Pd (OAc)$_2$ (30 mol%), PPh$_3$ (60 mol%), and NaOPiv (3 equiv) in N,N-dimethyl-acetamide (DMA) at 110°C to achieve the desired transformation [17]. The crude product was then directly reduced to **5** with NaBH$_4$ as the authors noted that it was readily hydrolyzed during purification by silica gel chromatography. Overall, biaryl **5** was prepared in 86% yield using this two-step protocol. Although the catalyst loading is relatively high (30 mol%), this noteworthy synthesis represents one of the earliest complex examples in the field [18,19]. Indeed, the direct arylation protocol was performed in the presence of multiple functional groups, including an aryl chloride, to selectively produce the highly sterically congested biaryl bond in excellent yield.

Allocolchicine (**7**), a potential therapeutic derivative of the microtubule depolymerizing agent colchicine, represents an interesting synthetic target for the
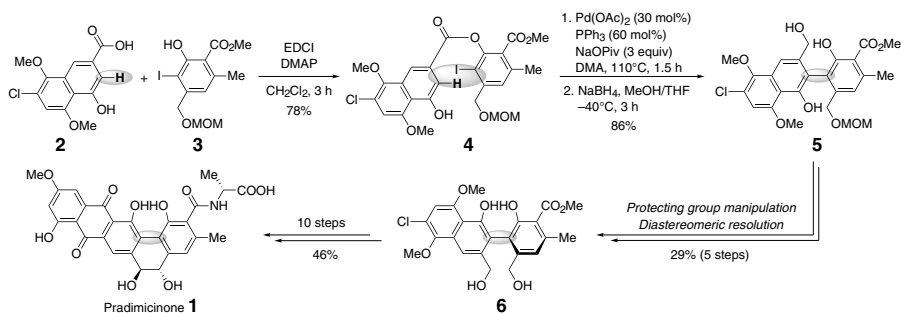
SCHEME 1.3　Synthesis of pradimicinone by Suzuki and coworkers.

application of intramolecular direct arylation due to its tricyclic core containing a biaryl linkage and a seven-membered ring. Leblanc and Fagnou applied two halide-selective palladium-catalyzed cross-coupling reactions prior to a challenging intramolecular direct arylation step in their formal enantioselective synthesis of this compound in 2005 (Scheme 1.4) [20]. Starting from alkyne **8** and acyl chloride **9**, possessing in total three carbon–halide bonds of varying reactivities, a Sonogashira reaction selectively afforded the desired propargyl ketone. Next, an (*S*)-pinene/9-BBN-mediated asymmetric reduction followed by the protection of the resulting alcohol as a MOM ether afforded **10** in 69% yield over three steps. Diimide reduction of the triple bond and subsequent bromide-selective palladium-catalyzed methyl ester formation yielded the direct arylation precursor **11**. With **11** in hand, the key intramolecular reaction was investigated. It should be noted that, at the time, the formation of a seven-membered ring by direct arylation as well as the use of an aryl chloride as a coupling partner had limited precedent [21]. A combination of Pd(OAc)$_2$


Entry	Ligand	Ligand (mol%)	Temp (°C)	Conv (%)	12 : 13
1	Ph-DavePhos	40	130	88	0.3 : 1
2	Ph-DavePhos	10	130	15	5.0 : 1
3	DavePhos	10	130	64	12.0 : 1
4	DavePhos	10	145	94	14.0 : 1

SCHEME 1.4　Formal enantioselective synthesis of allocolchicine by Leblanc and Fagnou.

(10 mol%), phosphine ligand Ph-DavePhos (40 mol%), and K_2CO_3 (2 equiv) in DMA at 130°C afforded the desired product **12** and dechlorinated by-product **13**, the latter being favored. Further optimization revealed an important relationship between the ligand to palladium ratio and the formation of **13**. Indeed, decreasing this ratio from 4:1 to 1:1 led to a significant increase in the formation of cyclized product **12** over reduced product **13**, however, at the cost of loss in conversion (Scheme 1.4, entries 1 and 2). A simple ligand change from Ph-DavePhos to DavePhos not only increased the conversion to 64% but also improved the **12/13** ratio to 12:1 (Scheme 1.4, entry 3). Finally, raising the reaction temperature to 145°C gave 94% conversion and a 14:1 ratio of **12/13**, providing **12** in 73% isolated yield as a 10:1 mixture of atropisomers (Scheme 1.4, entry 4). MOM cleavage gave **14** in 94% yield and 97% ee, an intermediate that had previously been converted to allocolchicine (**7**) by Wulff and coworkers [22].

1.3. PALLADIUM(0)-CATALYZED INTRAMOLECULAR ALKENYLATION OF sp² C–H BONDS

The direct coupling of an alkenyl (pseudo)halide with a simple (hetero)arene C–H bond to produce an alkenylated (hetero)arene has been investigated due to its complementary relationship with the Heck reaction [23,24]. Pd(0)-catalyzed alkenylation of sp² C–H bonds can be paralleled to direct arylation reactions where the aryl (pseudo)halide has been replaced by a vinyl (pseudo)halide coupling partner (see Section 1.2).

In 2002, Hughes and Trauner reported the total synthesis of (−)-frondosin B **15** using a palladium-catalyzed intramolecular alkenylation of a benzofuran C–H bond as the key cyclization step (Scheme 1.5) [25]. The frondosin family of marine terpenoids had generated significant attention owing to their potential use as inhibitors of inflammatory response, for example, in the treatment of rheumatoid arthritis [26], and their HIV inhibitory properties [27]. Frondosin B represents an appealing synthetic challenge not only due to its interesting biological activity but also due to its unusual tetracyclic core. The latter features a 2,3-disubstituted benzofuran component, a seven-membered ring, and a tetrasubstituted alkene. Hughes and Trauner chose to join the benzofuran and alkene moieties, simultaneously generating
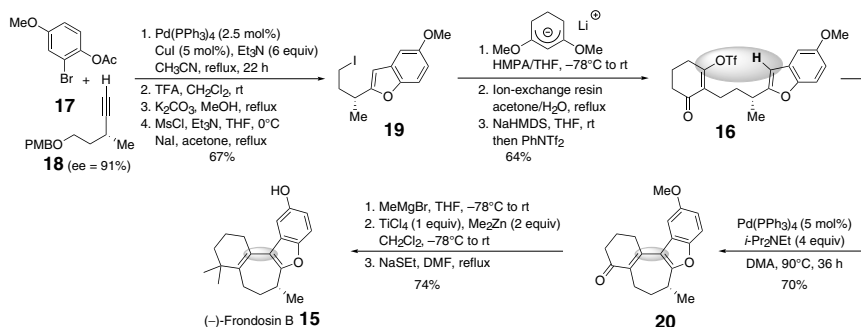

SCHEME 1.5   Synthesis of (−)-frondosin B by Hughes and Trauner.

the seven-membered ring, through an intramolecular palladium-catalyzed carbon–carbon bond-forming reaction (Scheme 1.5). Cyclization precursor **16** was generated in seven steps and in enantiomerically pure form from aryl bromide **17** and alkyne **18** via alkyl iodide **19**. The key carbon–carbon bond-forming reaction was effected by syringe pump addition of vinyl triflate **16**, over 3 h, to a preheated (90°C) solution of Pd(PPh$_3$)$_4$ (5 mol%) and i-Pr$_2$NEt (4 equiv) in DMA (N,N-dimethylacetamide, 0.01 M). After stirring for 36 h at 90°C, the desired tetracycle **20** was isolated in 70% yield. Although the adjacent stereocenter had not racemized under these conditions, partial racemization was found to occur at higher reaction temperatures.

Several experiments provided insight into the mechanism of this transformation. The use of various Lewis acids, including ZnCl$_2$, MgBr$_2$, and BF$_3$·OEt$_2$, in control experiments ruled out the possibility of a conjugate addition/elimination process for carbon–carbon bond formation. The potential for nucleophilic catalysis by triphenylphosphine or i-Pr$_2$NEt was also excluded, indicating that oxidative addition of the vinyl triflate to Pd(0) must occur for C–H bond functionalization to proceed. Three potential mechanisms were discussed for the latter event (Scheme 1.6): a Heck pathway (route a), nucleophilic attack of the electron-rich benzofuran onto the Pd(II) intermediate **21** (S$_E$Ar, route b; see also Scheme 1.2a), and oxidative addition of the C–H bond to generate a Pd(IV) intermediate (route c). On the basis of the complete retention of stereochemistry at the proximal stereocenter, the authors excluded the Heck pathway, which would presumably have led to racemic product. However, MacMillan and coworkers have recently reevaluated the mechanism of this transformation (see below) and concluded that a Heck pathway cannot be excluded at this time [28].

At this point, it should be noted that the stereocenter of (−)-frondosin B **15** was inadvertently misassigned by Hughes and Trauner. Several syntheses have independently confirmed that (−)-frondosin B is in fact of (S)-configuration instead of (R)-configuration as shown above [28,29]. MacMillan and coworkers have proposed that the inversion of configuration at the stereogenic center in Trauner's and Hugues' synthesis must have occurred during the direct alkenylation key step. Presuming that this transformation proceeds through a Heck pathway (route a, Scheme 1.6), MacMillan and coworkers invoke a selective protonation of the enol ether intermediate via stereorelay from the benzofuran C3 stereogenic center to yield (S)-**20** [28].
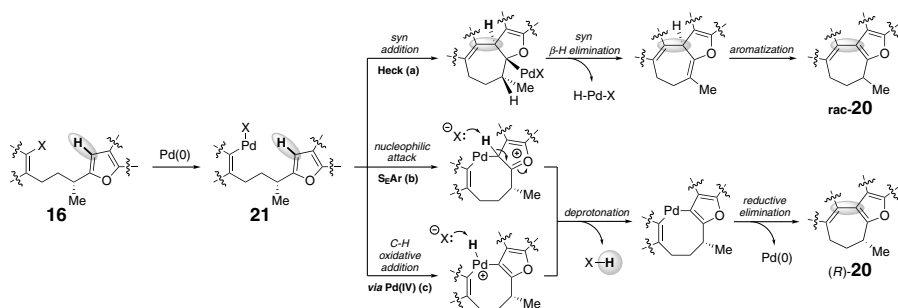

SCHEME 1.6 Proposed mechanisms for Pd(0)-catalyzed benzofuran alkenylation in the synthesis of (−)-frondosin B.

# 1.4. PALLADIUM(0)-CATALYZED INTRAMOLECULAR ARYLATION OF sp^3 C–H BONDS

While numerous methods have been developed and exploited for the functionalization of sp^2 C–H bonds, transformations at aliphatic C–H bonds have been significantly less investigated. The difficulty in functionalizing these positions has been attributed to the lack of beneficial catalyst–substrate interactions through the π-system of the latter [7,30]. Reactions at aliphatic positions are also inherently more challenging due to the possibility of by-product formation via β-hydride elimination [31].

Pd(0)-catalyzed arylation of "unactivated" [32] sp^3 C–H bonds generally involves intramolecular processes, not only to avoid problems of regioselectivity (see Section 1.2) but also to promote interactions between the catalyst and the C–H bond by limiting the degree of freedom in the system [1k,33]. Pioneering work by Dyker demonstrated that oxidative addition of a Pd(0) catalyst into an aryl halide bond, which lies in close proximity to the aliphatic position to be functionalized, could be used as a tool to guide reactivity and selectivity (Scheme 1.7) [34]. Since then, several intramolecular alkane arylation reactions proceeding through an ArPdX intermediate have been reported [1k]. Significant advances were limited in this field until the last decade, potentially due to the lack of knowledge related to the mechanism of C–H bond cleavage in these reactions. However, recent computational and experimental studies have shed light in this area and highlighted a potential common mechanism for C–C bond formation at both aromatic and aliphatic C–H bonds [35]. The proposed concerted metalation–deprotonation (CMD) pathway for sp^3 C–H bond cleavage is similar to that proposed for Pd(0)-catalyzed direct arylation reactions (Scheme 1.7; see also Section 1.2).

Recent efforts by Baudoin and coworkers have led to the development of a Pd (0)-catalyzed synthesis of benzocyclobutenes (BCBs) via the functionalization of methyl sp^3 C–H bonds [36]. Benzocyclobutenes are widely recognized as important synthetic intermediates [37]. Their inherent ring strain allows them, for example, to readily ring open, making them useful starting materials for the synthesis of more complex structures. Baudoin and coworkers have capitalized on this reactivity to synthesize (±)-coralydine (**22**), a tetrahydroprotoberberine alkaloid, using an interesting sp^3 C–H activation/electrocyclization strategy to build its core (Scheme 1.8) [38]. BCB **25** was isolated in 76% yield after treating aryl bromide **24** with Pd(OAc)$_2$ (10 mol%), P(t-Bu)$_3$·HBF$_4$ (20 mol%), and K$_2$CO$_3$ (1.3 equiv) in
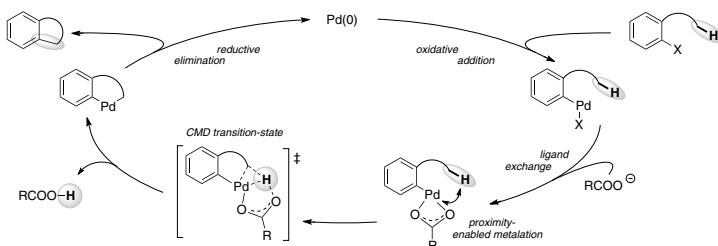
SCHEME 1.7 Catalytic cycle for Pd(0)-catalyzed intramolecular arylation of sp^3 C–H bonds.
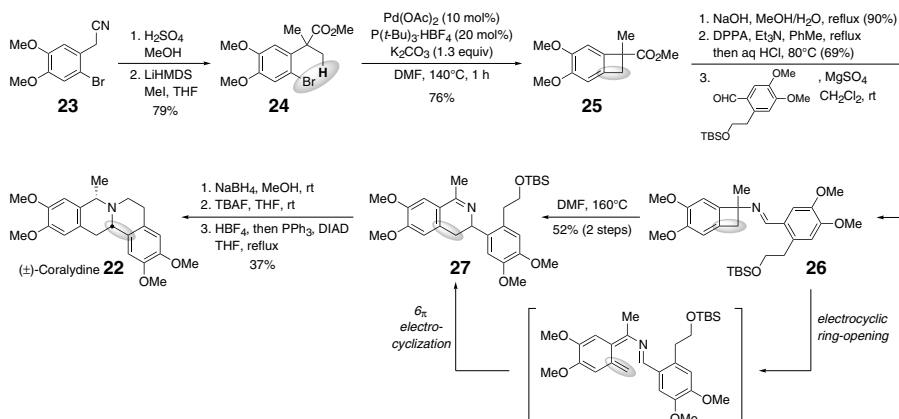
**SCHEME 1.8** Synthesis of (±)-coralydine by Baudoin and coworkers.

DMF at 140°C for 1 h. Following hydrolysis, Curtius rearrangement, and imine formation, BCB **26** underwent a tandem thermal electrocyclic ring-opening/6π-electrocyclization to produce dihydroisoquinoline **27**. Imine reduction by NaBH$_4$ produced a 6:1 mixture of diastereomers in favor of the desired *cis* product in nearly quantitative yield. Isolation of the major diastereomer, TBAF-promoted desilylation, and subsequent Mitsunobu reaction afforded (±)-coralydine (**22**).

1.5. PALLADIUM(II)-MEDIATED INTRAMOLECULAR OXIDATIVE ALKENYLATION OF sp^2 C–H BONDS

Discovered in the early 1970s [39], the Mizoroki–Heck reaction has become a reliable and practical method for the formation of a carbon–carbon bond between an arene and an olefin [23]. While this reaction is a powerful tool for natural product synthesis [40], the required use of an aryl (pseudo)halide as one of the coupling partners leads to additional synthetic operations associated with its preparation, a challenging task in some situations. The direct coupling of a (hetero)arene C–H bond with an unfunctionalized alkene, namely, an oxidative Heck process, represents the chemical ideal in this field (Scheme 1.9a). Initially reported in the late 1960s by Fujiwara and coworkers [41], considerable progress has been made in this field over the past 40 years; while originally mediated by stoichiometric quantities of Pd(II), catalytic processes have been developed in which a terminal oxidant, such as Ag(I), Cu(II), O$_2$, *t*-BuOOH, or *t*-BuOOBz, is added to regenerate the active catalyst [42].

Mechanistic studies have led to a clearer understanding of the Pd(II)-catalyzed coupling of (hetero)arenes with alkenes [43]. The catalytic cycle is initiated by the formation of ArPdX intermediate **28**, generated by the electrophilic substitution of an sp^2 C–H bond by a cationic Pd(II) species (Scheme 1.9b). Subsequent olefin coordination and 1,2-migratory insertion (similar to the traditional Heck reaction) lead to the formation of Pd(II) intermediate **29**. β-Hydride elimination produces the
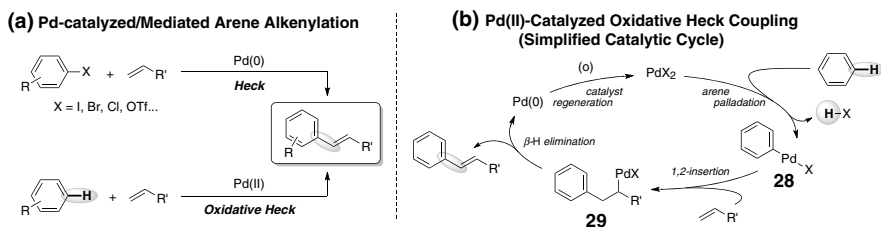
SCHEME 1.9   Pd-catalyzed arene alkenylation.

desired product together with Pd(0), which is reoxidized to Pd(II) in the presence of a terminal oxidant.

As with other C–H functionalization processes, oxidative Heck reactions tend to suffer from drawbacks associated with regioselectivity. While similar strategies to those employed in direct arylation reactions have been developed, these inherently limit the substrates that may be efficiently coupled [42]. For example, electron-rich (hetero)arenes, which typically undergo electrophilic palladation with high levels of selectivity at the most nucleophilic position, have been extensively studied in these processes. Indeed, furan, thiophene, pyrrole, and indole derivatives have all been successfully employed [44]. On the other hand, methods using functional groups that are able to chelate Pd(II) species in order to direct palladation have also been described [45].

In the past 30 years, several groups have applied Pd(II)-enabled oxidative carbon–carbon bond formation to natural product synthesis. The examples discussed in the following section will focus on the use of *stoichiometric palladium* for heteroarene alkenylation/alkylation that proceed through a common mechanism. The use of *Pd(II)-catalyzed* oxidative Heck reactions as a synthetic strategy will be exemplified by Gaunt and coworkers synthesis of rhazinicine (Section 1.9).

The 1978 synthesis of (+)-ibogamine (**30**) by Trost and coworkers is one of the earliest examples of Pd(II)-mediated olefin arylation in natural product synthesis [46]. This member of the iboga alkaloid family was rapidly prepared in only four steps using a simple yet elegant strategy (Scheme 1.10). A boron trifluoride-catalyzed diastereoselective Diels–Alder reaction of chiral diene **31** and acrolein afforded cyclohexene **32** as a 4:1 mixture of diasteromers in 92% yield. Reductive amination of the latter with tryptamine and subsequent intramolecular Pd(0)-catalyzed allylic
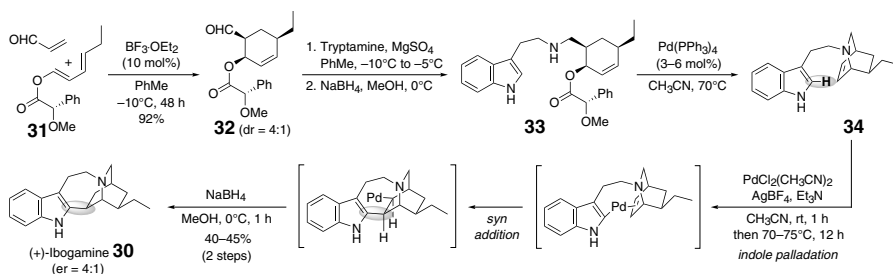
SCHEME 1.10   Synthesis of (+)-ibogamine by Trost et al.
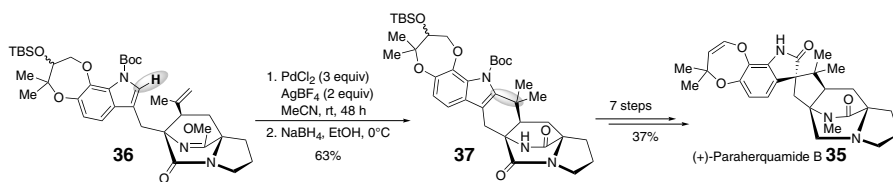
SCHEME 1.11   Synthesis of (+)-paraherquamide B by Williams and coworkers.

amination of **33** provided the desired precursor for the key carbon–carbon bond forming event. Treatment of **34** with stoichiometric PdCl$_2$(CH$_3$CN)$_2$, silver tetrafluoroborate, and triethylamine in acetonitrile, followed by reductive NaBH$_4$ workup to cleave the palladated intermediate, gave (+)-ibogamine (**30**) in a 4:1 er. The mechanism of this key cyclization step was investigated using NaBD$_4$ in MeOD since this reductive workup for σ-palladium complexes had been previously shown to proceed with retention of stereochemistry [47]. Deuterio-ibogamine was isolated with deuterium incorporation occurring *syn* to the indole motif. This observation eliminated the possibility of product formation via initial complexation of palladium to the olefin, activating it toward nucleophilic attack by the electron-rich indole moiety, as this would lead to an *anti*-relationship between the nucleophile and the palladium. However, the *syn* deuterium incorporation lends strong support for a reaction pathway involving indole palladation via C–H bond functionalization, olefin coordination, and *syn* 1,2-insertion (Scheme 1.10).

The first total synthesis of (+)-paraherquamide B (**35**), the simplest member of a family of antiparasitic agents possessing a complex heptacyclic core, was reported by Williams and coworkers in 1993 (Scheme 1.11) [48]. Their synthetic plan featured an indole cyclization to simultaneously form a new carbon–carbon bond and the heptacyclic tetrahydrocarbazole core. Unfortunately, all attempts to effect the cationic cyclization of **36** to **37** using strong protic acids, Lewis acids, or TMSOTf were unsuccessful and led to decomposition of the starting material. Inspired by the work of Trost and coworkers [46,49], indole **36** was treated with a premixed solution of PdCl$_2$ (3 equiv) and AgBF$_4$ (2 equiv) in acetonitrile at room temperature for 48 h. Subsequent slow addition of NaBH$_4$ at 0°C afforded tetrahydrocarbazole **37** in 63% yield [48b]. Intermediate **37** was then converted to (+)-paraherquamide B (**35**), the enantiomer of the naturally occurring compound.

In 2002, Baran and Corey reported the first enantioselective total synthesis of (+)-austamide (**38**) using an intriguing palladium-mediated carbon–carbon bond-forming cyclization at an indole C–H bond (Scheme 1.12) [50]. The viability of converting an intermediate such as indoloazocine **39** to **38** having been previously demonstrated by Hutchison and Kishi [51], Baran and Corey set out to develop a novel method for the rapid construction of **39**. Thus, *N*-prenylated intermediate **40**, prepared quantitatively in three steps from the methyl ester of (*S*)-tryptophan, was treated with Pd(OAc)$_2$ (1 equiv) in acidic media under an oxygen atmosphere at room temperature to afford **39** in 29% yield. From this intermediate, (+)-austamide (**38**) was obtained in four steps. On the basis of the success of this C–H functionalization protocol, Corey and coworkers employed the same strategy in their synthesis of okaramine N, a structural analogue of austamide **38** [52].
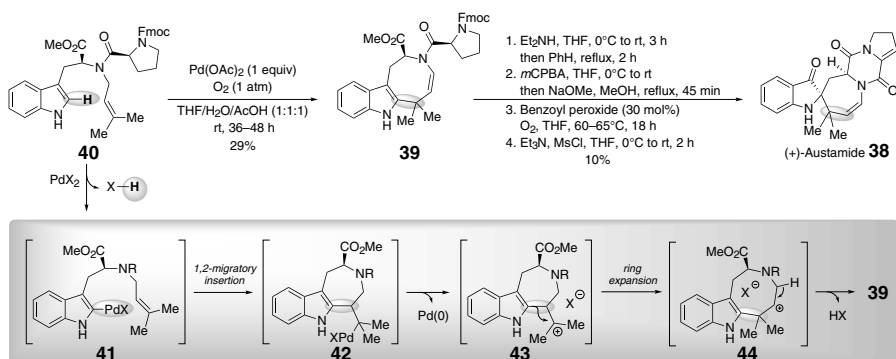
SCHEME 1.12 Synthesis of (+)-austamide by Baran and Corey.

Several important observations were made during the development of the key Pd-mediated cyclization reaction, which provided valuable mechanistic insight. First, acetic acid appeared to play a crucial role in the reaction since no cyclized product was observed in its absence. When the reaction was performed with C2 chloromercurated indole as the cyclization precursor, an increase in reaction rate was observed. From these results, a reaction pathway involving C–H bond cleavage via electrophilic palladation of indole **40** at C2 was proposed, followed by 1,2-migratory insertion, much like the Heck-type processes involved in the synthesis of (+)-ibogamine (**30**) and (+)-paraherquamide B (**35**). Owing to the use of a very polar reaction medium, the authors proposed that the heterolysis of palladated intermediate **42** occurred to produce cationic intermediate **43**. Ring expansion via migration of the electron-rich indole moiety followed by elimination of HX would provide **39**. Alternatively, one could imagine that **39** could be obtained from **42** via β-hydride elimination, followed by reprotonation and ring expansion.

The antiviral marine alkaloid dragmacidin F (**45**) has piqued the interest of the synthetic community due to both its intriguing pyrazinone core and its complex [3.3.1]-bridged ring system [53]. Stoltz and coworkers applied a Pd(II)-mediated oxidative Heck cyclization to prepare the latter moiety in their synthesis of this natural product in 2004 (Scheme 1.13) [54]. Starting from commercially available (–)-quinic acid, pyrrole **46** was prepared in seven steps (32% overall yield). Addition of a stoichiometric quantity of Pd(OAc)$_2$ and 2 equiv of DMSO as a ligand to a solution of **46** in *tert*-butanol and acetic acid yielded the desired [3.3.1]-bicyclic compound in 74% yield after stirring for 10 h at 60°C. Surprisingly, all attempts to form this carbon–carbon bond using a traditional Heck reaction (i.e., from the corresponding 3-bromopyrrole starting material) were met with starting material decomposition or synthetically unacceptable product mixtures. Efforts were also made to render this process catalytic in palladium via the addition of a stoichiometric terminal oxidant to the reaction mixture. Unfortunately, this led to both starting material and product decomposition, presumably through an oxidative pathway.

The transformation of pyrrole **47** to boronic ester **50** proceeded in good yield over a four-step sequence, including a diastereoselective hydrogenation of the exocyclic alkene, a methyl ether formation, a regioselective bromination, and a subsequent metal–halogen exchange. With **50** in hand, a regioselective Suzuki
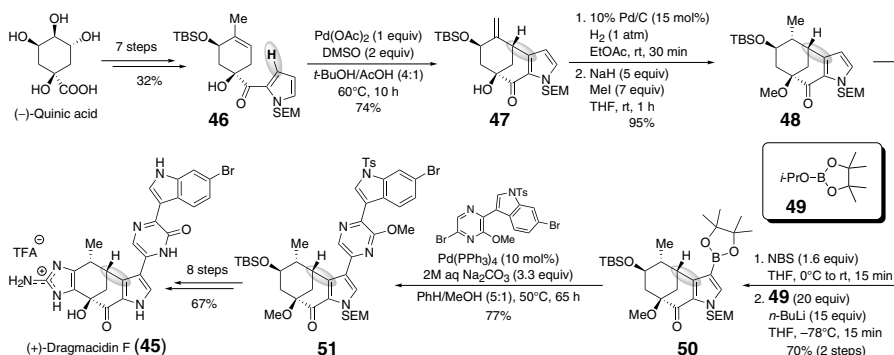
SCHEME 1.13 Synthesis of (+)-dragmacidin F by Stoltz and coworkers.

cross-coupling reaction was performed. Indeed, as previously observed in their related synthesis of dragmacidin D [55], this reaction is selective for the oxidative addition of the more electron-deficient pyrazinyl bromide to Pd(0), leaving the 6-bromoindole fragment untouched. It should be noted that the reaction outcome is highly temperature dependent and significant erosions in selectivity are observed at higher temperatures (80°C). From intermediate **51**, functional group interconversions, a challenging Neber rearrangement, and finally formation of the aminoimidazole moiety completed the total synthesis of (+)-dragmacidin F (**45**).

## 1.6. DIRECTING GROUP-ASSISTED PALLADIUM(II)-ENABLED CARBON–CARBON BOND FORMATION AT sp^3 C–H BONDS

Selective metalation of arene or alkane C–H bonds may be achieved with the assistance of Lewis basic directing groups within the substrate [10,45]. These moieties have been demonstrated to act as ligands for electron-deficient metal centers, mediating carbon–carbon or carbon–heteroatom bond formation at C–H bonds through the formation of stable five- or six-membered metalacyclic intermediates. Since initial examples of stoichiometric cyclometalation reactions using Ru, Rh, Pt, and Pd first appeared in the literature [56], several catalytic processes employing this strategy have been reported. Owing to its compatibility with a broad scope of directing groups and its ability to functionalize both sp^2 and sp^3 C–H bonds, a preference for Pd(II) catalysis has emerged [11]. Lewis basic functional groups including, but not limited to, pyridines, oxime ethers, ketones, amides, and oxazolines have all been employed in these transformations. One should note, however, that while this strategy efficiently overcomes the hurdle of C–H bond selectivity in targets containing multiple potential reaction sites, its application in the synthesis of complex natural products has been less forthcoming. This may be attributed to the nature of some of these directing groups that may be irremovable, such as pyridine, and unfortunately not desired in the final target. Significant strides are currently being made to develop directing groups that may be easily removed or transformed into other desirable functional groups [10,45].
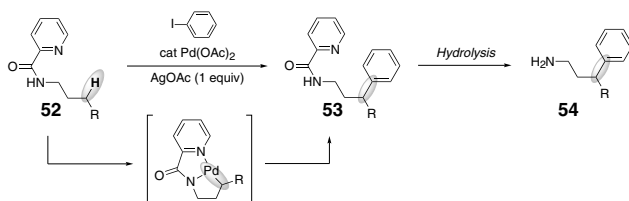
SCHEME 1.14 Picolinamide-directed Pd(II)-catalyzed sp³ C–H bond arylation.

In 2005, Daugulis and coworkers reported a highly selective Pd(OAc)$_2$-catalyzed arylation of aliphatic C–H bonds using pyridine directing groups as removable auxiliaries (Scheme 1.14) [57]. For example, *N*-alkylpicolinamides **52** efficiently underwent regioselective arylation in the presence of catalytic Pd(OAc)$_2$, stoichiometric AgOAc, and an excess of the aryl iodide coupling partner. Subsequent hydrolysis of the auxiliary yielded the γ-arylated amine **54**. Inspired by the efforts of Daugulis and coworkers, Corey and coworkers reported the Pd(OAc)$_2$-catalyzed auxiliary-directed acetoxylation and arylation of β sp³ C–H bonds of α-amino acid derivatives in 2006 [58]. These contributions allowed Feng and Chen to develop a strategy for the total synthesis of celogentin C [59], a bicyclic nonribosomal peptide that acts as an antimitotic agent by inhibiting tubulin polymerization [60].

Celogentin C (**55**) possesses a highly unusual peptidic structure characterized by its Trp C2–His N1 and Trp C6–Leu Cβ linkages (Scheme 1.15). The latter is an extremely rare linkage between amino acids and poses a significant synthetic challenge; however, Feng and Chen were able to apply an auxiliary-directed Pd(II)-catalyzed sp³ C–H arylation reaction to form this key carbon–carbon bond. The 6-iodotryptophan coupling partner **57** was prepared from commercially available Boc-protected tryptophan using a five-step sequence, including a nitration, a reduction, and a Sandmeyer reaction. The sp³ C–H arylation of *N*-phthaloyl leucine derivative **56** (2 equiv) with **57** was effected by Pd(OAc)$_2$ (0.2 equiv) and AgOAc
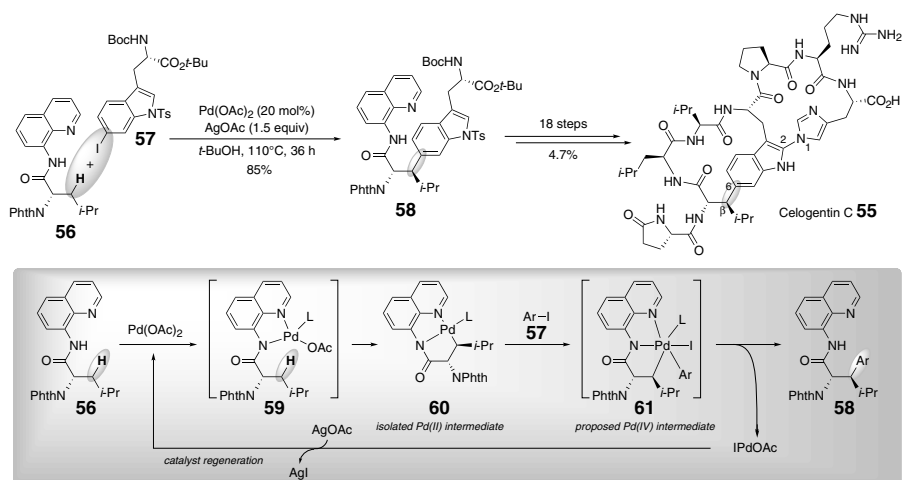

SCHEME 1.15 Synthesis of celogentin C by Feng and Chen.

(1.5 equiv) in *t*-BuOH at 110°C over 36 h in 85% yield. This reaction was performed on a 4 g scale to afford the desired product as a single diastereomer, demonstrating the robustness of this method. With the challenging Trp C6–Leu Cβ bond formed, the total synthesis of celogentin C (**55**) was completed in 18 steps using simple amino acid building blocks.

Mechanistically, this C–H bond functionalization has been proposed to proceed via a Pd(II)/Pd(IV) pathway [57,58]. Chelation of electrophilic Pd(II) to the amino-quinoline auxiliary promotes regio- and diastereoselective C–H bond cleavage, generating the sterically favored *trans*-palladacyclic complex **60**. An analogous Pd(II) species had previously been isolated by Corey and coworkers in their evaluation of the sp³ C–H bond acetoxylation of α-amino acid derivatives [58][i]. Oxidative addition of the aryl iodide to **60** is then proposed to generate Pd(IV) intermediate **61**, which can reductively eliminate the desired product with concomitant catalyst regeneration via salt metathesis in the presence of AgOAc.

Auxiliary-directed Pd(II)-enabled sp³ C–H bond functionalization was relied upon in two key carbon–carbon bond forming events in the synthesis of the teleocidin B4 core (**62**) by Sames and coworkers, the auxiliary-directed Pd(II)-enabled sp³ C–H bond functionalization relied upon two key carbon–carbon bond forming events (Scheme 1.16) [61]. Schiff base **63** was chosen as a key synthetic intermediate owing to its ability to chelate palladium and direct cyclometalation of the adjacent *tert*-butyl group. More important, this intermediate tolerates directing group removal via hydrolysis, an important feature since the latter is absent from the desired product. A screening of metal salts revealed that PdCl$_2$ (1.2 equiv) in the presence of NaOAc (3 equiv) furnished cyclometalated product **64** in 75% yield. The *ortho*-methoxy substituents in the directing group appeared to play a pivotal role as no cyclopalladated product was detected in their absence. Key to the stability of complex **64** is the lack of a β-hydrogen atom that could lead to the formation of undesired olefin by-products. This intermediate underwent transmetalation with boronic acid **65**
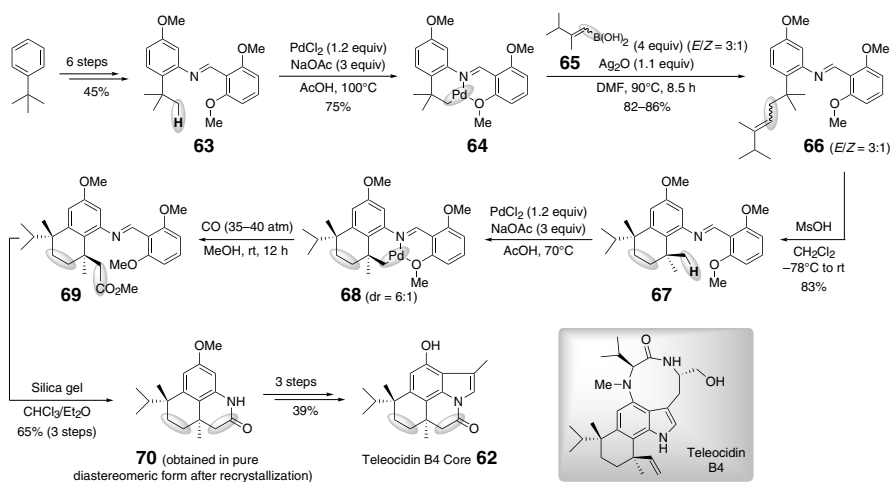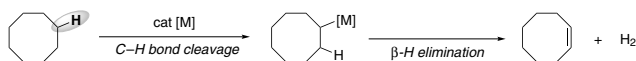

SCHEME 1.16 Synthesis of teleocidin B4 by Sames and coworkers.

(4.0 equiv) in the presence of Ag_2O (1.1 equiv) in DMF at 90°C to afford **66** in 82–86% yield. Following methanesulfonic acid-mediated cyclohexane ring closure to afford **67**, a second cyclopalladation reaction was performed. Treatment of **67** with $PdCl_2$ in the presence of NaOAc in freshly distilled glacial acetic acid at 70°C afforded **68** as a 6:1 mixture of diastereomers. The stereochemical outcome of this transformation appears to indicate a preference for the isopropyl group to occupy the pseudo-equatorial position, predisposing the *anti*-methyl group to react with palladium due to its accessibility (pseudo-equatorial as well). Methoxycarbonylation of **68** by addition of CO (35–40 atm) and methanol yielded **69**, which was directly converted to lactam **70** via acidic hydrolysis of the chelating auxiliary. After recrystallization and three additional synthetic operations, the core of teleocidin B4 **62** was obtained.
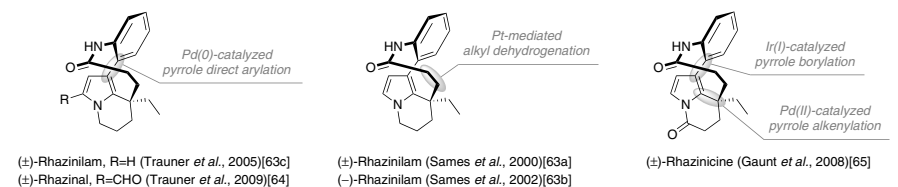
1.7. PLATINUM(II)-MEDIATED ALKANE DEHYDROGENATION

While the discussion has thus far focused on the formation of carbon–carbon bonds, C–H bond functionalization has also been investigated in the context of alkane dehydrogenation [1e,62]. These reactions typically occur at electrophilic Rh, Ir, Re, and Pt centers as a two-step process consisting of a C–H bond cleavage generating a metal–carbon bond, followed by a β-hydride elimination generating the desired alkene (Scheme 1.17). The release of H_2 gas entropically favors these reactions, yet most dehydrogenation processes are overall thermodynamically disfavored due to the high energetic cost associated with the cleavage of sp^3 C–H bonds (endothermic process). In the past, reactions were carried out under extreme temperatures ($>500°C$) or in the presence of a sacrificial alkene as an H_2 acceptor to render these processes more favorable, thus making dehydrogenation not amenable to total synthesis. However, milder techniques to drive the reaction equilibrium toward product formation have been developed, including the removal of H_2 gas from the reaction mixture or the use of photochemical rather than thermal energy.

Rhazinilam, rhazinal, and rhazinicine, three members of the *Aspidosperma* family of natural products, have received significant attention from the synthetic community due to their ability to interfere with tubulin polymerization, making them potential anticancer agents. More specifically, their intriguing structure, consisting of an axially chiral nine-membered lactam ring containing a heterobiaryl unit, has made them excellent candidates for the application of C–H functionalization reactions. In fact, several independent syntheses have been reported using such strategies. Remarkably, these efforts utilize very different transformations at C–H bonds, demonstrating the power of this method in natural product synthesis (Scheme 1.18) [63–66]. Representative syntheses will be discussed in the next section


SCHEME 1.17   Transition metal-catalyzed alkane dehydrogenation.

(±)-Rhazinilam, R=H (Trauner *et al.*, 2005)[63c]
(±)-Rhazinal, R=CHO (Trauner *et al.*, 2009)[64]

(±)-Rhazinilam (Sames *et al.*, 2000)[63a]
(−)-Rhazinilam (Sames *et al.*, 2002)[63b]

(±)-Rhazinicine (Gaunt *et al.*, 2008)[65]

SCHEME 1.18 Various C–H bond functionalization strategies for the synthesis of rhazinilam, rhazinal and rhazinicine.

(synthesis of rhazinilam by Sames and coworkers) and in Section 1.9 (synthesis of rhazinicine by Gaunt and coworkers.).

In 2000, Johnson and Sames reported the total synthesis of (±)-rhazinilam using a Pt(II)-mediated alkane dehydrogenation strategy [63a]. Two years later, enantioenriched (−)-rhazinilam (**71**) was prepared with the assistance of a chiral oxazoline-derived auxiliary to guide the key C–H functionalization event (Scheme 1.19) [63b]. Their synthesis began with the preparation of intermediate **72** in five steps from readily available starting materials. Compound **72** possesses two enantiotopic ethyl groups whose selective dehydrogenation via asymmetric C–H bond functionalization poses a formidable synthetic challenge. Schiff base formation from **72** and chiral oxazolinyl ketone **73** followed by the addition of [Me₂Pt (μ-SMe₂)]₂ (0.5 equiv) afforded platinum complex **74** in 29% yield over two steps. Treatment of this intermediate with 1 equiv of triflic acid generated cationic platinum species **75** (3:2 mixture of isomers) with concomitant loss of methane. Upon addition of 2,2,2-trifluoroethanol and heating for 72 h, diastereospecific dehydrogenation took place to provide **76**. The diastereoselectivity and yield of this process were found to be highly dependent on the reaction temperature and the steric bulk of the auxiliary. Greater yields were obtained at higher temperatures, unfortunately at the expense of diastereoselectivity. In addition, while bulkier substituents at the auxiliary stereo-center improved diastereoselectivities, the preparation of the corresponding platinum complexes was often problematic and low yielding (<10%). On the basis of these results, the authors settled on heating at 70°C for 72 h to perform the desired transformation, obtaining **76** as a 4.5:1 ratio of isomers. With intermediate **76** in
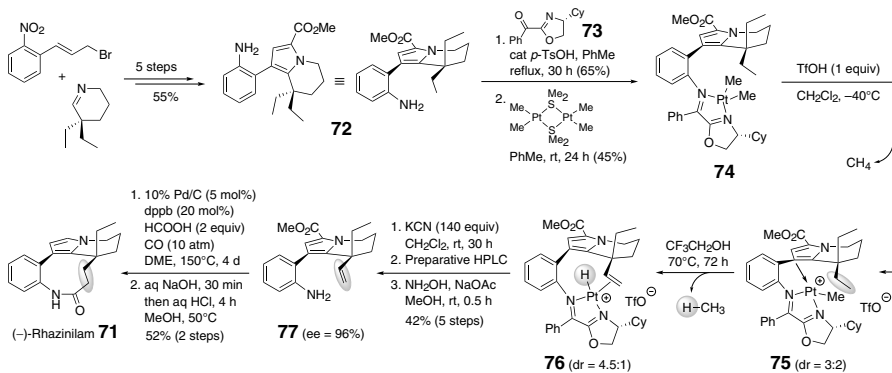
**SCHEME 1.19** Synthesis of (−)-rhazinilam by Johnson and Sames.

hand, platinum decomplexation was facilitated by the addition of potassium cyanide (140 equiv). Separation of the resulting diastereomers by reverse-phase preparative HPLC and subsequent auxiliary removal afforded **77** in 96% ee, which was readily converted to (−)-rhazinilam (**71**).

1.8. PALLADIUM(II)-ENABLED CARBON–OXYGEN BOND FORMATION AT sp^3 C–H BONDS

The selective transformation of simple C–H bonds into carbon–heteroatom bonds is a much sought after process due to its significant potential to facilitate functional group installation in complex organic syntheses. C–H oxidation is of particular interest due to the high degree of oxygenation contained in several classes of natural products and the versatility of these derivatives as synthetic intermediates. Historically, this field has been focused on the conversion of methane to methanol, a very simple yet highly attractive transformation. More recently, efforts have been focused on the oxidation of C–H bonds in more complex systems, with Pd(II) and Pt(II) catalysts being efficiently utilized.

As is common to most C–H bond functionalization processes, site selectivity poses a significant challenge to the application of C–H bond oxygenation in natural product synthesis. Two principal strategies have been employed to overcome this hurdle. Lewis basic functional groups found within the substrate have been used to chelate the metal center and direct cyclometalation to effect site-specific C–H bond functionalization. This general concept is discussed in Section 1.6. A second strategy involves the functionalization of allylic C–H bonds, which is believed to proceed via alkene coordination to the metal and directed intramolecular C–H bond cleavage (see below).

In 1985, Baldwin and coworkers published an insightful report on the use of cyclopalladation reactions for the functionalization of unactivated methyl C–H bonds [67]. This study revealed that a carefully designed oxime-directed Pd(II)-based system could selectively oxidize a single methyl C–H bond within a complex natural product. Since then, Baldwin's method has been applied to the synthesis of several natural product targets [68], including lobatoside E (**78**) [69], a member of the cyclic bisdesmosides family. Yu and coworkers envisioned that the C23 hydroxyl group in the pentacyclic triterpene core of lobatoside E could arise from the selective oxidation of oleanolic acid, a highly abundant natural triterpene (Scheme 1.20). To this effect, oleanolic acid derivative **79**, containing a chelating oxime functional group, was prepared. Addition of Na$_2$PdCl$_4$ (1.1 equiv) and sodium acetate (1.1 equiv) in acetic acid (0.02 M) yielded complex **80** after 72 h of stirring at room temperature. Compound **80** was further transformed into an *O*-acetylated pyridine-ligated complex since intermediates of this type had previously been demonstrated to readily oxidize when treated with Pb(OAc)$_4$ [67]. Subsequent reductive workup with NaBH$_4$, required to remove Pd(II) salts coordinated to the product, afforded **81** in good yield (72% from **79**). The complete selectivity for C–H oxidation of the equatorial methyl group can be explained by its coplanar arrangement with the oxime directing group.
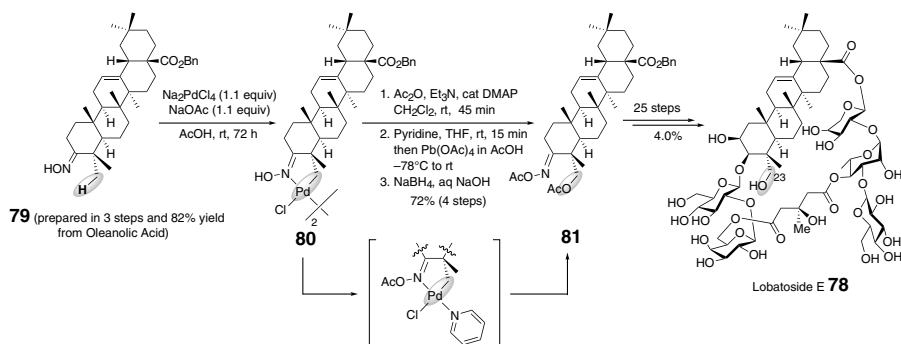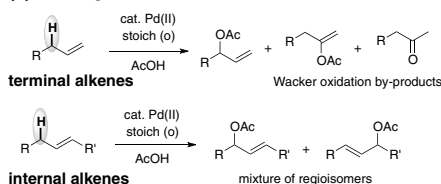
**SCHEME 1.20**   Synthesis of lobatoside E by Yu and coworkers.

The oxidation of allylic sp^3 C–H bonds by palladium(II)-based systems has been a method of interest for over 40 years [70,71]. These reactions are typically carried out using catalytic Pd(OAc)$_2$ in combination with a stoichiometric amount of a terminal oxidant, for example, benzoquinone, MnO$_2$, or O$_2$. Although traditional stoichiometric methods have now been replaced by milder catalytic conditions, many limitations, especially concerning regioselectivity, still restrict the application of this process in total synthesis. For example, terminal alkenes usually undergo competitive Wacker oxidation processes, while internal alkenes typically give mixtures of regioisomeric allylic acetates (Scheme 1.21a). Some of these problems are currently being addressed, notably through the development of new catalytic systems incorporating novel ligands that significantly alter product distributions [72]. Mechanistically, catalyst coordination to the alkene is believed to direct selective C–H bond cleavage, generating π-allyl Pd(II) intermediate **82** (Scheme 1.21b). Carbon–oxygen bond formation yields both corresponding products and Pd(0), which is in turn reoxidized to Pd(II) in the presence of a terminal oxidant.

In 2006, White and coworkers reported a novel method for the preparation of macrocycles employing an allylic C–H bond oxidation strategy [73]. Based on their Pd(OAc)$_2$/sulfoxide-catalyzed benzoquinone-promoted regioselective allylic oxidation system [72a,b], a wide range of 14- to 19-membered macrolides were prepared in synthetically useful yields (Scheme 1.22a). Mechanistic investigations revealed that this reaction proceeds through the formation of a π-allyl Pd-carboxylate complex, with C–O bond formation occurring via an inner sphere pathway (reductive
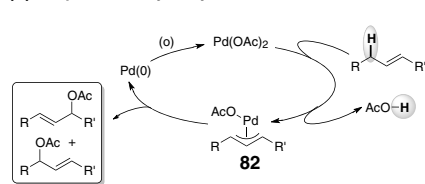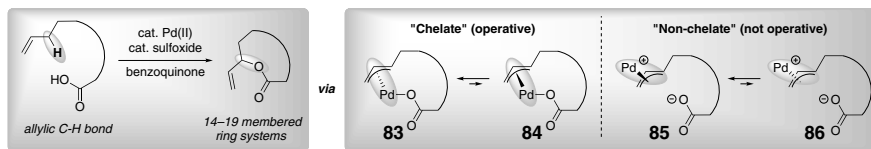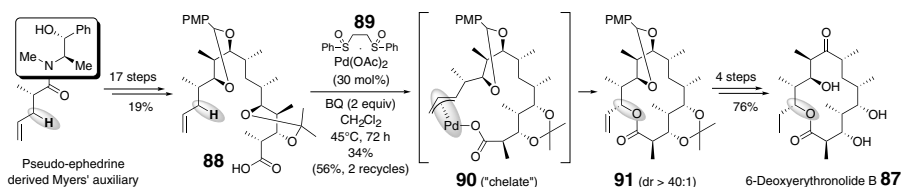

SCHEME 1.21   Pd(II)-catalyzed allylic C–H oxidation.

(a) Macrocycle synthesis *via* Pd(II)-catalyzed Allylic C–H Oxidation

**(b) Total synthesis 6-deoxyerythronolide B**

SCHEME 1.22   Synthesis of 6-deoxyerythronolide B by Stang and White.

elimination). Interestingly, benzoquinone plays an active and crucial role in the latter event as reductive elimination does not occur in its absence. Stang and White later applied this macrolactonization strategy to the total synthesis of 6-deoxyerythrono-lide B (**87**), the aglycone of the antibiotic erythromycin (Scheme 1.22b) [74]. The key C–H oxidation precursor **88** was prepared using traditional synthetic methods for polyketide synthesis, that is, a linear and iterative combination of stereoselective aldol and alkylation reactions. Treatment of **88** with 10 mol% of Pd(OAc)₂/bis-sulfoxide catalyst **89** (generated *in situ*) unfortunately led to only trace amounts of product even over prolonged reaction times. However, by increasing the catalyst loading to 30 mol % and the concentration of the reaction medium to 0.02 M, **91** could be obtained in 34% yield. Recycling (twice) the unreacted starting material afforded 56% isolated yield of macrocycle **91** with excellent levels of diastereoselectivity (dr > 40:1). Based on previous mechanistic findings [72b], deuterium-labeling experiments, and molecular modeling studies, the reaction is believed to proceed through rapidly interconverting π-allyl Pd-carboxylate intermediates **83** and **84** (Scheme 1.22a, intermediate **90** in Scheme 1.22b). The high level of diastereoselectivity arises from the product-like transannular character of the transition state for C–O bond formation (reductive elimination), favoring a pseudoequatorial positioning of the exocyclic alkene.

1.9. IRIDIUM-CATALYZED BORYLATION OF sp²
C–H BONDS

Arylboronate esters and acids hold a privileged place as important synthetic intermediates in the areas of fine chemical production and material sciences, as well as in natural product synthesis [75]. Notably, these versatile synthons participate in metal-catalyzed cross-coupling reactions as well as in 1,2- and 1,4-additions to carbonyls [76]. Typically, they are prepared from the corresponding aryl halides, which are derived from simple arenes, therefore limiting their scope and availability

(a) Traditional methods for the preparation of ArB(OR)$_3$
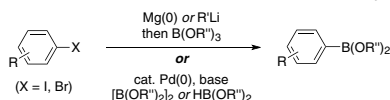
(b) Transition metal-catalyzed direct C–H borylation
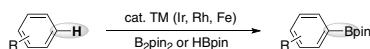
(c) Ir(I)-catalyzed direct C–H borylation of heteroarenes

electron-rich heteroarenes

electron-poor heteroarenes

1 : 2
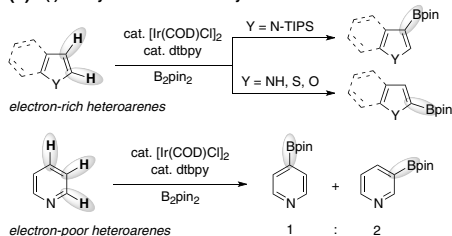
(d) Ir(I)-catalyzed direct C–H borylation (catalytic cycle)
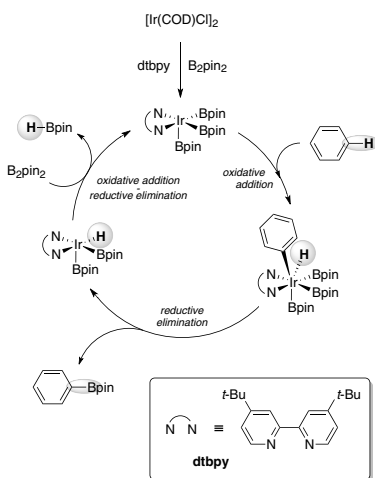
SCHEME 1.23   Transition metal-catalyzed C–H borylation.

(Scheme 1.23a). A recent alternative involves the transition metal-catalyzed direct borylation of simple arene C–H bonds (Scheme 1.23b) [77].

While iron and rhodium have been reported to effect sp^2 C–H borylation, iridium-based catalysts have been more extensively investigated. In 1999, Iverson and Smith disclosed the borylation of deuterated benzene in the presence of excess HBpin catalyzed by Cp*Ir complexes [78]. Since then, more active catalyst combinations have been developed, consisting of an iridium precatalyst and, for example a, phosphine- [79] or bipyridine-derived [80] ligands for example. The regioselectivity of these reactions is predominantly controlled by steric effects, with the least hindered C–H bond typically reacting. As a result, this provides complementary products to those obtained using more conventional methods for which the regioselectivity is driven by electronic effects (S$_E$Ar) or directing groups (such as directed *ortho*-metalation [81]. It should, however, be noted that directing groups can also be used in direct C–H borylation to provide *ortho*-borylated arenes [82].

C–H borylation of π-electron-rich and electron-deficient heteroarenes has also been investigated. Treatment of thiophene, furan, pyrrole, and indole derivatives with B$_2$pin$_2$ and catalytic [Ir(COD)Cl]$_2$/dtbpy (dtbpy = di-*tert*-butylbipyridine) selectively provides C2 borylated heteroarenes (Scheme 1.23c) [83]. A reversal in regioselectivity favoring C3 borylation is observed when bulky *N*-substituted pyrroles and indoles are subjected to the same reaction conditions. This result capitalizes on previous observations of slower reaction rates for borylation at sterically encumbered C–H bonds (i.e., control of regioselectivity based on steric effects). In the case of π-deficient heteroarenes, such as pyridine, slightly higher reaction temperatures are required (100°C instead of 80°C) for C–H borylation to occur in good yield (Scheme 1.23c). Unfortunately, product mixtures are usually obtained; in the case of pyridine, for example, a 2:1 ratio of 3- and 4-borylpyridine is observed. Although

the origin for this regioselectivity is not well understood, reversible boron or iridium binding to the nitrogen lone pair has been proposed to activate the substrate toward C–H bond functionalization while blocking the C2 reaction site [84].

The mechanism of bipyridine-ligated Ir-catalyzed C–H borylation has been extensively studied [84,85]. The isolation of kinetically competent catalytic intermediates, NMR experiments, kinetic studies, and theoretical investigations using DFT calculations have led to the proposed catalytic cycle shown in Scheme 1.23d. The active catalytic species is believed to be the trisboryl iridium–dtbpy complex generated from the iridium precatalyst, dtbpy, and B_2pin_2. This Ir(III) complex is involved in the rate-limiting C–H bond cleaving event, which most likely proceeds via oxidative addition of the aryl C–H bond, leading to the formation of an Ir(V) intermediate. Reductive elimination of the borylated arene, followed by oxidative addition of B_2pin_2 and reductive elimination of HBpin, regenerates the active Ir(III) catalyst. It should be noted that an alternative mechanism for C–H bond cleavage via σ-bond metathesis between Ir(dtbpy)(Bpin)$_3$ and Ar–H has also been proposed.

A concise synthesis of the pyrrole alkaloid rhazinicine (**92**), a member of the *Aspidosperma* family of natural products (see Section 1.7), featuring two different key C–H bond functionalization events was reported by Gaunt and coworkers in 2008 (Scheme 1.24) [65]. The densely functionalized pyrrole nucleus of **92** was elaborated using a C3-selective C–H borylation reaction and a Pd(II)-catalyzed oxidative Heck cyclization (see Section 1.5). Based on the strategy previously outlined for C–H borylation of electron-rich heteroarenes (Scheme 1.23c) [83], *N*-Boc-protected pyrrole **93** was submitted to a one-pot Ir-catalyzed C–H borylation and Pd(0)-catalyzed Suzuki coupling sequence. The borylation protocol occurred with excellent regioselectivity for the most sterically accessible C–H bond to give **95** in 78% yield as a single isomer. Boc removal followed by *N*-acylation provided **97** in 69% yield over two steps. With this intermediate in hand, the second key C–H bond functionalization was performed to access the tetrahydroindolizine ring. The prior installation of a TMS group on the pyrrole nucleus offered the advantage of temporarily blocking the more accessible C5 position and therefore favoring Pd(II)-catalyzed oxidative Heck cyclization at C2. Treatment of **97** with Pd(TFA)$_2$ (10 mol%), using *t*-BuOOBz as the oxidant, in a dioxane/DMSO/AcOH solvent mixture at 70°C for 24 h afforded **98**
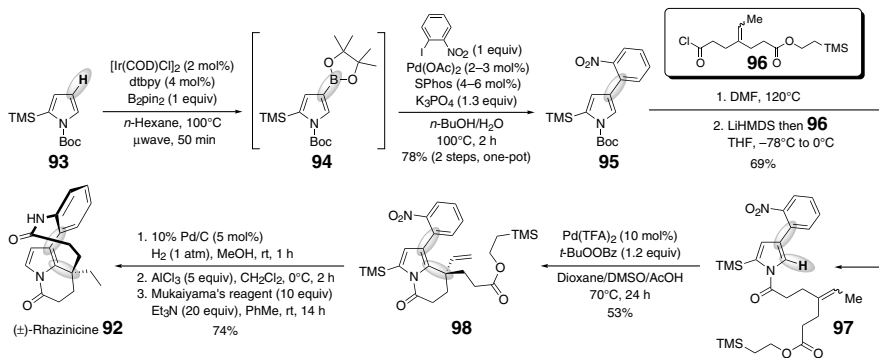
**SCHEME 1.24**   Synthesis of (±)-rhazinicine by Gaunt and coworkers.
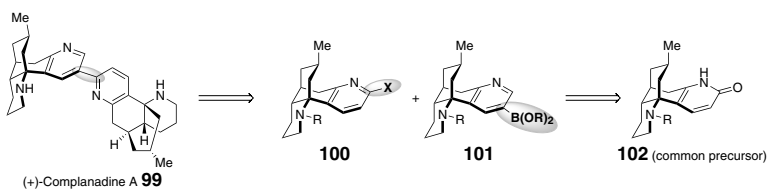
SCHEME 1.25 Retrosynthetic analysis of (+)-complanadine A by Fischer and Sarpong.

in 53% yield [86]. Owing to the significant steric hindrance at C2, the more active Pd(TFA)$_2$, instead of the more traditional use of Pd(OAc)$_2$ for oxidative Heck reactions, was required to obtain **98** in acceptable yield. Hydrogenation of the nitro and alkene moieties, followed by removal of the silyl protecting groups and macrolactamization delivered (±)-rhazinicine (**92**).

The *Lycopodium* alkaloid complanadine A (**99**) enhances the secretion of nerve growth factor in human glial cells, making it an attractive compound for the treatment of neurodegenerative diseases [87]. As a synthetic target, it represents an interesting challenge due to its unsymmetrical dimeric structure. While its synthesis can be simplified to the preparation of the monomeric unit lycodine, the unsymmetrical nature of the dimer requires the selective installation of cross-reactive functional groups at C3 of one monomer and C2 of the other in order to combine the two halves (Scheme 1.25). To this effect, Fischer and Sarpong relied on a late-stage Suzuki cross-coupling reaction between C2 triflate **100** and C3 boronic ester **101** in their total synthesis of complanadine A (**99**) [88]. Compounds **100** and **101** were prepared from a common synthetic intermediate **102**, employing an Ir-catalyzed C–H borylation strategy in the case of **101**.

Key precursor **103** was prepared based on the synthesis of racemic *N*-desmethyl-α-obscurine by Schumann and Naumann (Scheme 1.26) [89]. Treatment of **103** with Boc$_2$O and triethylamine provided the mono-Boc-protected intermediate, which was oxidized to pyridinone **102** using Pb(OAc)$_4$. This species was finally converted to triflate **100** in 72% yield using triflic anhydride in pyridine. Having prepared one of the monomeric units, the preparation of boronic ester **101** was initiated by removal of the triflate functional group under palladium catalysis.
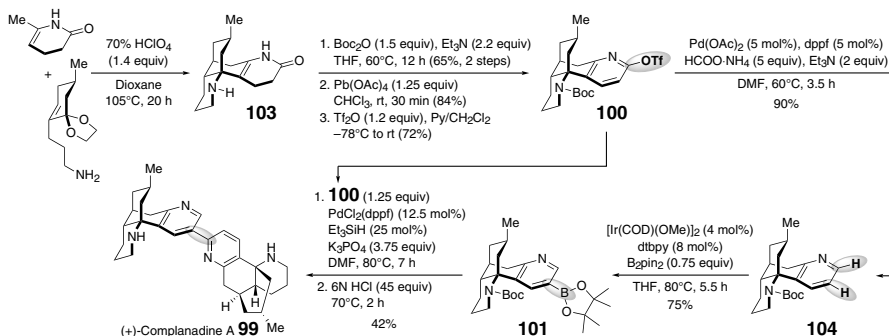
SCHEME 1.26 Synthesis of (+)-complanadine A by Fischer and Sarpong.

Subsequent treatment of **104** with [Ir(COD)(OMe)]$_2$ (4 mol%), dtbpy (8 mol%), and B$_2$pin$_2$ (0.75 equiv) in THF at 80°C provided **101** in 75% yield. This C–H bond functionalization occurred with high levels of selectivity at the C3 position, which is consistent with previous observations for pyridine derivatives (Scheme 1.23c) [83] and highlights the role of steric effects on regioselectivity in C–H borylation chemistry. With the second coupling partner in hand, palladium-catalyzed Suzuki cross-coupling between **100** and **101** followed by protecting group removal afforded (+)-complanadine A (**99**).

1.10.   RHODIUM(I)-CATALYZED INTRAMOLECULAR DIRECTED ALKYLATION OF sp² C–H BONDS

Similar to palladium-based systems, rhodium catalysts have been significantly investigated in the context of C–C bond formation at C–H bonds due to the variety of transformations they can perform and their general functional group tolerance [90]. The use of Rh(I) catalysis has emerged as a powerful tool for the addition of an sp² C–H bond across an unsaturation, leading to the formal alkylation or alkenylation of arenes and olefins [91,92]. Typically, chelating functional groups on the substrate are required to direct site-selective C–H bond functionalization (see Section 1.6), with pyridine and more recently imine moieties having been exploited to this effect.

Compared to Rh(I)-catalyzed (hetero)arene C–H functionalizations, the equivalent reactions using olefin C–H bonds are significantly less developed (see Section 1.10). This can be attributed to two inherent challenges in these systems [90b]. First, olefin isomerization under the reaction conditions leads to product mixtures. Moreover, carbonyl-derived chelating groups (i.e., imines) not only direct cyclorhodation but also activate the alkene toward competitive side reactions such as conjugate additions. Although the latter challenge has traditionally been overcome by using heterocycle-containing directing groups [92a], the development of new catalysts that combine a Rh(I) precatalyst with an electron-donating phosphine ligand has enabled the efficient use of imines as directing groups [92c–e]. With the establishment of these more efficient catalysts for C–H functionalization, reaction temperatures can be significantly decreased, thus minimizing the problems ensuing from olefin isomerization. It should also be noted that this issue is much less problematic in intramolecular reactions.

The scope of *intermolecular* arene alkylation reactions is unfortunately very limited with respect to the olefin coupling partner. For example, internal olefins rapidly isomerize to terminal olefins, leading exclusively to linear substituted products. As well, olefins with heteroatom substituents, for example, vinyl ethers, are not tolerated in these reactions. However, these problems can be avoided by performing the reaction in an *intramolecular* fashion, where the alkene is tethered *meta* to the directing group.

In 2005, Bergman, Ellman, and coworkers reported the total synthesis of (+)-lithospermic acid (**105**) [93], a compound of interest in the development of a treatment for AIDS due to its ability to inhibit HIV-1 integrase [94]. The highly functionalized dihydrobenzofuran core of this target was prepared using an
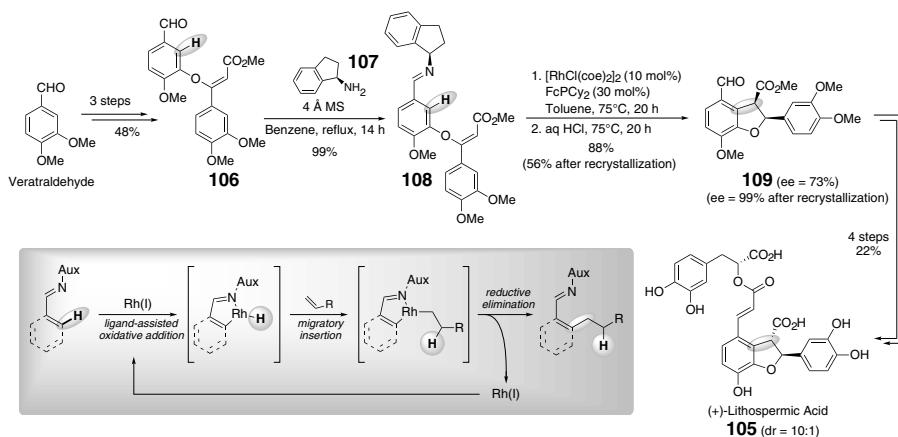
SCHEME 1.27 Synthesis of (+)-lithospermic acid by Bergman, Ellman, and coworkers.

unprecedented diastereoselective Rh(I)-catalyzed intramolecular alkylation of an arene C–H bond (Scheme 1.27). Starting from veratraldehyde, alkene **106** was obtained in three steps and with 55% yield. The transformation of this intermediate to enantioenriched dihydrobenzofuran **109** was investigated using both chiral catalysts and chiral auxiliaries. Unfortunately, inadequate yields and enantioselectivities were obtained with the wide range of chiral catalytic systems that were tested. However, optically pure aminoindane **107** was identified as optimal for inducing diastereoselective olefin insertion during a screen of potential chiral imine auxiliary directing groups. Accordingly, imine **108** was prepared by refluxing **106** and (*R*)-aminoindane **107** in benzene for 14 h in the presence of 4 Å molecular sieves. Subsequent treatment of **108** with [RhCl(coe)$_2$]$_2$ (10 mol%) and (dicyclohexylphosphinyl)ferrocene (FcPCy$_2$) (30 mol%) yielded dihydrobenzofuran **109** in 88% yield and 73% ee after hydrolysis. The product was further purified by recrystallization in benzene/pentane mixtures to obtain **109** in 56% yield as a single enantiomer. The synthesis of (+)-lithospermic acid **105** was completed in four additional synthetic steps. The mechanism of this transformation is proposed to occur via a three-step process involving: (i) auxiliary-directed oxidative addition of the C–H bond to the rhodium(I) catalyst, (ii) diastereoselective *syn*-olefin insertion, and (iii) reductive elimination of the new carbon–carbon bond with concomitant regeneration of Rh(I) (Scheme 1.27).

With the development of new catalysts for the intramolecular alkylation of olefin C–H bonds [92b], Tsai and coworkers were able to apply this strategy toward the asymmetric synthesis of (−)-incarvillateine (**110**) (Scheme 1.28) [95]. This monoterpene alkaloid, which exhibits analgesic properties [96], presents an interesting synthetic challenge due to the five contiguous stereocenters found in the bicyclic piperidine moieties it contains. The intramolecular alkylation precursor **112** was prepared from commercially available **111** in 85% yield using an asymmetric allylation, TBS protection, and cross-metathesis sequence, followed by imine formation. Treatment of imine **112** with [RhCl(coe)$_2$]$_2$ (2.5 mol%) in the presence of phosphine ligand **113** (5 mol%) provided the desired cyclized product **114** as a
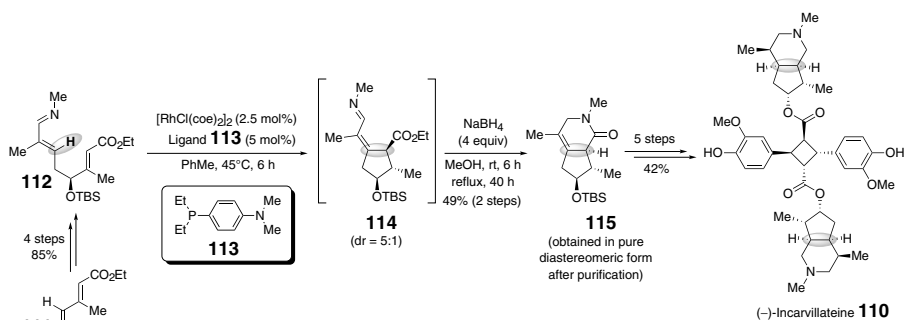
SCHEME 1.28   Synthesis of (−)-incarvillateine by Tsai, Bergman and Ellman.

5:1 mixture of diastereomers. A screen of ferrocenyl dialkyl phosphines and 4-(dimethylamino)phenyl dialkyl phosphines led to the choice of ligand **113** for this transformation as it provided **114** in the greatest diastereomeric ratio. Crucial to the success of this strategy was the development of a highly active catalyst system that enabled the reaction to occur at 45°C and avoided olefin isomerization, which would have led to erosion of the diastereo isomeric ratio. Since **114** readily isomerizes to the ester-conjugated alkene, the crude product was directly reduced using $NaBH_4$ and transformed into lactam **115**. The synthesis was completed using a short five-step sequence, providing (−)-incarvillateine **110** in 15% overall yield.

1.11.   RHODIUM(III)-CATALYZED SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES

Compared to Pd(II)/Pd(0) processes for oxidative carbon–carbon bond formation (see Section 1.5), the equivalent Rh(III)/Rh(I) catalytic systems have remained relatively unexplored until recently. Indeed, in the past 5 years, there has been a flurry of reports on the oxidative coupling of (hetero)arenes containing chelating functional groups with alkynes and alkenes under rhodium catalysis [90c]. Carboxylic acids, alcohols, imines, and amides have all been used to direct selective C–H bond cleavage, yielding a wide range of heterocyclic products when reacted with an alkyne (Scheme 1.29a). These reactions are proposed to occur through a Rh(III)-catalyzed ligand-directed C–H bond cleavage to produce rhodacycle **116** (Scheme 1.29b). Following alkyne insertion into the rhodium–carbon bond, reductive elimination delivers the desired
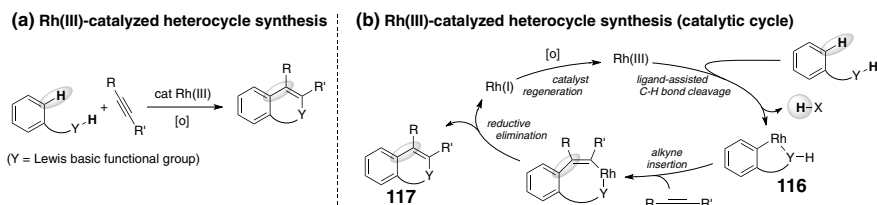
SCHEME 1.29   Rh(III)-catalyzed heterocycle synthesis.
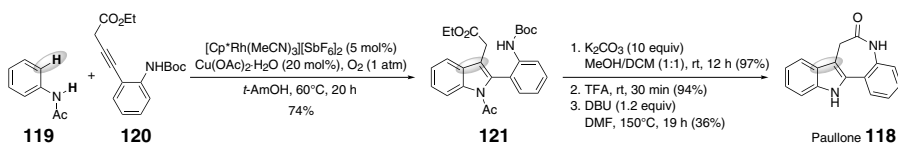
**SCHEME 1.30**   Synthesis of paullone by Fagnou and coworkers.

heterocycle **117**. The resulting Rh(I) species is reoxidized to Rh(III) by an external oxidant, such as $Cu(OAc)_2$, present in stoichiometric quantities or as a cocatalyst under an atmosphere of O_2.

Despite the relative infancy of Rh(III)-catalyzed C–H bond functionalization reactions, the power of this method for the rapid construction of heterocyclic scaffolds has recently been demonstrated by Fagnou and coworkers in the synthesis of paullone **118** (Scheme 1.30) [97], an inhibitor of cyclin-dependent kinases (CDKs) [98]. The indole core of paullone was formed using a Rh(III)-catalyzed oxidative coupling of acetanilide with a strategically functionalized internal alkyne [99]. Alkyne **120**, readily prepared in four steps in 50% overall yield from *o*-iodoaniline, was coupled with acetanilide **119** in the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%), copper(II) acetate (20 mol%), and molecular oxygen (1 atm) as the terminal oxidant to provide indole **121** in 74% yield as a single regioisomer. Despite the presence of a structurally similar *N*-Boc-aniline moiety in **120**, exclusive chemoselectivity was obtained for acetanilide cyclorhodation, confirming previous results that *N*-Boc-anilines are not compatible directing groups for this Rh(III) catalyst. From indole **121**, paullone (**118**) was obtained following a three-step sequence consisting of indole and aniline deprotections, followed by lactam formation.

1.12.   CONCLUSION

The development of transition metal-catalyzed transformations taking place at C–H bonds has provided chemists with a variety of new tools for the efficient formation of carbon–carbon and carbon–heteroatom bonds. Efforts during the past decade have led to highly chemoselective reactions with increased functional group compatibility, making these transformations more amenable to the synthesis of complex natural products. The syntheses discussed in this chapter highlight the wealth of methods that have been utilized in this context and demonstrate how C–H bond functionalization has matured as a field.

Having demonstrated its viability in this context, the future of the discipline will rely on its successful application in an industrial setting and its ability to truly render traditional chemical processes more efficient. Examples of the use of direct arylation (see Section 1.2) in a pharmaceutical context have appeared, proving that some of these methods are possible on multikilogram scale. Noticeably, Merck Research Laboratories employed a Pd(0)-catalyzed direct arylation reaction in their synthesis of $GABA_A$ agonist **122** (Scheme 1.31) [100]. More recently, the same process department used a Ru-catalyzed direct arylation reaction to access the biaryl core of anacetrapib (**123**), a target of interest for the treatment of hypercholesterolemia [101].
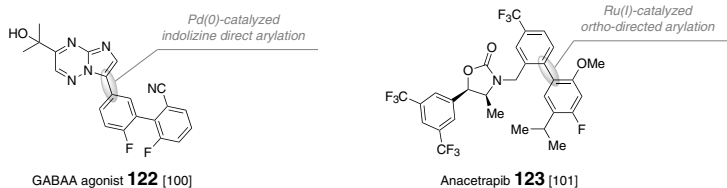
SCHEME 1.31 Structures of a GABA$_A$ agonist and anacetrapib.

These applications further highlight the remarkable and exciting growth in the area of C–H bond functionalization.

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