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Synthetic Strategy

C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals

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The direct functionalization of C–H bonds in organic compounds has recently emerged as a powerful and ideal method for the formation of carbon–carbon and carbon–heteroatom bonds. This Review provides an overview of C–H bond functionalization strategies for the rapid synthesis of biologically active compounds such as natural products and pharmaceutical targets.

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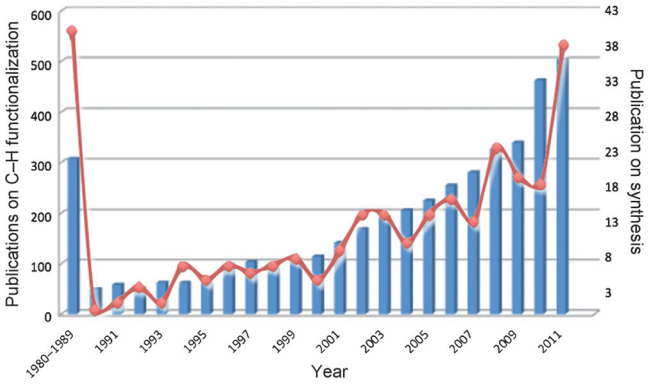
1. Introduction

The direct functionalization of carbon–hydrogen bonds of organic compounds has recently emerged as a powerful and ideal method for carbon–carbon (C–C) and carbon-heteroatom (C–X) bond formation. This approach not only streamlines existing syntheses of useful molecular entities, but also contributes to changing the way chemists think about chemical reactivity and plan chemical syntheses. A growing repertoire of C–H bond-functionalization reactions have been reported lately, including arylation,[1] alkylation,[2] alkenylation,[3] insertion,[4] amination,[5] oxidation,[6] borylation,[7] and halogenation.[8] Despite significant advances in method development, the application of C–H functionalization to the synthesis of structurally complex molecules remains a formidable challenge to the chemical community.[9] This Review provides an overview of C–H functionalization strategies for the rapid synthesis of biologically active compounds such as natural products and pharmaceutical targets.

2. Overview of C–H Functionalization and its Utility in the Synthesis of Natural Products and Pharmaceuticals

In a broad sense, the term "C–H functionalization" (synonyms include C–H activation, C–H bond activation and C–H transformation) can be defined as the conversion of carbon–hydrogen bonds into carbon–carbon or carbon–heteroatom bonds. Many definitions have been proposed by chemists from various communities (e.g., organometallic chemistry, total synthesis, or method development), thus rendering a unified definition difficult. Therefore, this Review does not necessarily categorize C–H functionalization reactions on the basis of the mechanism by which they occur, but rather classifies them on the basis of the net structural change engendered by the given transformation. Nonetheless, this Review does not cover the more "classic" topics of Friedel–Crafts acylation/alkylation, oxidative phenol–phenol coupling, allylic oxidation using selenium dioxide or stoichiometric transition-metal catalysts such as chromium, and *ortho*- or remote metalation[10] using stoichiometric strong bases such as alkyllithium derivatives. Instead, the focus is on recent developments in C–H functionalization using transition-metal catalysis, as well as on the innovative utility of C–H bonds for the synthesis of complex organic molecules.

The concept of "C–H functionalization" has garnered significant attention from the synthetic community as an ideal method for the formation of carbon–carbon and carbon–heteroatom bonds, and this field has thus witnessed intensified competition. Indeed, the number of publications on the topic of "C–H functionalization" has markedly increased, with more than 500 papers having been published in 2011 (Scheme 1, blue bars). Although the development of new reactions and catalysts continues to evolve at a rapid pace, successful applications of these methods to the synthesis of complex natural products are still rare (although it is also showing a similar rate of increase; Scheme 1, red dots and lines). However, developing a total synthesis-oriented mind-



Scheme 1. The number of publications on the topic of C–H functionalization (blue bars) and on the synthesis of natural products and pharmaceuticals by C–H functionalization (red dots and line) between 1980 and 2011. Data for the bar chart were obtained by a SciFinder search in February 2012 using keywords "C–H functionalization", "C–H activation", and "carbon–hydrogen activation". Data for the line chart were obtained by a manual count of relevant articles after an exhaustive search of the literature.

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set when studying C–H functionalization would arguably help in generating useful reactions of broad applicability.

For example, palladium-catalyzed cross-coupling methods progressed out of necessity when it was required in the total synthesis of complex natural products such as palytoxin, taxol, dynemicin A, and brevetoxin A.[11] Furthermore, it has been used for the large-scale industrial syntheses of bioactive compounds, including the herbicide Prosulforon, the anti-inflammatory drug Naproxen, the asthma drug Singulair, a 5-HT1 A agonist, and the fungicide Boscalid[12]—only then was it found to be a useful and reliable synthetic tool. A similar phenomenon has been observed for olefin metathesis, and will likely be seen for the field of organocatalysis in the near future. Assessing the utility of existing methods for a practical synthesis allows one to evaluate current needs and to recognize what can and cannot be done using state-of-the-art chemistry.

A chronological evolution of previously reported C–H functionalization reactions and their utility in the synthesis of biologically active compounds are shown in Scheme 2. Early contributions in C–H functionalization were mostly reported between 1970 and 1990. For example, Moritani and Fujiwara discovered the C–H alkenylation of benzene with styrene (i.e., an alkene) in 1967,[13] and then expanded this reaction in 1970 to the coupling between two arenes (see Sections 3.1.3 and 3.2.1). In 1982, Janowicz and Bergman demonstrated the activation of an alkane C–H bond by an oxidative addition to a transition-metal complex.[14] In 1982, Nakamura et al. discovered the intermolecular palladium-catalyzed C–H arylation of heteroarenes with aryl halides (see Section 3.1.3).[15] In 1989, Jordan and Taylor demonstrated the catalytic C–H alkylation of pyridine (as an example of an electron-deficient heteroaromatic compound),[16f] and in 1993, Murai et al. discovered the ruthenium-catalyzed direct alkylation of aromatic compounds.[17] Despite these important contributions to and perceptions of the field of C–H functionalization, most of the above was considered esoteric and impractical, thus impeding further research development.

Although the synthesis of natural products and pharmaceuticals through C–H functionalization had been reported during the same time frame, they mainly consisted of intramolecular transformations of C–H bonds into C–C and C–X bonds (X = heteroatom). The application of C–H functionalization to the synthesis of complex molecules only truly began at the start of the 21st century. The effort of such syntheses was accompanied by the development of methods, as more practical reactions for complex molecule synthesis were deemed necessary.

An ideal synthesis would bring similarly sized fragments together in a convergent manner by only coupling C–H bonds to forge the requisite C–C bonds of the target compound. Such a "direct" synthesis achieved through C–H functionalization would necessarily imply a step-economical synthesis (Scheme 3). For example, the synthesis of racemic austamide (**1**) by Hutchison and Kishi in 1979[18a] was completed in 29 steps, whereas that of (+)-**1** in 2002 by Baran and Corey[18b] based on C–H alkylation took only 5 steps. Another striking comparison is 67-step synthesis of (−)-tetrodotoxin (**2**) published by Isobe and co-workers in 2003,[19a] versus the 32-step synthesis by Hinman and Du Bois[19b] that made use of a C–H insertion and amination method, published in the same year. Further examples can be found in the total synthesis of (−)-incarvillateine (**3**), which compares the 20-step synthesis by Kibayashi and co-workers (2004)[20a] to the 11-step achievement by Ellman, Bergman, and Tsai (2008),[20b] and the synthesis of dragmacidin D (**4**), which contrasts the 25-step completion by Stoltz and co-workers (2002)[21a] to the 15-step accomplishment by Yamaguchi, Itami, and co-workers (2011).[21b] Moreover, "classic" synthetic strategies and tactics can be fundamentally revised by using C–H functionalization.

In the synthesis of 6-deoxyerythronolide B (**5**),[22] an allylic C–H oxidation strategy provided a novel mode of retrosynthetic analysis (macrocyclization of a seco acid was previously the common procedure). In the synthesis of piperarborenine B (**6**),[23] a C–H arylation approach allowed for an imaginative disconnection strategy to construct its unsymmetrically substituted diarylcyclobutane framework ([2+2] photocycloaddition was known to be the general method for the synthesis of such structures). The larger-scale synthesis of molecules through C–H functionalization is slowly starting to be implemented, as exemplified by the industrial synthesis of flubendiamide (**7**)[24] and the kilogram-scale synthesis of a GABA agonist **8**.[25] Thus, the advent of C–H functionalization has led to the beginning of a revolution in the way one synthesizes biologically active compounds.

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Atsushi D. Yamaguchi *was born in 1987 in Aichi (Japan). He received a BSc in chemistry from Nagoya University and is currently a graduate student in the group of Prof. Kenichiro Itami, focusing on the rapid synthesis of biologically active compounds by C–H functionalization.*

In this Review, almost all the syntheses of natural products and pharmaceuticals that use C–H functionalization are listed and discussed, and we classify them according to the formation of carbon–carbon (Section 3) or carbon–heteroatom bonds (Section 4). As a general note to the reader, carbon–carbon bonds formed by C–H functionalizations are indicated by blue bold lines, and carbon–heteroatom bonds formed by C–H functionalizations are shown as red bold lines.

3. C–C Bond Formation

3.1. Aromatic C–H Arylation (Aryl–Aryl Bond Formation)

3.1.1. Classical Aromatic C–H Arylation (Biaryl Coupling of Electron-Rich Aromatic Compounds)

(Hetero)biaryl structures are predominant structural motifs in natural products and pharmaceuticals and, therefore, the construction of aryl–aryl bonds to generate biaryls is a key method in organic synthesis. Currently, the most reliable method for synthesizing biaryl compounds is the transition-metal-catalyzed cross-coupling reaction of arylmetal compounds with aryl halides (C–M/C–X coupling, M = metal), namely the Kumada–Tamao–Corriu, Negishi, Migita–Kosugi–Stille, Suzuki–Miyaura, and Hiyama cross-coupling reactions.[26] However, prior to these important discoveries, oxidative coupling (C–H/C–H coupling) of electron-rich aromatic compounds (such as phenols and protected phenols) and heteroaromatic compounds was the best method to form aryl–aryl bonds. Moreover, the coupling of electron-rich aromatic compounds and aryl halides (C–H/C–X coupling) under radical or photochemical conditions was a common method to provide (hetero)biaryls. Organic chemists have been synthesizing natural products by using these "classic" coupling reactions for a long time, with representative natural products and coupling conditions shown in Scheme 4.

In 1993, Evans et al. reported the synthesis of a vancomycin subunit (**10**) by using an oxidative coupling (C–H/C–H coupling) reaction (Scheme 5).[27] Tripeptide **9** was cyclized in the presence of VOF_3 in a $CF_3CO_2H/(CF_3CO)_2O$ solution to afford the corresponding biaryl product **10** in 58% yield.

Kenichiro Itami *was born in Pittsburgh, USA (1971) and raised in Tokyo. He studied chemistry at Kyoto University, Japan, and completed his PhD in 1998 with Prof. Yoshihiko Ito. From 1997 to 1998, he was a predoctoral researcher in the group of Prof. Jan-E. Bäckvall at Uppsala University, Sweden. After his PhD, he became an Assistant Professor (with Prof. Jun-ichi Yoshida) at Kyoto University. He then moved to Nagoya University as an Associate Professor (with Prof. Ryoji Noyori) in 2005, and was promoted to Full Professor in 2008. His research focuses on the development of new synthetic methods, strategies, and concepts to solve challenging synthetic problems for realizing ideal chemical synthesis.*

In 2003, Harran and co-workers demonstrated a photomediated intramolecular C–H/C–X coupling in a total synthesis of diazonamide A (**14**; Scheme 6).[28] Treatment of aryl bromide **11** with LiOH under irradiation with light provided coupling product **13** in 72% yield through biradical intermediate **12**.

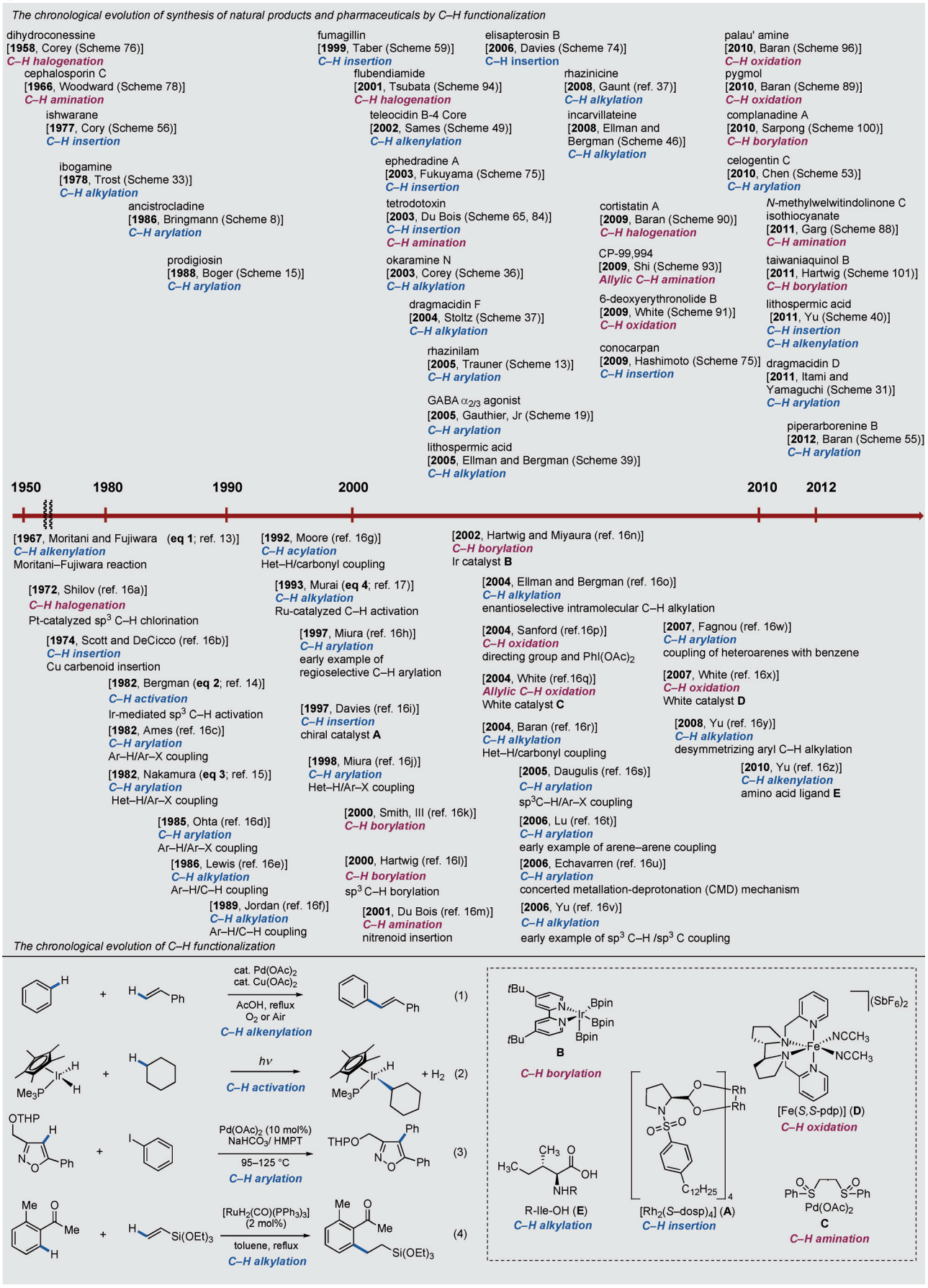
Although two impressive studies using "classic" C–H arylation are shown above, it is often difficult to control the chemo- and regioselectivity, as well as to ensure sufficient reactivity (except for phenols and electron-rich (hetero)aromatic compounds), without using arylmetal/aryl halide cross-coupling methods. To address these selectivity and reactivity problems, transition-metal-catalyzed C–H arylation of arenes is rapidly developing, both in the context of method development and natural product synthesis.

3.1.2. Metal-Catalyzed Intramolecular Aromatic C–H Arylation (C–H/C–X Coupling)

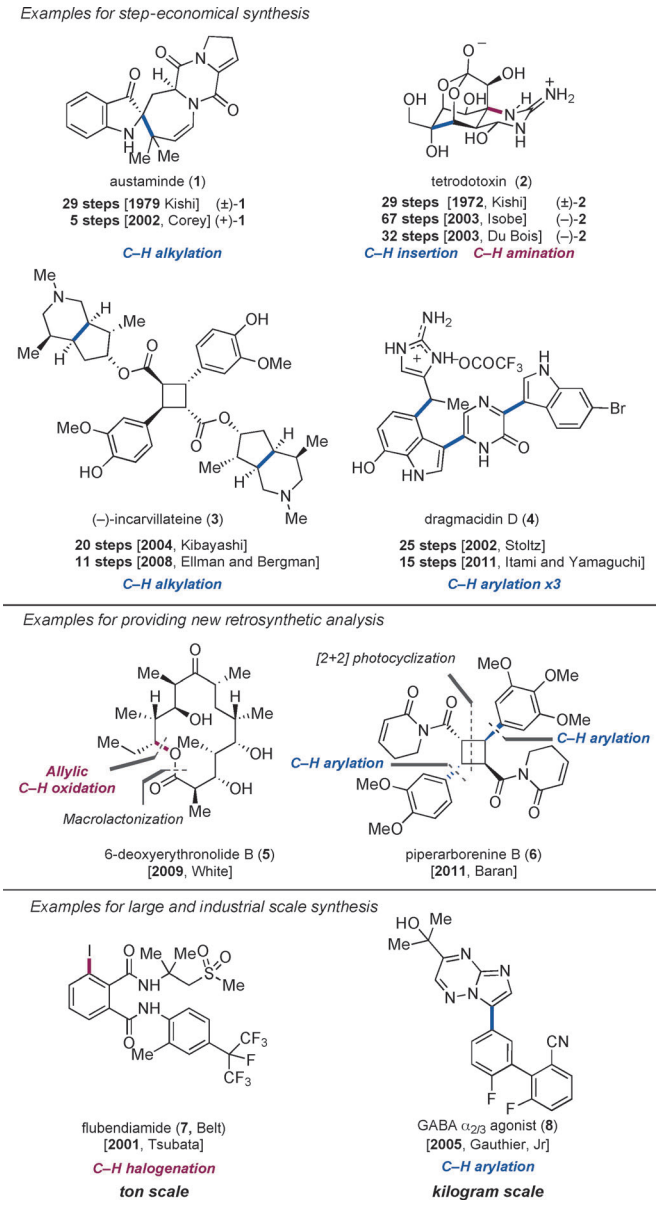
Metal-catalyzed intramolecular coupling of arene C–H bonds with aryl halides (C–H/C–X coupling), mostly involving palladium catalysis, has been used as a practical and powerful method for the construction of biaryl units. Typical examples of (hetero)biaryl frameworks that can be constructed with this method are shown in Scheme 7, wherein electron-rich, electron-neutral, and electron-poor arenes have been linked together. Various "tethered" aryl halides and aryl triflates can be converted into tricyclic (hetero)biaryl moieties.

Early applications of intramolecular C–H arylation to total synthesis was spearheaded by the Bringmann research group. In 1986, they utilized a palladium-catalyzed C–H coupling in the synthesis of (−)-ancistrocladine (**18**),[29] as shown in Scheme 8. Aryl naphthalenecarboxylate **15**, which was readily prepared by condensation of an acyl chloride with a phenol, was treated with a catalytic amount of $[PdCl_2(PPh_3)_2]$ and NaOAc in dimethylacetamide (DMAc) to afford lactone **17** in 49% yield (3:1 mixture of atropisomers). The most likely mechanism for the C–H arylation involves: 1) oxidative addition of the carbon–bromide bond to Pd^0 to form intermediate **16**, 2) C–H palladation of the adjacent aromatic ring, and 3) reductive elimination of Pd^0. After removal of the undesired atropisomer, reduction of the ester moiety to a methyl group and debenzoylation completed the first total synthesis of **18**. The two-step sequence for the formation of the aryl ester and intramolecular C–H coupling is extremely useful for the synthesis of biaryl natural products. Compared to photolysis conditions,[30] the C–H arylation method is experimentally simpler and proceeds in higher yield.

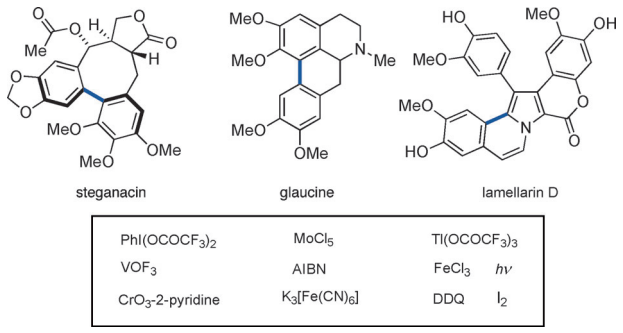
Further examples in intramolecular C–H arylation were described in 1992 and 1994, when Suzuki and co-workers applied a direct arylation protocol to synthesize (−)-gilvocarcin M (**22**).[31a,b] Although the key C–H arylation step (**19**→**21**) had already been conducted on similar structures by Deshpande and Martin en route to the synthesis of a gilvocarcin aglycone,[31c] it was valuable to find that the coupling reaction proceeds in excellent yield in the presence of a complex sugar moiety. After a successful C–H coupling



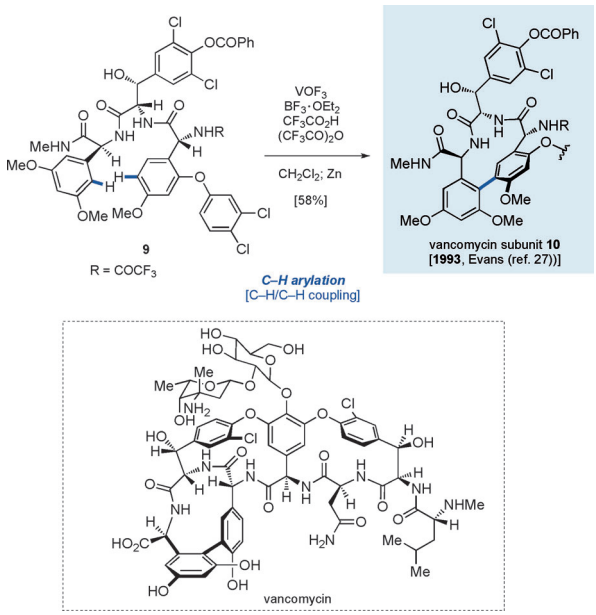
Scheme 2. The chronological evolution of C–H functionalization and applications to the synthesis of natural products and pharmaceuticals. THP = tetrahydropyran, HMPT = hexamethylphosphoric triamide, Bpin = pinacolyl boronate.



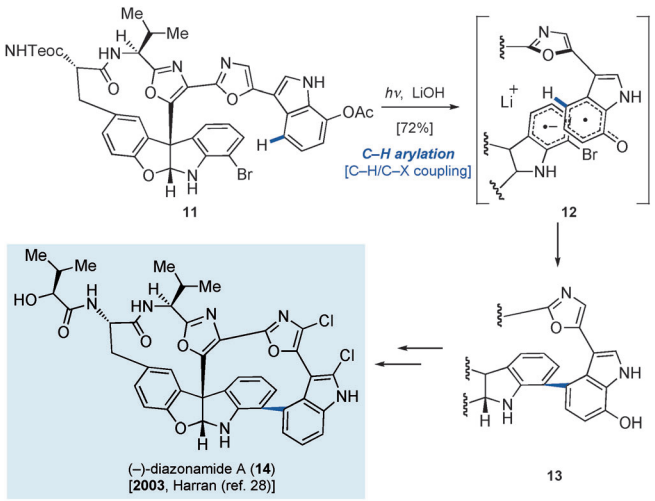
Scheme 3. Selected examples in the evolution of the synthesis of biologically active compounds with the advent of C–H functionalization.



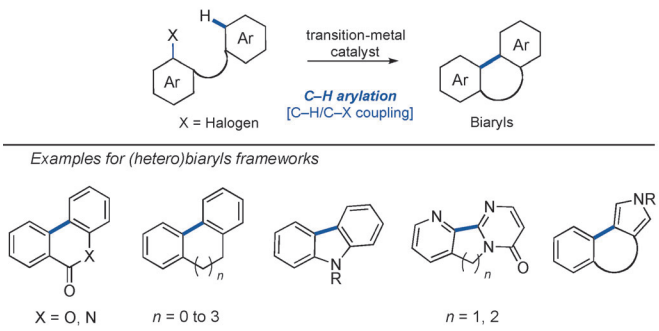
Scheme 4. Representative natural products synthesized by "classic" C–H biaryl coupling reactions. AIBN = 2,2′-azobisisobutyronitrile, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.



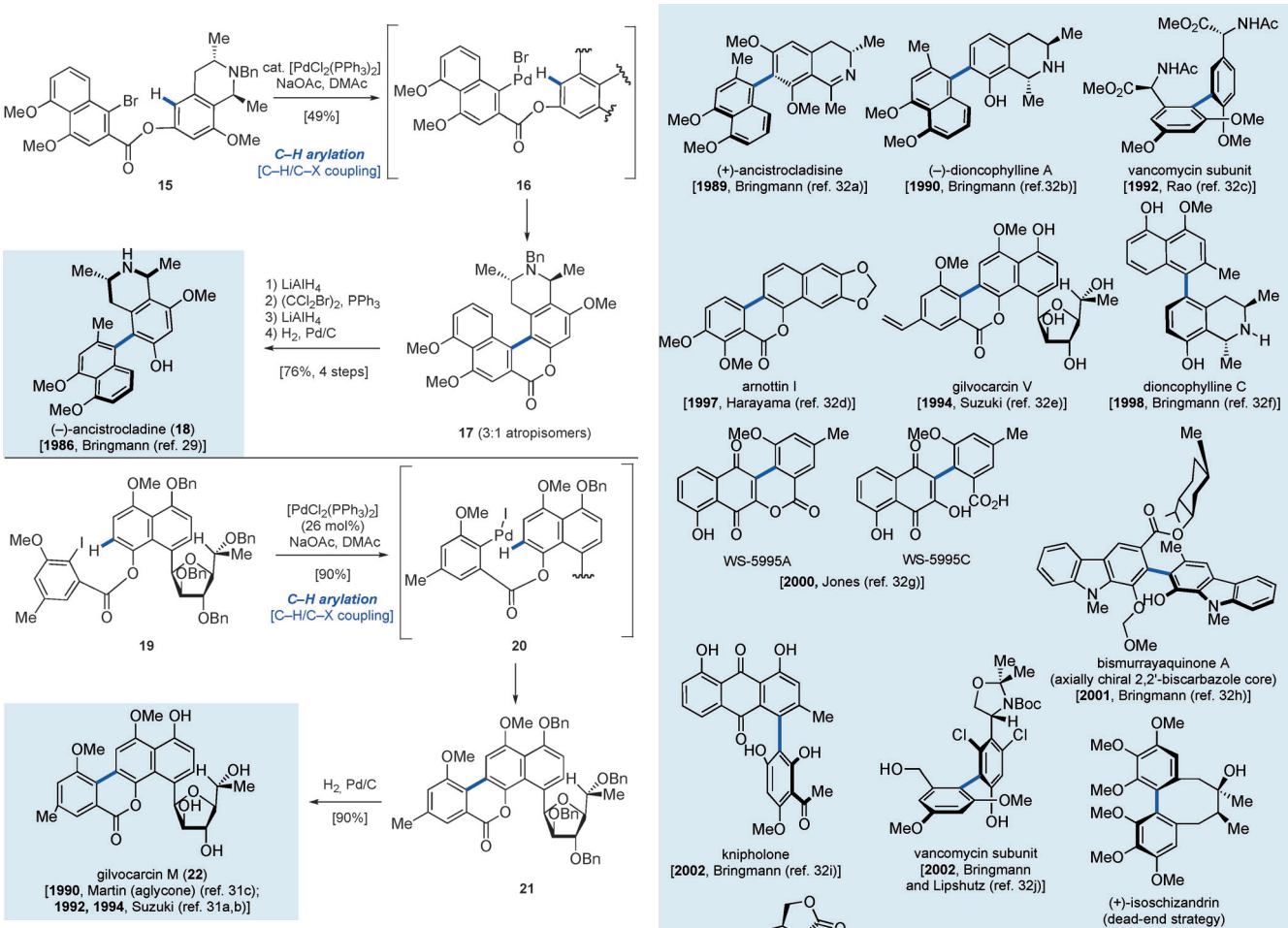
Scheme 5. VOF_3-mediated aromatic C–H arylation: Synthesis of vancomycin subunit **10**.



Scheme 6. Total synthesis of diazonamide A (**14**) by "classic" C–H/C–X coupling (Harran and co-workers). Teoc = 2-(trimethylsilyl)ethoxycarbonyl.



Scheme 7. Metal-catalyzed intramolecular C–H/C–X biaryl coupling for the synthesis of biologically active biaryl compounds



Scheme 8. Pd-catalyzed intramolecular C–H/C–X biaryl coupling: Syntheses of (–)-ancistrocladine (**18**) and (–)-gilvocarcin M (**22**). Bn = benzyl.

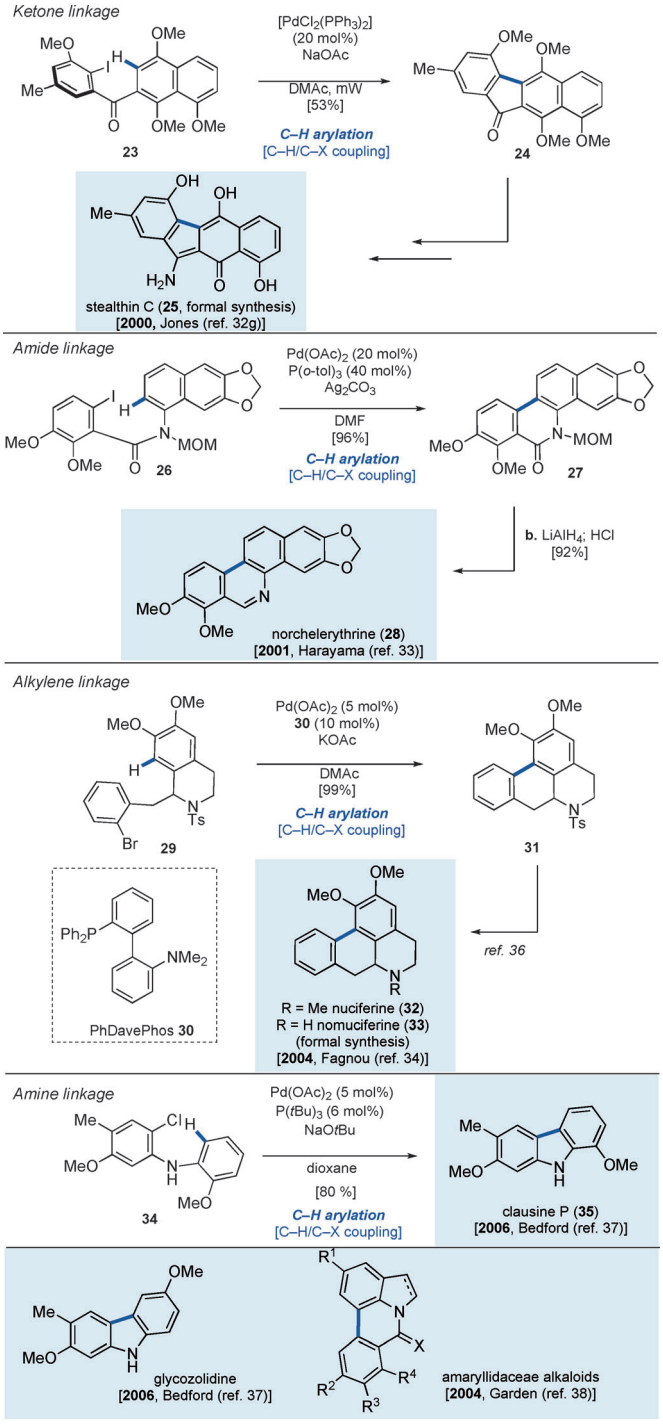
step, removal of four benzyl groups by hydrogenation gave (–)-gilvocarcin M (**22**) in 90% yield.

Thereafter, many synthetic chemists including the research groups of Bringmann and Suzuki reported the use of intramolecular C–H coupling to synthesize biaryl frameworks from 2-haloaryl esters in the context of natural product and pharmaceutical synthesis (Scheme 9).[32]

The palladium-catalyzed intramolecular C–H/C–X biaryl coupling is not only effective in generating biaryls with ester linkages (pseudolactone moiety), but is also useful for making biaryls with ketone, amide, alkylene, and amine linkages (Scheme 10). For example, Qabaya and Jones applied Bringmann's protocol for the formal synthesis of stealthin C (**25**) in 2000.[32g] In the presence of a palladium catalyst and a base under microwave irradiation, 2-(2-iodobenzoyl)naphthalene **23** underwent intramolecular C–H coupling to deliver **24**, a biaryl compound with a ketone linker. In 2001, Harayama et al. demonstrated a similar coupling reaction using *N*-naphthylbenzamide **26**. After reduction of the amide moiety in **27** and deprotection of the MOM group, the total synthesis of norchelerythrine (**28**) was accomplished.[33]

In 2004, Fagnou and co-workers reported the formal synthesis of the aporphine alkaloids nuciferine (**32**) and nomuciferine (**33**).[34] Numerous methods for the preparation

Scheme 9. Biologically active molecules synthesized by intramolecular C–H/C–X biaryl coupling.

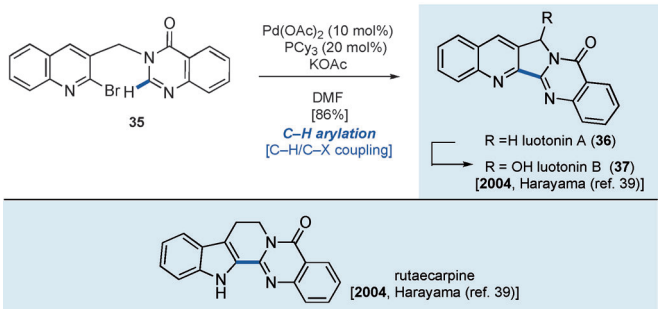


Scheme 10. Pd-catalyzed intramolecular C–H/C–X biaryl coupling: Application to the synthesis of various natural products. MOM = methoxymethyl, Ts = *p*-toluenesulfonyl.

of aporphine alkaloids had already been reported, but the formation of the key aryl–aryl bond was still of great concern in terms of efficiency (yield and catalyst loading). Eventually, they successfully applied an intramolecular C–H coupling strategy involving bromoarenes with Pd catalysis ($Pd(OAc)_2$ and PhDavePhos (**30**)[35]) and KOAc to afford **31** in 99% yield. The key intermediate **31** was then transformed into **32** and **33** according to known procedures.[36]

Intramolecular C–H coupling also proved to be effective for the synthesis of carbazole alkaloids with amine linkers, as reported by Bedford and Betham in 2006.[37] The Buchwald–Hartwig coupling of an aryl bromide and an aniline derivative generated aryl chloride **34**, which was easily cyclized in situ under palladium catalysis to give clausine P (**35**) in 80% yield. They also synthesized glycozolidine, whereas similar amaryllidaceae alkaloids were synthesized by Garden and coworkers.[38]

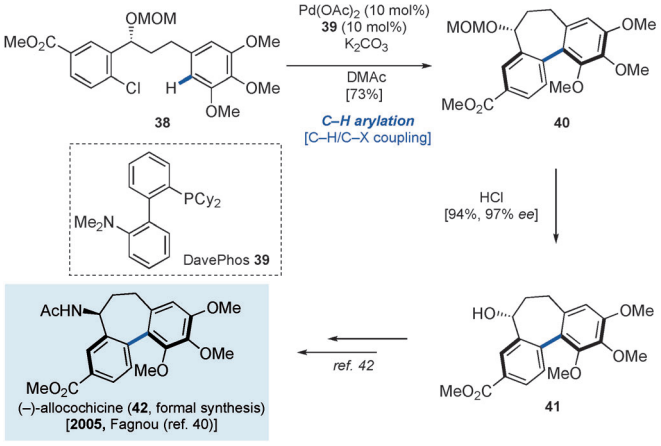
In 2004, Harayama et al. reported an intramolecular C–H arylation between two heteroarenes (Scheme 11).[39] The coupling precursor **35**, which was synthesized by N-alkylation



Scheme 11. Intramolecular C–H/C–X coupling of two heteroarenes.

of 4-quinazolinone with 2-bromo-3-(bromomethyl)quinoline, was cyclized in the presence of a palladium catalyst to give luotonin A (**36**) in 66% yield. This natural product was then hydroxylated in two steps to provide luotonin B (**37**).

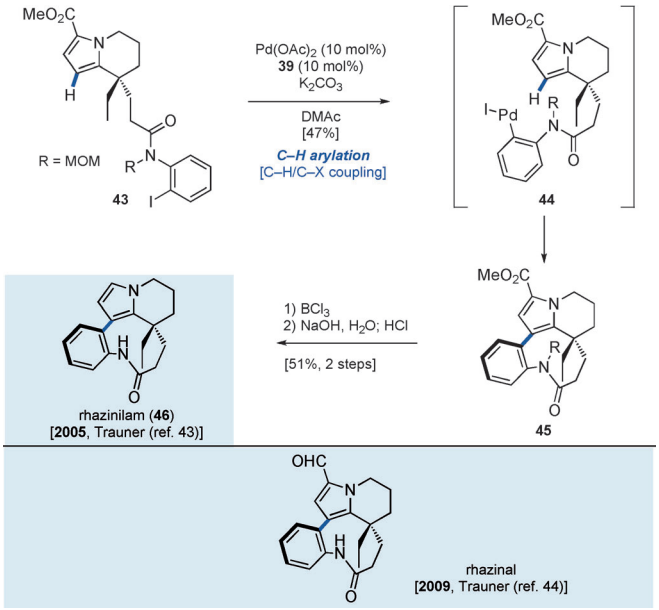
In 2005, Leblanc and Fagnou reported the formal synthesis of (−)-allocochicine (**42**) through a palladium-catalyzed intramolecular C–H/C–X biaryl coupling (Scheme 12).[40] Although it is generally difficult to form a seven-membered ring, they successfully identified the conditions to provide the key macrocycle **40**. The intramolecular biaryl coupling of diarylpropane precursor **38** proceeded in the presence of the catalyst system of $Pd(OAc)_2$/DavePhos (**39**)[41] and K_2CO_3 in DMAc at 145 °C to furnish **40**



Scheme 12. Formal synthesis of (−)-allocochicine (**42**) through Pd-catalyzed C–H biaryl coupling. Cy = cyclohexyl.

in 73% yield. Cleavage of the MOM ether by treatment with HCl in methanol provided alcohol **41** in 94% yield, which was then converted into **42** using known procedures.[42]

Also in 2005, Trauner and co-workers reported the synthesis of rhazinilam (**46**) by a palladium-catalyzed intramolecular C–H arylation of a pyrrole unit with an iodoarene (Scheme 13).[43] Treatment of compound **43** with similar conditions to those used by Fagnou for the arylation step

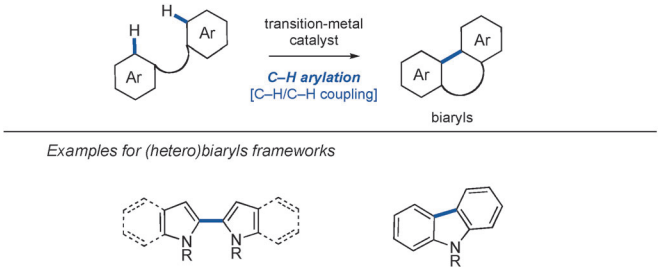


Scheme 13. Synthesis of rhazinilam (**46**) and rhazinal by intramolecular C–H/C–X biaryl coupling (Trauner and co-workers).

resulted in the formation of coupling product **45** via intermediate **44**. The synthesis of **46** was achieved after cleavage of the MOM group and decarboxylation. In 2009, Bowie and Trauner also reported the synthesis of rhazinal, a congener of **46**, by extending this intramolecular coupling strategy.[44] Incidentally, Sames and Gaunt also reported the synthesis of **46** and its congeners by other C–H functionalization strategies (see Schemes 95 and Scheme 36).

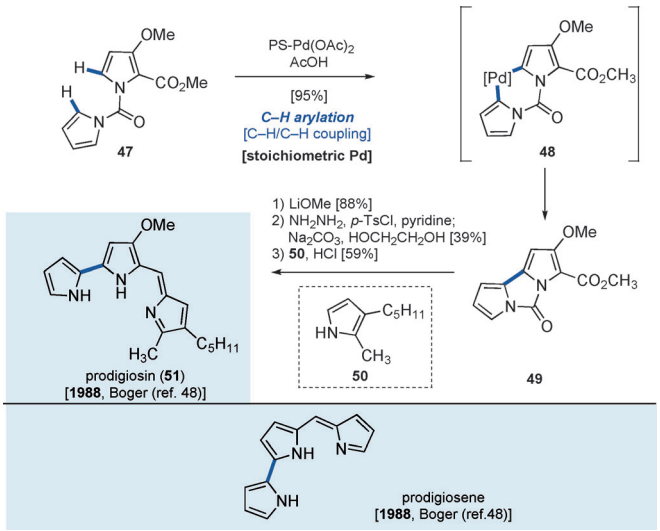
3.1.3. Metal-Catalyzed Intramolecular C–H/C–H Biaryl Coupling

The palladium-catalyzed homocoupling of benzene is arguably the most impressive transformation in the field of C–H functionalization. For example, in 1970, Moritani, Fujiwara, and co-workers found a catalytic system (olefin/$PdCl_2$ catalyst and $AgNO_3$ as a co-catalyst) that couples benzene to afford biphenyl in quantitative yield.[45] This coupling method is the most direct approach for making biaryl linkages, that is, through oxidative formation of the C–C bond with a net loss of two protons. However, its efficiency (TON), reactivity, and regioselectivity still present challenges despite recent progress in the area.[46] Meanwhile, the *intramolecular* version of C–H/C–H coupling between two arenes[47] under palladium catalysis has been in use over the last few decades. This section describes the synthesis of natural products, particularly those that contain bisindole, bispyrrole, and carbazole moieties, which utilize palladium-catalyzed intramolecular C–H/C–H coupling as a key step (Scheme 14).



Scheme 14. Intramolecular C–H/C–H coupling of two aromatic rings.

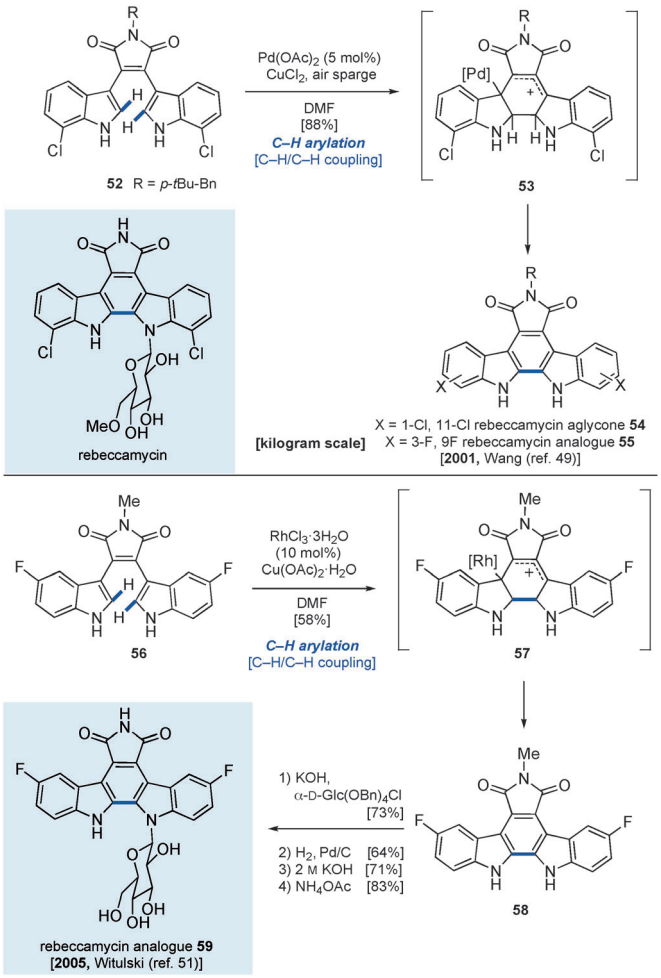
In 1988, the synthesis of natural products through the use of an intramolecular C–H/C–H coupling strategy was reported by Boger and Patel (Scheme 15). 1,1′-Carbonyldipyrrole derivative **47** was treated with a polymer-supported $Pd(OAc)_2$ catalyst in AcOH to afford **49** in 95% yield. This transformation most likely occurs through double C–H



Scheme 15. Synthesis of prodigiosin (**51**) and prodigiosene by Boger and co-workers in 1988. Ps = polystyrene.

palladation of two pyrrole rings to Pd^{II}, followed by reductive elimination of **49** from intermediate **48**. After three more steps, the total synthesis of prodigiosin (**51**) was achieved.[48] By using this C–H/C–H coupling strategy, they also synthesized a related family member, prodigiosene.

In 2001, Wang et al. from Bristol–Myers Squibb applied the palladium-catalyzed C–H/C–H coupling to the synthesis of rebeccamycin aglycone **54** (Scheme 16).[49] Although the construction of the indolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole ring system from bisindolylmaleimide **52** had already been achieved with oxidants such as DDQ, phenyliodinebis(trifluoroacetate) (PIFA), phenyliodinediacetate (PIDA), I_2, $CuCl_2$,



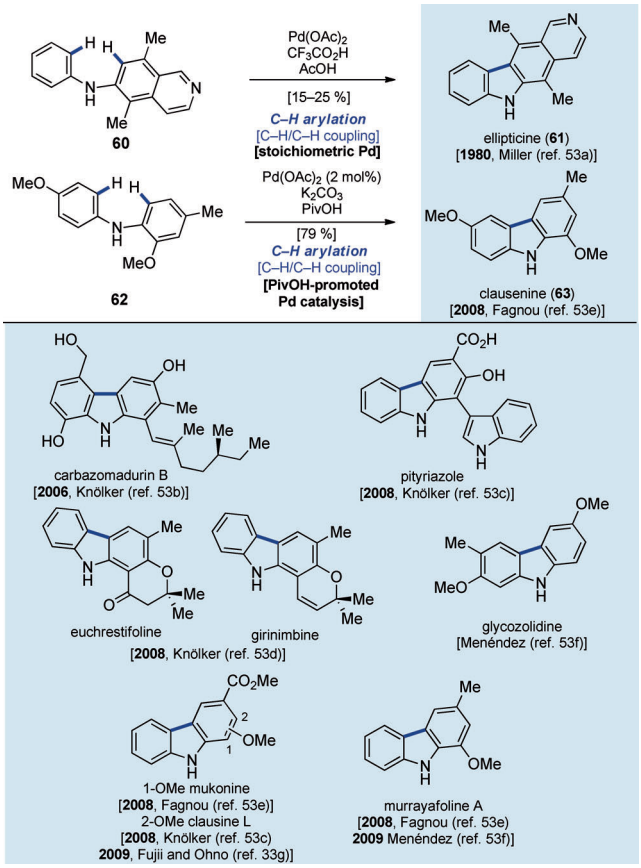
Scheme 16. Synthesis of rebeccamycin aglycone and analogue by intramolecular C–H/C–H biaryl coupling.

and a stoichiometric amount of a palladium complex,[50] there had been no reports of catalytic conditions to achieve this transformation in high chemical yield. The desired oxidative cyclization successfully occurred in the presence of 5 mol% $Pd(OAc)_2$ and $CuCl_2$ as the co-oxidant under air to provide **54** in 88% yield without protection of the indole NH group, likely going through intermediate **53**. This method is extremely practical, as rebeccamycin analogue **55** was synthesized under otherwise identical conditions in 81% yield and in greater than 3 kg scale.

In 2005, Witulski and Schweikert demonstrated a similar coupling reaction involving rhodium catalysis.[51] The cyclization of **56** was thought to proceed through a similar mechanism as with palladium (i.e., via intermediate **57**). This step was instrumental in a short, six-step synthesis of the potent topoisomerase I active rebeccamycin analogue **59**.

We have described above some carbazole syntheses that employ palladium-catalyzed intramolecular C–H/C–X coupling (specifically Scheme 9 in Section 3.1.2). However, an intramolecular oxidative coupling of two arenes (Ar–H/Ar–H coupling) is a more ideal transformation, since simple arenes can be used directly without any prefunctionalization.[52] This strategy was successfully employed by Miller and Moock in their synthesis of ellipticine (**61**) through the use of a stoichiometric amount of $Pd(OAc)_2$ in CF_3CO_2H and AcOH, albeit in somewhat low yield (15–25%). Fagnou and co-workers then discovered that the reaction yield increased dramatically in this type of reaction when $tBuCO_2H$ (PivOH) was employed as an additive. For example, compound **62** was treated under PivOH-promoted palladium catalysis to afford clausenine (**63**) in 79% yield. They also achieved the concise synthesis of mukonine, clausine L, and murrayafoline A. These elegant and short total syntheses are outlined in Scheme 17.[53]

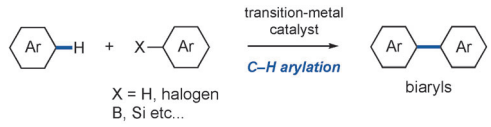
Although the substrate scope of these reactions is still narrow, this intramolecular C–H/C–H coupling strategy is beginning to flourish in the synthesis of natural products and pharmaceuticals.



Scheme 17. Intramolecular C–H/C–H biaryl coupling: Synthesis of carbazole alkaloids. Piv = pivaloyl.

3.1.4. Metal-Catalyzed Intermolecular Aromatic C–H Arylation

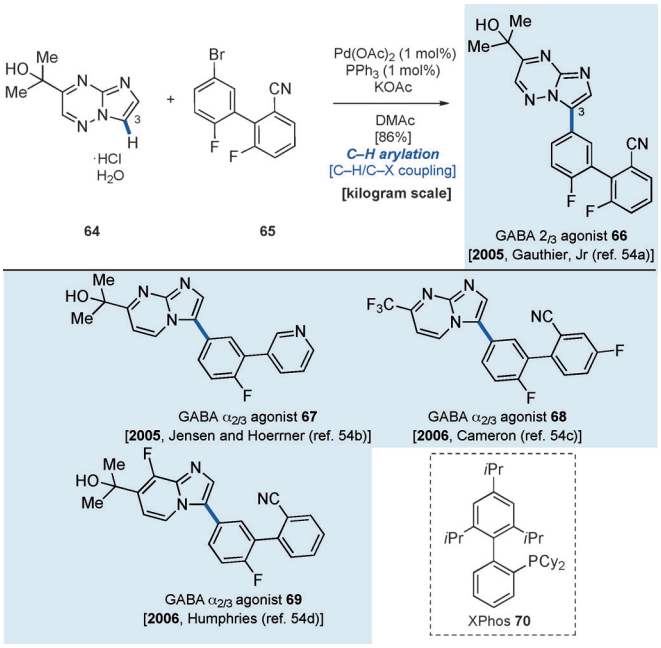
Numerous types of intermolecular C–H arylations of arenes to construct biaryl compounds have been developed to date, particularly using transition-metal catalysts (Scheme 18).[1] Although the rapid construction of aryl–aryl bonds in this manner can approach "ideality" in synthesis by skipping the prefunctionalization step, the application of such reactions to the synthesis of natural products and pharmaceuticals is still rare. This scarcity is partly due to the general



Scheme 18. Intermolecular aromatic C–H arylation.

difficulty associated with intermolecular C–H arylation: it is often hard to control the chemo- and regioselectivity, as well as to ensure sufficient reactivity. Despite these challenges, several research groups, including our own, have been able to synthesize bioactive compounds by utilizing an intermolecular C–H arylation strategy.

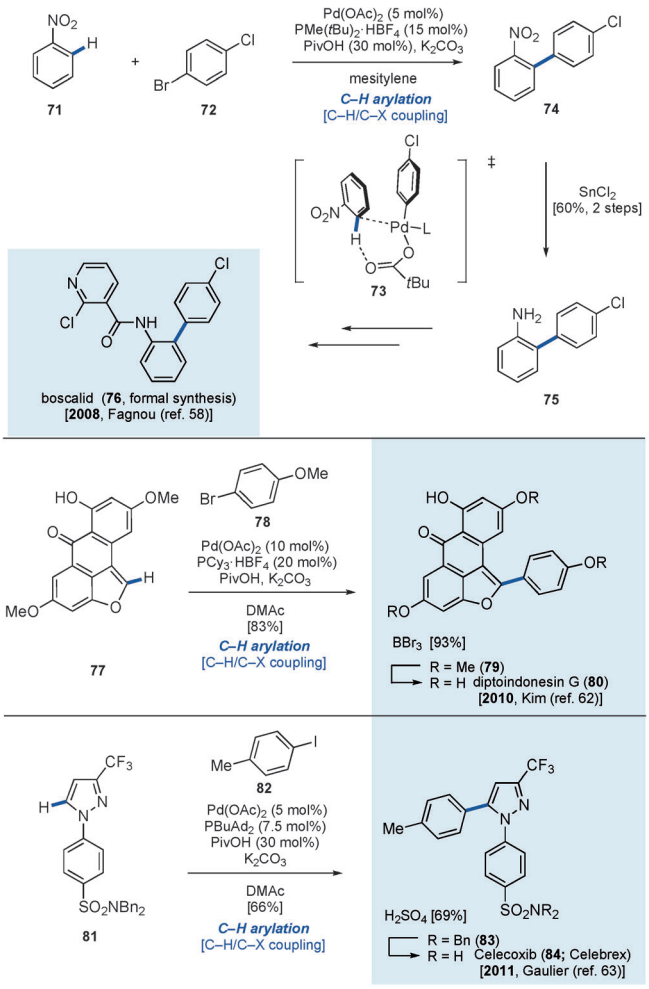
In 2005 and 2006, researchers at Merck demonstrated the first application of transition-metal-catalyzed intermolecular C–H arylation of arenes to the synthesis of biological compounds [GABA (γ-aminobutyric acid) agonists; Scheme 19].[54] It had already been known that various



Scheme 19. Synthesis of GABA $\alpha_{2/3}$ agonists through palladium-catalyzed C–H arylation of imidazopyrimidines.

electron-rich heteroaromatic compounds such as furans, thiophenes, imidazoles, and oxazoles can be coupled directly with aryl halides at their most nucleophilic positions, mainly by using palladium catalysts (palladium-catalyzed C–H/C–X coupling of heteroaromatic compounds with haloarenes).[55] In the case of an imidazo[1,2-*a*]pyrimidine (e.g., in **64**), the most nucleophilic position is the C3-position; consequently, the Merck researchers realized that this scaffold can also be utilized in a direct coupling reaction with haloarenes.[56] In the presence of a catalytic amount of $Pd(OAc)_2/PPh_3$ and KOAc, imidazopyrimidine **64** was coupled with aryl bromide **65** to afford the corresponding coupling product **66** as the sole regioisomer in excellent yield. This direct coupling reaction has been applied in a kilogram-scale synthesis. The synthesis of GABA $\alpha_{2/3}$ agonist **69** involved a slightly modified protocol (with aryl chloride, XPhos (**70**)[57] as ligand, and Bu_4NHSO_4 as additive).[54c]

In 2008, Fagnou and co-workers reported the formal synthesis of boscalid (**76**), a commercially available agrochemical compound, by applying their own C–H arylation method (Scheme 20).[58] The research group of Fagnou explored and discovered various methods in C–H arylation,

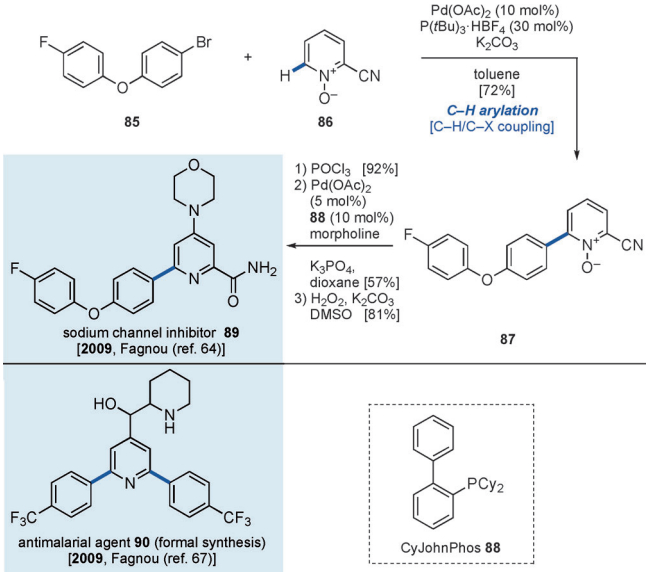


Scheme 20. A formal synthesis of boscalid (**76**) and syntheses of diptoindonesin G (**80**) and Celecoxib (**84**) by palladium-catalyzed concerted metalation/deprotonation processes. Ad = adamantyl.

notably by using a Pd/PivOH system.[59] They also proposed the concerted metalation/deprotonation (CMD) pathway in palladium-catalyzed C–H arylation reactions of electron-deficient aromatic compounds with haloarenes.[60] For example, treatment of 1-bromo-4-chlorobenzene (**72**) with nitrobenzene (**71**) in the presence of a catalytic amount of $Pd(OAc)_2/PMe(tBu)_2$, PivOH, and K_2CO_3 in mesitylene provided the coupling product **74**. Subsequent reduction of the nitro group gave aniline **75**, a synthetic intermediate toward boscalid (**76**). Key to the efficiency of this coupling was the utilization of PivOH, since it seems to have played an important role in the CMD process, such as in transition state

73.[61] This protocol is also effective for electron-rich heteroaromatic compounds. For example, the Kim research group was able to implement the synthesis of diptoindonesin G (**80**) in the presence of a similar catalyst system that coupled benzofuran **77** and bromoarene **78**.[62] In another example, Gaulier et al. reported the synthesis of Celecoxib (**84**; Celebrex) by C–H arylation of pyrazole **81** with aryl bromide **82** in the presence of a similar catalyst system.[63]

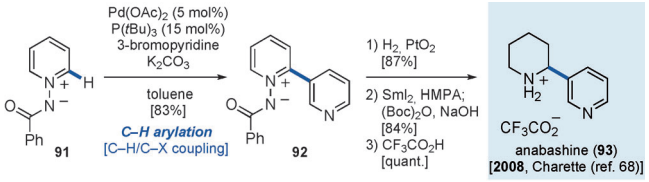
In 2009, the synthesis of sodium channel inhibitor **89** was accomplished by Fagnou and co-workers by effecting a palladium-catalyzed C–H arylation of an azine *N*-oxide with a haloarene as the key reaction (Scheme 21).[64] Conventional



Scheme 21. Direct coupling of azine *N*-oxides with haloarenes: Synthesis of bioactive compounds containing a pyridine moiety.

cross-coupling methods such as the Suzuki–Miyaura coupling of azine derivatives and arenes often encounter the instability problem of azineboronic acids. In a more direct approach, azine *N*-oxides, which are typically more electron deficient than their parent azines, can be used as nucleophiles in the coupling step after deprotonation of their most acidic protons in situ by Pd^{II}.[65] For example, pyridine *N*-oxide **86** was treated with aryl bromide **85** under palladium catalysis to afford the corresponding coupling product **87** in 72% yield. A sequence of deoxygenation and chlorination steps on **87**, Buchwald–Hartwig amination of the resultant aryl chloride with morpholine,[66] and hydrolysis of the nitrile group gave target **89** in good overall yield. As such, this method improved the efficiency of the synthesis of arylated pyridine compounds. It is of note that this method was used in the synthesis of antimalarial reagent **90** (formal synthesis).[67]

In 2008, Charette and co-workers demonstrated a direct C–H arylation of "pyridine *N*-oxide" analogues such as iminopyridium ylides with aryl halides. Iminopyridium ylide **91** and pyridine *N*-oxide have similar abilities to furnish arylated products such as **92** by activating the C2-position using a palladium catalyst. After hydrogenation of **92**, SmI_2-mediated reductive cleavage of the nitrogen–nitrogen bond and Boc protection of the exposed secondary amine gave a Boc-protected intermediate, which was treated with CF_3CO_2H to give anabashine (**93**) in good yield over three steps (Scheme 22).[68]

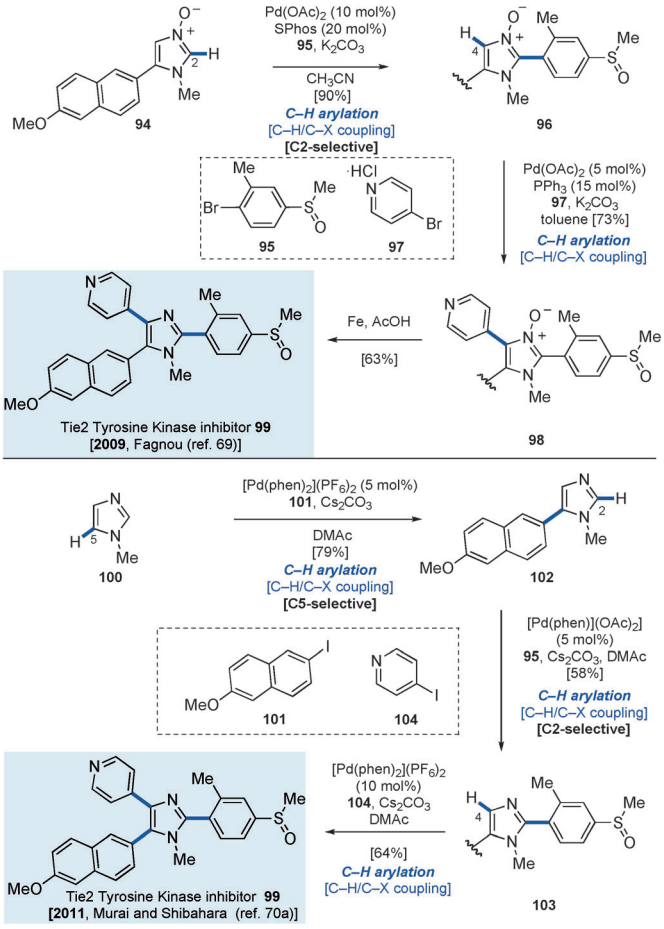


Scheme 22. Palladium-catalyzed C–H arylation of *N*-iminopyridium ylides: Synthesis of anabashine (**93**). Boc = *tert*-butyloxycarbonyl.

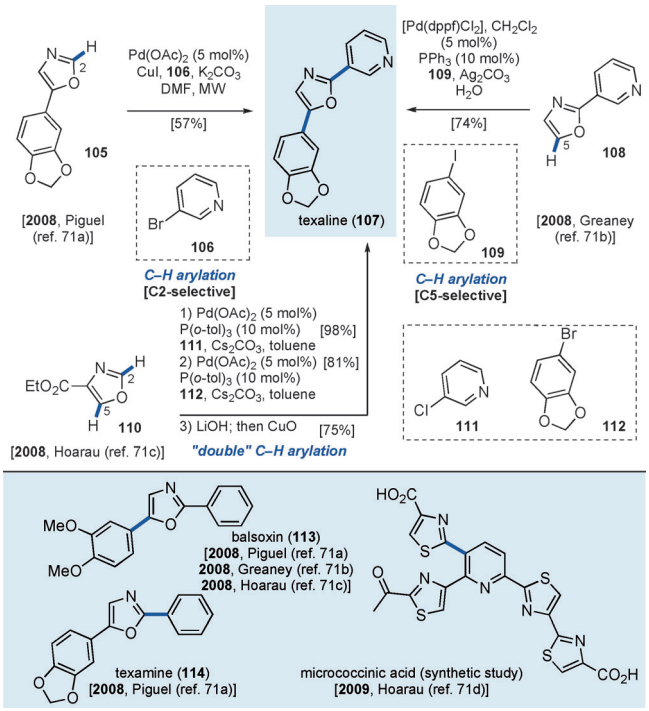
The *N*-oxide reaction presented above is also useful for the functionalization of nitrogen-containing five-membered heteroaromatic compounds such as thiazoles, oxazoles, and imidazoles. For example, the Tie2 tyrosine kinase inhibitor **99** was synthesized using multiple C–H arylations of imidazole *N*-oxide **94** (Scheme 23).[69] Starting from C5-arylated imidazole *N*-oxide **94**, palladium-catalyzed C–H arylation with aryl bromide **95** occurred at 70 °C to give the coupling product **96** in 90% yield with complete regioselectivity at the C2-position of the imidazole *N*-oxide (which is also the most acidic proton in **94**). Subsequently, **96** was coupled with pyridyl bromide **97** at its C5-position in the presence of a palladium catalyst at elevated temperatures (110 °C) to deliver bisarylated imidazole *N*-oxide **98** in 73% yield. The regioselectivity of these two sequential C–H arylation steps (C2 and C5) was controlled by the reaction temperature. Finally, the reduction of *N*-oxide **98** was achieved by treatment with iron in acetic acid, thus completing the synthesis of **99**.

In 2010, Murai, Shibahara, and Yamaguchi successfully synthesized the same target **99** by sequential C–H arylation of imidazole with their own catalytic system.[70a] They discovered that cationic palladium species $[Pd(phen)_2](PF_6)_2$ is more effective than neutral Pd catalysts for the C–H arylation of 1,3-azoles[70b] and, to demonstrate the utility of their catalyst, the synthesis of **99** was carried out. Their synthesis commenced with simple *N*-methylimidazole (**100**), onto which a C5-selective C–H arylation with aryl iodide **101** in the presence of $[Pd(phen)_2](PF_6)_2$ and Cs_2CO_3 gave coupling product **102** in 79% yield. Subsequent C2-selective coupling of imidazole **102** proceeded in moderate yield, and the final pyridine moiety was installed with the same cationic palladium catalyst to complete the synthesis of **99**.

In 2008, the research groups of Piguel, Greaney, and Hoarau independently synthesized texaline (**107**), a natural product that displays antitubercular activity, by using their own palladium-catalyzed C–H coupling protocols (Scheme 24).[71] Piguel and co-workers developed the coupling reaction between oxazole **105** and bromoarene **106** in the presence of a $Pd(OAc)_2/CuI/K_2CO_3$ catalytic system under microwave irradiation, and then applied it to the synthesis of **107** and the related compound texamine (**114**).[71a] Greaney and co-workers conducted a C5-arylation of oxazole



Scheme 23. The synthesis of Tie2 tyrosine kinase inhibitor **99** by using multiple C–H arylations of azole *N*-oxide or azole. phen = 1,10-phenanthroline.



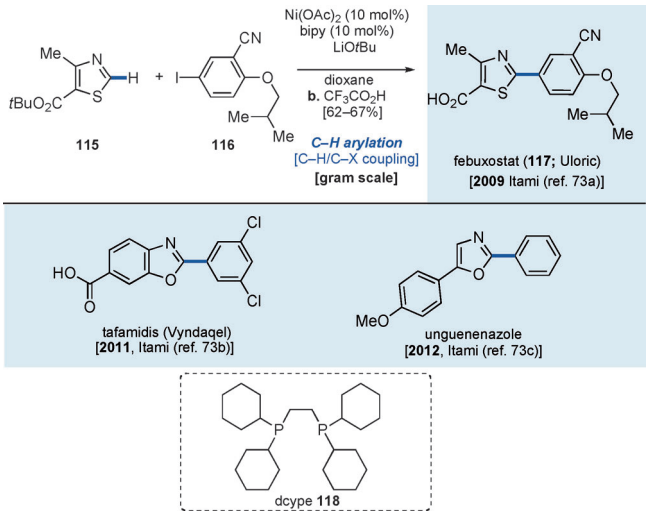
Scheme 24. Synthesis of 1,3-azole-containing natural products such as texaline (**107**) by using various palladium catalysts. mW = microwaves, tol = tolyl.

under palladium catalysis on water to access **107**. Their original method was also applied to the synthesis of balsoxin (**113**), which displays antimycobacterial activity.[71b] Hoarau and co-workers achieved two sequential C–H arylations of oxazole **110** at its C2- and C5-positions, followed by decarboxylation to give **107**.[71c] Our research group synthesized **107**, **113**, and **114** by using novel nickel-based catalytic systems (see below). Furthermore, Hoarau and co-workers reported a study toward the synthesis of micrococcinic acid, in which the key step involves the construction of the thiazole–pyridine bond by a palladium-catalyzed C–H arylation method.[71d]

Despite the impressive utility of these catalytic reactions, palladium complexes are expensive even when used in catalytic amounts. More recently, C–H arylation methods involving ubiquitous metals such as copper and iron have been reported.[72] We have also developed the first, inexpensive, nickel-catalyzed C–H arylation of azoles with haloarenes in 2009.[73a] By using this nickel-based system, we achieved the rapid synthesis of febuxostat (**117**; Uloric,[74] Scheme 24), an inhibitor of xanthine oxidase, which was developed by Teijin Pharma as a new drug for the treatment of gout and hyperuricemia. In the presence of a catalytic amount of $Ni(OAc)_2$/bipy and LiO*t*Bu or $Mg(OtBu)_2$, thiazole **115** and iodoarene **116** underwent C–H/C–X coupling in 1,4-dioxane to furnish the corresponding coupling product. Subsequent treatment with CF_3CO_2H afforded **117** in 62–67% overall yield. The synthesis is extremely efficient, since both of the coupling partners (**115** and **116**) can each be quickly derivatized in one step from commercially available compounds. This method has also been implemented in the synthesis of tafamidis (Vyndaqel: effective for the treatment of TTR amyloid polyneuropathy) and texaline (**107**; Scheme 25).[73b]

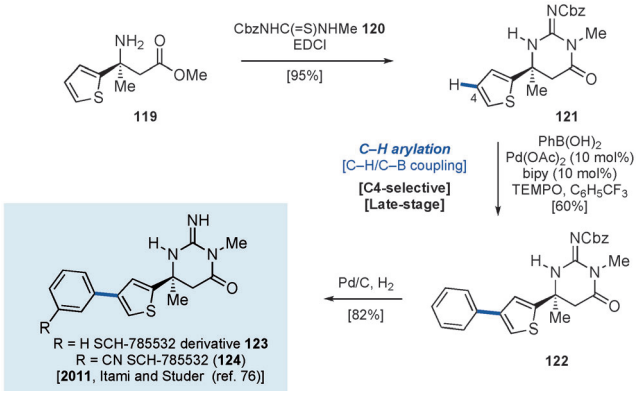
In 2012, our research group established that a C–H arylation of azoles with phenol derivatives can be achieved by using a new $[Ni(cod)_2]$/dcype (1,2-bis(dichlorophosphanyl)-ethane) catalyst system.[73c] These findings not only push the limit of biaryl coupling into a C–H/C–O manifold, but the $[Ni(cod)_2]$/dcype catalyst should also enable novel modes of reactivity of phenol derivatives to be identified. We have also successfully achieved the concise synthesis of the oxazole alkaloids texamine (**114**) and unguenenazole by using this novel nickel catalyst (Scheme 25).

Although the C–H arylation of heteroarenes has been reported on numerous occasions, it is difficult to change the regioselectivity that is innate to each heteroarene.[75] For example, the C–H arylation of thiophene with arylating agents typically proceeds at its α position (C2 or C5 of the thiophene ring). However, when there is a need to synthesize 2,4-disubstituted thiophenes such as SCH-785532 (**124**; R = CN), a lead compound to treat Alzheimer's disease, a protocol that allows for β-selective arylation of thiophene derivatives will be in high demand. After much investigation, we succeeded in overcoming the natural reactivity profile of



Scheme 25. Syntheses of febuxostat, tafamidis, and unguenenazole by nickel-catalyzed C–H arylation. bipy = 2,2′-bipyridine.

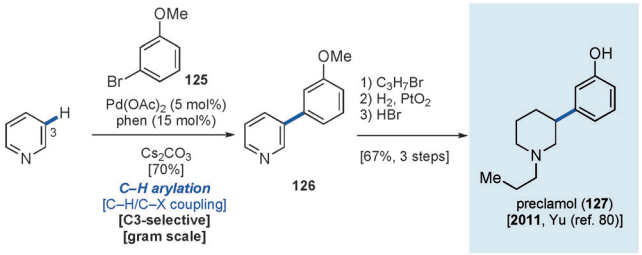
the thiophene ring. We developed a method for the β-selective C–H arylation of thiophenes with arylboronic acids under Pd/bipy/TEMPO catalysis, and applied it to the concise enantioselective synthesis of the core structure of SCH-785532 (**123**; R = H, Scheme 26).[76] Ester **119** was readily prepared from 2-acetylthiophene by using imine the method



Scheme 26. Synthesis of SCH-785532 derivative (**123**) through β-selective arylation of thiophenes with arylboronic acids. Cbz = carbobenzyloxy, EDCI = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxyl.

developed by Ellman and co-workers,[77] followed by condensation of **120** to afford **121** in excellent yield. The β-selective arylation of thiophene **121** with phenylboronic acid in the presence of $Pd(OAc)_2$/bipy/TEMPO proceeded smoothly to give β-arylated thiophene **122** in 60% yield with complete regioselectivity. After cleavage of the Cbz protecting group on the resulting coupling product **122**, the synthesis of **123** was completed. This method is expected to be useful in a drug discovery setting, wherein various arenes can be introduced onto the thiophene moiety at the late stages of the synthesis.

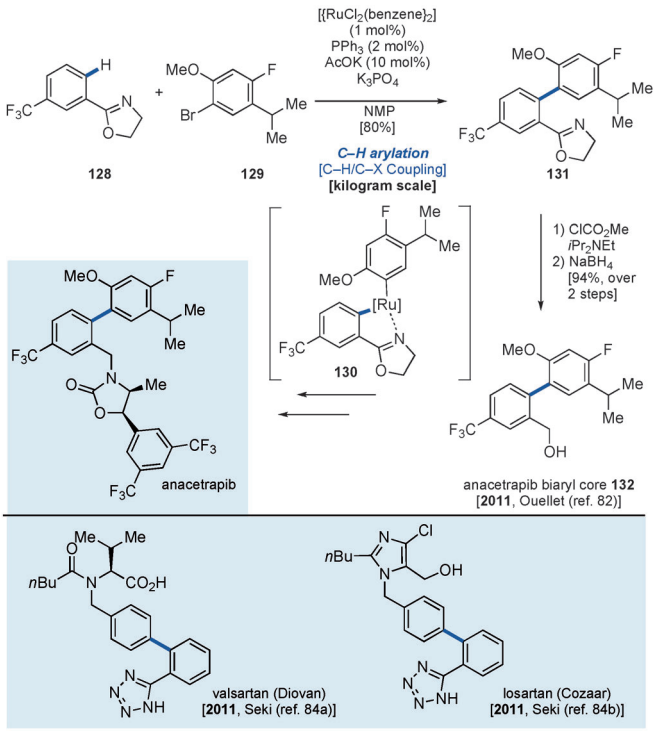
The first efficient C–H arylation with electron-deficient heteroaromatic compounds, such as pyridines, was reported by Ellman, Bergman, and co-workers by using rhodium catalysis,[78] wherein the C–H arylation proceeds at the C2-position of pyridine. Recently, directing group assisted C3- or C4-arylation of pyridine was reported by the research groups of Yu and Sames.[79] Later in 2011, the Yu research group also demonstrated a C3-selective C–H arylation of pyridine derivatives and applied it to a gram-scale synthesis of preclamol (**127**; Scheme 27).[80] The palladium-catalyzed C3-selective coupling of excess amounts of pyridine (37 equiv) with 1-bromo-3-methoxybenzene (**125**) in the presence of a $Pd(OAc)_2$/1,10-phenanthroline (phen)/Cs_2CO_3 catalyst system afforded the desired coupling product **126** in 70% yield. A subsequent sequence of 1) N-alkylation of **126** with 1-bromopropane, 2) hydrogenation of the pyridinium to piperidine using H_2/PtO_2, and 3) demethylation afforded **127** in good yield.



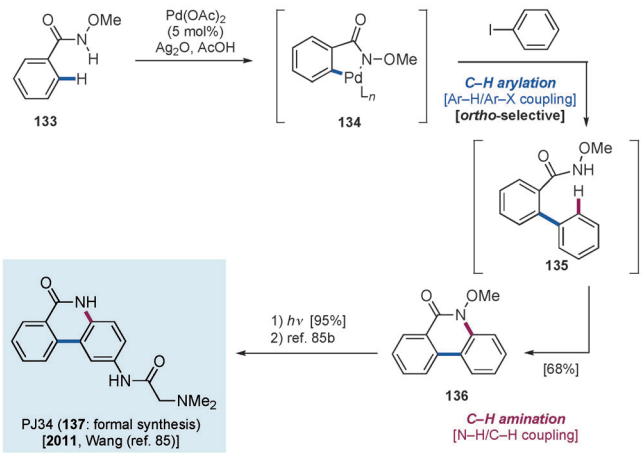
Scheme 27. Synthesis of preclamol (**127**) by the C3-selective arylation of pyridine.

In 2011, C–H biaryl coupling assisted by directing groups such as oxazolines, tetrazoles, *N*-methoxyamides, and carboxylates[81] was applied to the synthesis of bioactive compounds. Ouelett et al. at Merck reported the synthesis of the core structure of anacetrapib (**132**), a potent and selective inhibitor of CETP (cholesterylester transfer protein), by using ruthenium-catalyzed C–H arylation as the key step (Scheme 28).[82] The C–H arylation of oxazoline **128** with bromoanisole **129** under their robust ruthenium-based catalyst system, which was inspired by Ackerman's conditions,[83] yielded biaryl **131** via intermediate **130**. Notably, this reaction can be conducted on a kilogram scale. The catalyst-directing oxazoline moiety was easily converted into a hydroxymethyl group by N-alkylation followed by reductive cleavage to afford the anacetrapib biaryl core (**132**). Seki also reported the synthesis of vaisartan (Diovan) and losartan (Cozaar) by using a similar catalyst and triazole as the directing group.[84]

In 2011, Wang et al. reported the formal synthesis of the PARP inhibitorPJ34 (**137**; PARP: poly(ADP-ribose) polymerase) by employing two types of direct C–H functionalization: C–H arylation and amination (Scheme 29).[85a] The reactivity of the C–H arylation was enhanced using *N*-methoxyamide as the directing group. Treatment of *N*-methoxybenzamide (**133**) with iodobenzene in the presence of a catalytic amount of $Pd(OAc)_2$ and Ag_2O in AcOH formed five-membered palladacycle **134** by direct *ortho*-C–H palladation, which then produced biaryl intermediate **135**—



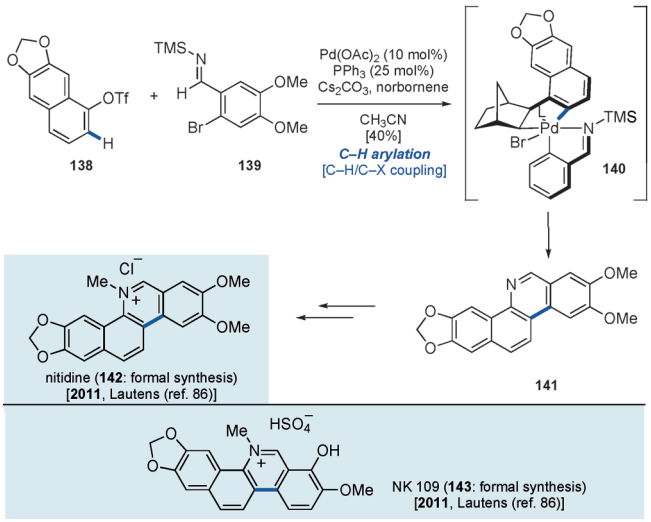
Scheme 28. Directing-group-assisted C–H arylation through ruthenium catalysis: A biaryl core synthesis of anacetrapib (**132**) as well as synthesis of valsartan and losartan.



Scheme 29. Directing-group-assisted C–H arylation and amination: Formal synthesis of PJ34 (**137**).

possibly through an oxidative addition of iodobenzene to the Pd^{II} species. Subsequent intramolecular oxidative N–H/C–H coupling (C–H amination) of **135** furnished tricyclic product **136** in 68% yield.

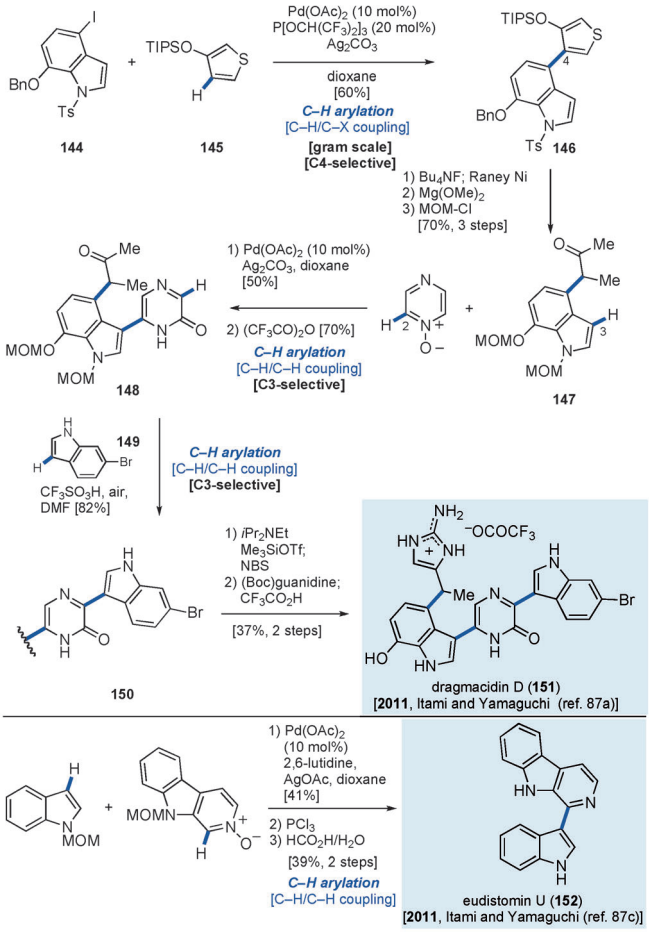
Recently, Lautens and co-workers achieved a formal synthesis of nitidine (**142**) and NK 109 (**143**) through a tandem direct arylation/N-arylation strategy (Scheme 30).[86] Thus, a mixture of aryl triflate **138** and imine **139** in the presence of a palladium catalyst and norbornene yielded coupling product **141**. This interesting



Scheme 30. Formal synthesis of nitidine (**142**) and NK109 (**143**) by domino C–H arylation/N-arylation of an aryl triflate. TMS = trimethylsilyl.

reaction might occur through a mechanism consisting of 1) C–OTf oxidative addition of **138** to Pd^0, 2) carbopalladation to norbornene, 3) intramolecular arene C–H palladation, 4) C–Br oxidative addition of **139** to the resultant palladacycle to form Pd^{IV} intermediate **140**, and 5) chemoselective reductive elimination with concomitant decarbopalladation (release of norbornene).

In 2012, our research group achieved the synthesis of dragmacidin D (**151**), a complex marine natural product, by using three direct C–H coupling reactions (Scheme 31).[87a] Our synthesis began with the coupling of iodoindole **144** and 3-triisopropylsilylthiophene (**145**) in the presence of a catalytic amount of $Pd(OAc)_2/P[OCH(CF_3)_2]_3$ and Ag_2CO_3 to deliver **146** in 60% yield with complete C4 regioselectivity.[87b] Heterobiaryl **146** was converted into ketone **147** through a three-step process. The C–H/C–H coupling of **147** and pyrazine *N*-oxide then took place under palladium catalysis [$Pd(OAc)_2$, 2,6-lutidine, AgOAc] to afford the corresponding coupling product. This catalytic C–H/C–H coupling was also effective in a concise total synthesis of eudistomin U (**152**).[87c] Treatment of the resulting product with trifluoroacetic anhydride furnished pyrazinone **148**. An oxidative C–H/C–H coupling reaction of pyrazinone **148** and 6-bromoindole (**149**) with a catalytic amount of CF_3SO_3H under air afforded the corresponding coupling product **150** with simultaneous removal of the two MOM groups. The final transformation from **150** to dragmacidin D (**151**) necessitated the following two steps: 1) treatment with iPr_2NEt/Me_3SiOTf then *N*-bromosuccinimide, and 2) aminoimidazole formation from the resultant α-bromoketone and Boc-guanidine, followed by cleavage of the Boc group. In this manner, the total synthesis of dragmacidin D (**151**) was completed through C–H coupling reactions in 15 steps, which is 10 steps shorter than the preceding synthesis that employed Suzuki–Miyaura coupling reactions.[88]



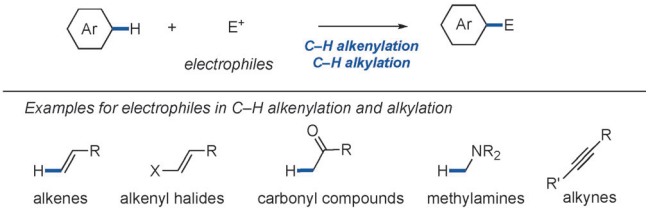
Scheme 31. Total synthesis of dragmacidin D (**151**) and eudistomin U (**152**) by C–H/C–H coupling between an indole and an azine. TIPS = triisopropylsilyl, NBS = *N*-bromosuccinimide.

3.2. C(sp^2)–H Alkenylation and Alkylation

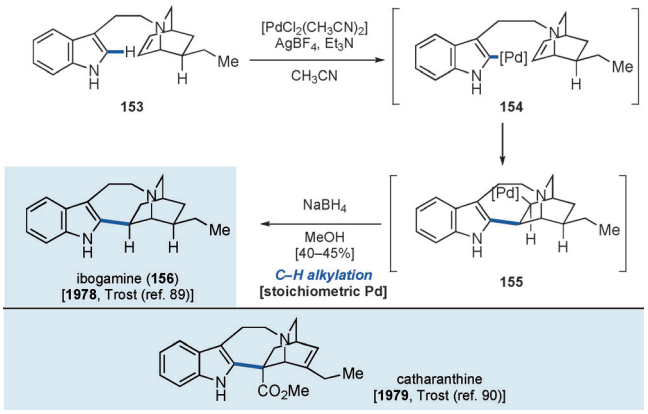
3.2.1. Aromatic C–H Alkenylation and Alkylation

There are numerous excellent syntheses of natural products and pharmaceuticals that utilize a direct alkenylation/alkylation of arene C–H bonds. In this Review, examples using Friedel–Crafts alkylation are not described. In the field of C–H activation, C–H alkenylation reactions involving alkenes and palladium catalysts have flourished, and are now often called Moritani–Fujiwara-type reactions (these can also be considered oxidative Mizoroki–Heck reactions, and result in Ar–H/alkene coupling).[13] The transition-metal-catalyzed C–H activation reaction of arenes through the agency of chelation groups (Murai-type C–H alkenylation/alkylation)[17] can also be used. In addition, various types of formal C–H alkenylations/alkylations between arene C–H bonds and electrophiles such as alkenyl halides, carbonyl compounds, alkynes, and methylamines have been developed. In this section, we describe the synthesis of biologically active compounds through such C–H alkenylation and alkylation reactions (Scheme 32).

In 1978, Trost et al. completed a total synthesis of ibogamine (**156**) by utilizing a reductive intramolecular C–H alkylation as the key step (Scheme 33).[89] In the presence of a Pd^{II} complex and silver(I) tetrafluoroborate, indole **153** underwent C–H palladation followed by intramolecular carbopalladation to give intermediate **155**. This alkylpalladium intermediate was then treated with $NaBH_4$ to afford **156** in 45% overall yield. They also reported the total synthesis of catharanthine through a similar strategic disconnection.[90] Despite the use of a stoichiometric amount of the Pd^{II} complex, the efficiency of the direct arene–alkene coupling (Het-H/alkene coupling) is a valuable outcome in this landmark synthesis.



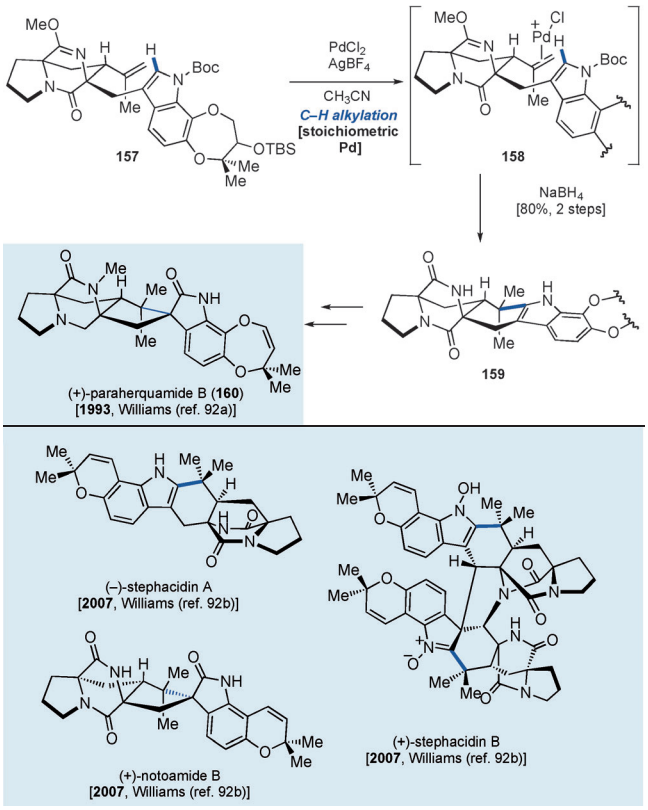
Scheme 32. Aromatic C–H alkylation and alkenylation.



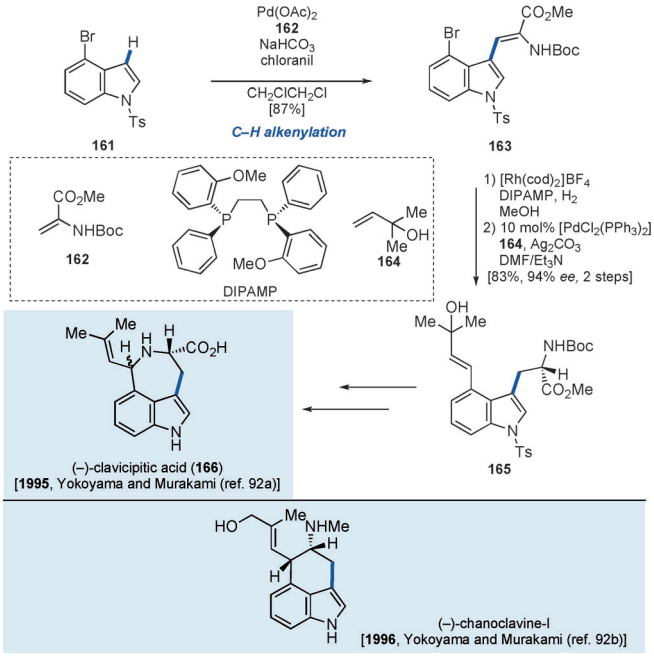
Scheme 33. Synthesis of ibogamine (**156**) through C–H alkylation (Trost and co-workers).

In 1993, the total synthesis of the complex natural product(+)-paraherquamide B (**160**) was reported by Williams and co-workers, who used a similar reductive C–H alkylation strategy (Scheme 34).[91a] Treatment of indole **157** with Pd^{II} according to Trost's C–H alkylation procedure afforded the corresponding heptacyclic compound **159**. The synthesis of (+)-paraherquamide B (**160**) was accomplished after several steps from **159**. In 2007, Williams and co-workers also achieved a concise, asymmetric, stereocontrolled total synthesis of stephacidins A and B as well as notoamide B.[91b]

In 1995, an asymmetric total synthesis of (−)-clavicipitic acid (**166**) through an intermolecular indole-alkene C–H/C–H coupling was reported by Yokoyama, Murakami et al. (Scheme 35).[92a] Their synthesis commenced with the coupling of bromoindole **161** with *N*-Boc-dehydroalanine methyl ester (**162**) by palladium catalysis. Although the previously reported conditions (1.0 equiv of $Pd(OAc)_2$ in AcOH at 120 °C)[92c] were ineffective, they found that a stoichiometric amount of $Pd(OAc)_2$ with chloranil as an oxidant in trichlorobenzene at 90 °C furnishes alkenylated product **163** in 87%



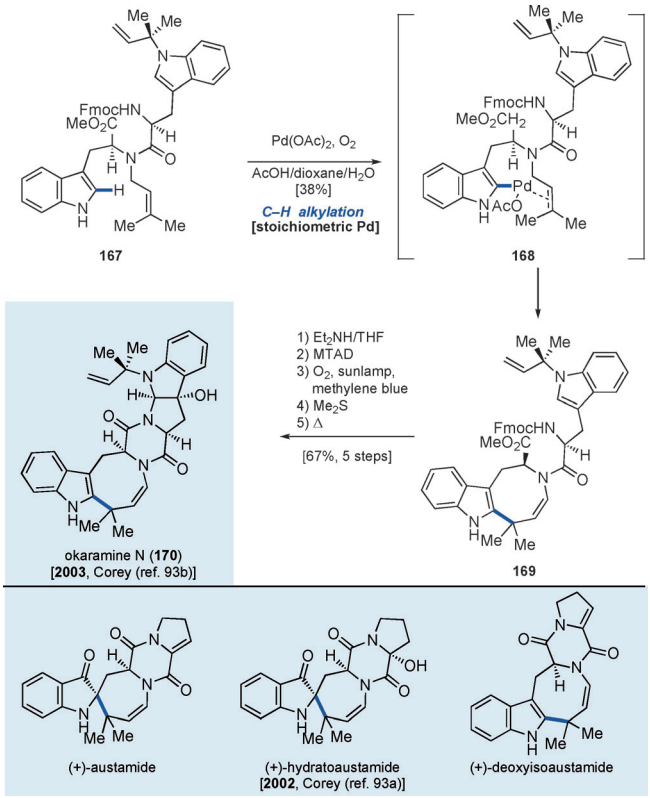
Scheme 34. Palladium-mediated reductive C–H alkylation of indoles in natural product synthesis.



Scheme 35. Intermolecular C–H alkenylation: Syntheses of clavicipitic acid (**166**) and chanoclavine-I.

yield. Asymmetric hydrogenation of **163** with a Rh-dipamp catalyst (94% *ee*), followed by vinylation under Heck conditions in the presence of Ag_2CO_3, provided coupling product **165** in 83% overall yield. After a few more steps, the synthesis of clavicipitic acid (**166**) was completed. The authors also reported the synthesis of (–)-chanoclavine I.[92b]

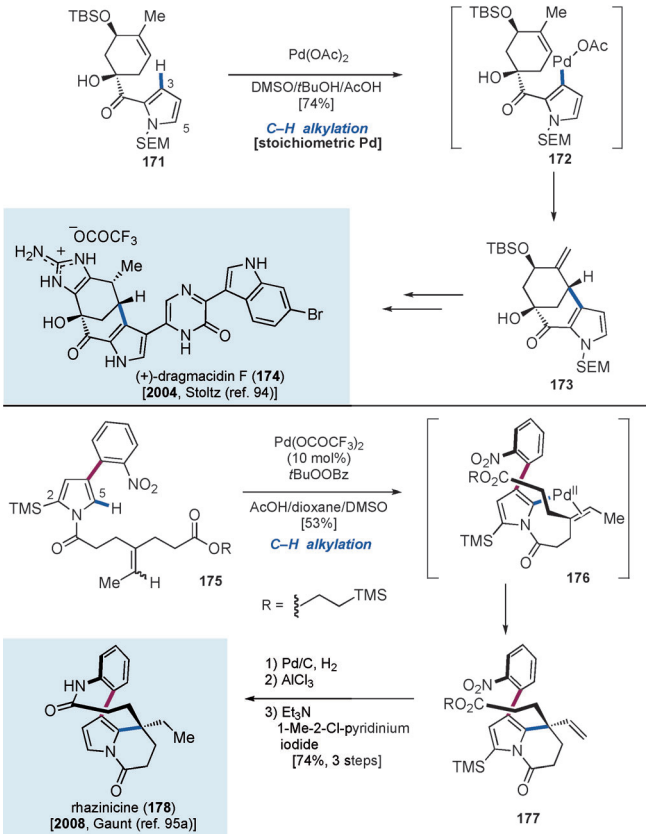
In 2002 and 2003, Corey and co-workers employed an intramolecular C–H alkylation as a key step for the total synthesis of okaramine N (**170**), austamide, hydratoaustamide, and deoxyisoaustamide,[93] which contain indoloazocine moieties (Scheme 36). The only previously reported total synthesis of these indole alkaloids was Kishi's pioneering



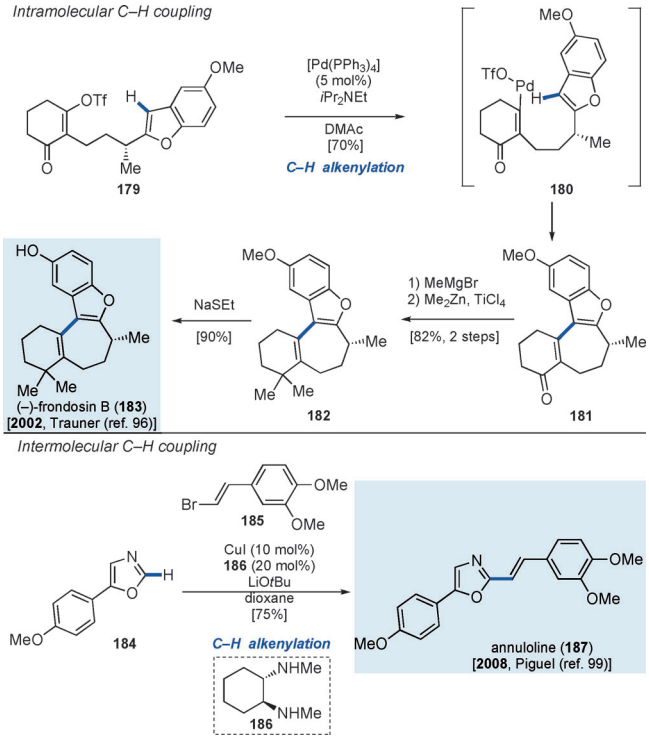
Scheme 36. Synthesis of indoloazocine alkaloids by Corey and co-workers. Fmoc = 9-fluorenylmethoxycarbonyl.

synthesis of racemic austamide in 29 steps. In contrast, Corey and co-workers conducted a palladium-catalyzed indole cyclization (C–H alkylation of indole with alkene) to synthesize austamide in only 5 steps.[93a] They also demonstrated a powerful cyclization reaction for the synthesis of okaramine N (**170**; Scheme 36). Bisindole **167**, which was readily prepared from tryptophan, was treated with $Pd(OAc)_2$ (1 equiv) in an AcOH/dioxane/H_2O solution under 1 atm of O_2 to afford indoloazocine **169** in 38% yield (44% based on recovered starting material).[93b] The total synthesis of **170** was successfully accomplished after cleavage of the Fmoc group by their own oxidative cyclization procedure.

Intramolecular C–H alkylation chemistry is also useful for pyrroles (Scheme 37). In 2004, Stoltz and co-workers reported the total synthesis of (+)-dragmacidin F (**174**) by using a palladium-catalyzed C–H alkylation as a key step.[94] Exposure of pyrrole **171** to $Pd(OAc)_2$ (1.0 equiv) and DMSO in *t*BuOH and AcOH provided cyclization product **173** in 74% yield. It is remarkable that oxidative Mizoroki–



Scheme 37. Total synthesis of dragmacidin F (**174**) and rhazinicine (**178**) through palladium-catalyzed aromatic C–H alkylation. TBS = *tert*-butyldimetylsilyl, SEM = trimethylsilylethoxymethyl, Bz = benzoyl.



Scheme 38. Total synthesis of *ent*-(–)-frondosin B (**183**) and annuloline (**187**).

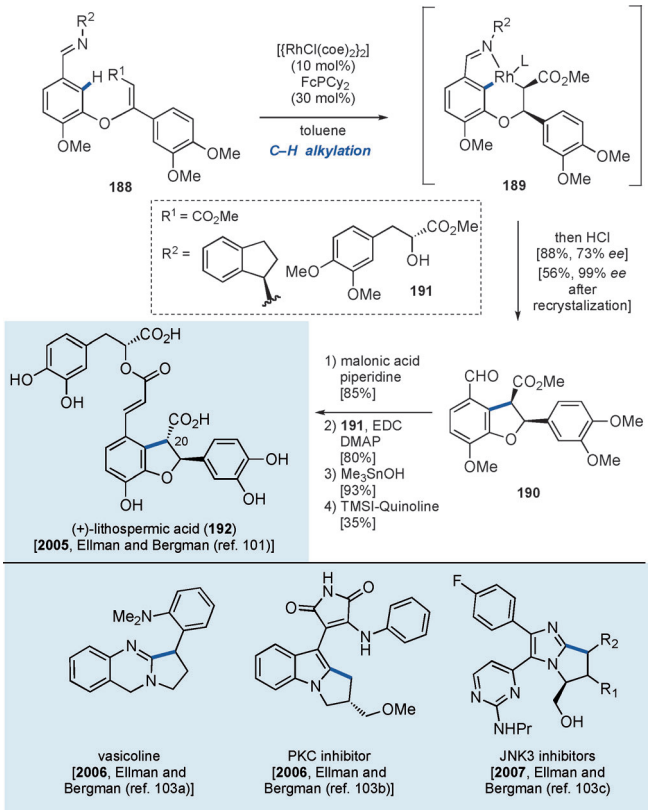
Heck-type cyclization occurs selectively from the C3-position, via intermediate **172**, to afford **173** as a single regioisomer. After 13 more steps, they accomplished the first total synthesis of **174.**

In 2008, Gaunt and co-workers achieved the concise total synthesis of rhazinicine (**178**) through an intramolecular C–H alkylation of pyrrole.[95a] They had already reported regioselectivity switches (at both the C4- and C5-positions) in the synthesis of alkenylated pyrroles by catalytic C–H alkenylation.[95b] Therefore, they planned to apply their own C5-selective C–H alkenylation protocol to this system. Pyrrole **175** was prepared by a regioselective iridium-catalyzed C–H borylation of a pyrrole precursor (see reaction details in Section 4.3) and a Suzuki–Miyaura coupling reaction with *o*-nitrobenzeneboronic acid in one pot. Treatment of **175** with a catalytic amount of $Pd(OCOCF_3)_2$ and *t*BuOOBz resulted in the formation of palladium complex **176**. Intramolecular carbopalladation of **176**, followed by β-hydrogen elimination, furnished the key cyclized product **177** as a single isomer in 53% yield. Hydrogenation of both the nitro and alkene groups, desilylation of the TMS group, and a final macrolactamization, delivered **178** in a total of 11 steps.

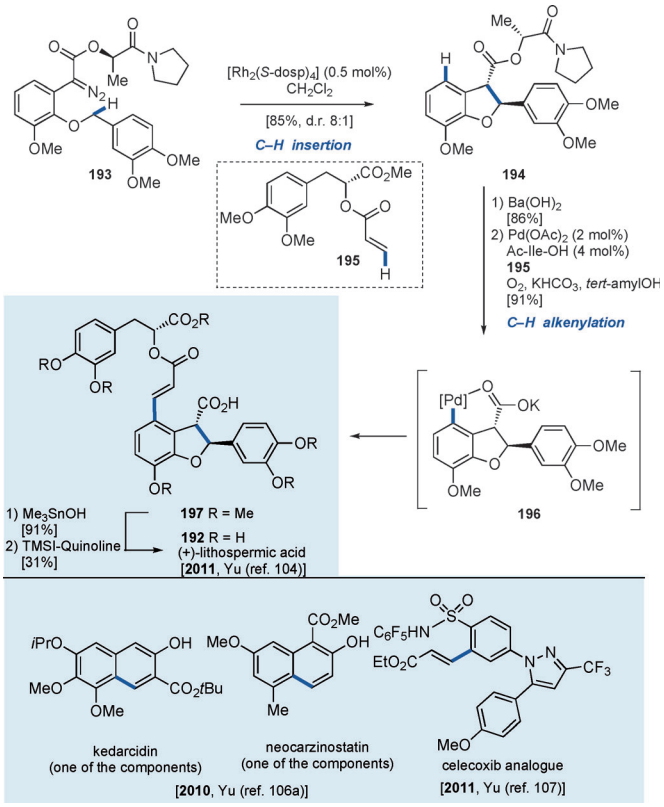
In 2002, Hughes and Trauner reported the total synthesis of (–)-frondosin B (**183**; Scheme 38).[96] In their synthesis, a palladium-catalyzed C–H alkenylation of benzofuran with an enol triflate was used for the construction of the seven-membered ring in **183**. Although similar palladium-catalyzed intra- and intermolecular coupling reactions between heteroaromatic compounds and aryl iodides had already been reported,[97] they had not been used for the total synthesis of natural products prior to their achievement. Treatment of triflate **179** with a $[Pd(PPh_3)_4]$ catalyst and iPr_2NEt in DMAc afforded cyclized product **181** in 70% yield. Although the mechanism of the coupling reaction is still unclear, the catalytic cycle might involve: 1) C–OTf oxidative addition of **179** to Pd^0, 2) C–H palladation of the benzofuran moiety in **180**, and 3) reductive elimination and concomitant regeneration of the Pd^0 species. Transformation of the ketone to a *gem*-dimethyl group, followed by demethylation of the methoxy moiety by NaSEt, accomplished the total synthesis of *ent*-**183**. This synthesis by Hughes and Trauner demonstrated one of the early applications of an aryl–H/alkenyl halide coupling. Recently, elegant and short syntheses of (+)-**183** and its analogues were reported by MacMillan.[98]

In 2009, Piguel and co-workers reported the synthesis of annuloline (**187**), the first isolated oxazole-containing natural product.[99] 5-Aryloxazole **184** was coupled with bromoalkene **185** in the presence of a copper catalyst (CuI and diamine **186**) and LiO*t*Bu to deliver **187** in 75% yield. Although a number of similar direct coupling reactions have been reported using transition-metal catalysts,[100] this synthesis is the only report of a natural product (albeit structurally simple) synthesized by intermolecular aromatic C–H alkenylation.

In 2005, Ellman, Bergman and co-workers reported the first total synthesis of (+)-lithospermic acid (**192**) by using diastereoselective intramolecular C–H alkylation with rhodium catalysis (Scheme 39).[101] They had already developed the synthesis of chiral dihydrobenzofurans, which represent



Scheme 39. Asymmetric intramolecular alkylation by rhodium-catalyzed C–H activation in natural product synthesis. Fc = ferrocenyl.

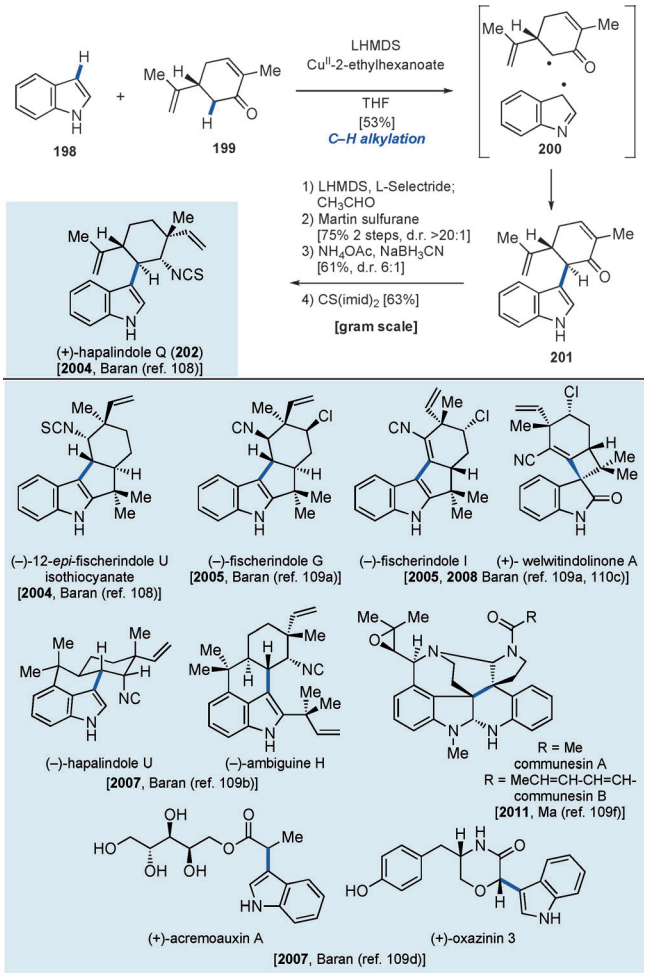


Scheme 40. Palladium-catalyzed intermolecular aromatic C–H alkenylation: Application to the synthesis of (+)-lithospermic acid (**192**), the kedarcidin core, the neocarzinostatin core, and a celecoxib analogue.

the core structure of **192**, by utilizing directing-group-assisted C–H activation.[102] Imine **188**, in the presence of 10 mol % of the $[RhCl(coe)_2]_2$ complex and 30 mol % ferrocenyl-PCy_2 ($FcPCy_2$), yielded dihydrobenzofuran **190** in 88 % yield and 73 % *ee*, through the intermediacy of **189**. A subsequent sequence of 1) Knoevenagel condensation of **190** with malonic acid, 2) decarboxylation, 3) epimerization of the C20 stereocenter, 4) condensation with **191**, followed by hydrolysis of the methyl ester, and 5) demethylation completed the asymmetric total synthesis of **192**. This synthesis elegantly showcased the utility of directing-group-assisted C–H alkylation using transition-metal catalysis (Murai-type C–H activation reaction) for the synthesis of complex natural products. They also applied their novel rhodium-catalyzed C–H activation method to the synthesis of vasicoline and biologically active compounds such as PKC and JNK3 inhibitors (Scheme 39).[103]

Very recently, the second total synthesis of (+)-lithospermic acid (**192**) was achieved by Wang and Yu (Scheme 40).[104] They employed two types of C–H functionalization, an intramolecular C–H insertion (see details in Section 3.4) and an intermolecular C–H alkenylation, to construct the dihydrobenzofuran unit and to connect the side chain. Treatment of diazo compound **193** with $[Rh_2(S\text{-dosp})_4]$ (Davies' catalyst; dosp = (*S*)-*N*-(dodecylbenzenesulfonyl)-prolinate)[105] at room temperature resulted in the C–H insertion to afford *trans*-dihydrobenzofuran **194** in 85 % yield with high diastereoselectivity (d.r. = 8:1). After hydrolysis of the chiral auxiliary group, C–H alkenylation of the resulting carboxylic acid with acrylate coupling partner **195** was carried out. In the presence of 2 mol % $Pd(OAc)_2$, 4 mol % Ac-Ile-OH, and 2.0 equiv of $KHCO_3$ under oxygen atmosphere, the corresponding coupling product **197** was synthesized in 91 % yield with complete *para* regioselectivity. As shown in intermediate **196**, the carboxylate unit in the substrate played a key role as a weakly coordinating directing group. The authors had already demonstrated that the key palladium-catalyzed C–H alkenylation of arenes provides the corresponding coupling product in good yield, when an amino acid ligand and an appropriate inorganic base are used.[106] Global demethylation was achieved by a two-step sequence with previously reported procedures,[101] thereby completing the total synthesis of **192**. Furthermore, the same research group reported the synthesis of aromatic components of natural products and the derivatization of a pharmaceutical (Celecoxib) by utilizing their palladium-catalyzed intermolecular C–H alkenylation reaction (see Scheme 40).[106a,107]

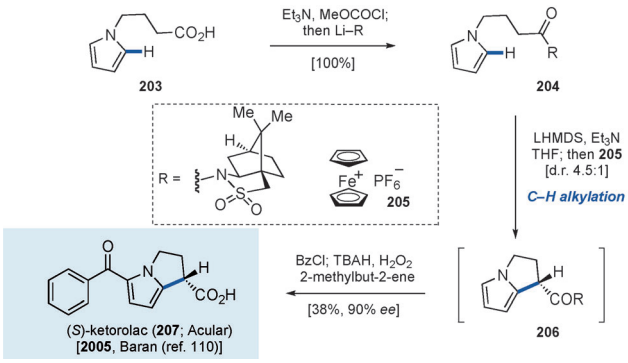
In 2004, Baran and Richter developed an oxidative cross-coupling of simple indoles and carbonyl compounds, and applied it to the elegant total synthesis of (+)-hapalindole Q (**202**; Scheme 41).[108] In terms of the reaction mechanism, this coupling reaction is completely different from the transition-metal-catalyzed aromatic C–H alkylation/alkenylation described above. Treatment of indole (**198**) with (*R*)-carvone (**199**) and LHMDS in the presence of copper(II)-2-ethylhexanoate afforded coupling product **201**. Although the



Scheme 41. Oxidative cross-coupling of indoles with carbonyl compounds: Application to the synthesis of natural products. LHMDS = lithium hexamethyldisilazide, imid = imidazolyl.

mechanism of C–C bond formation is still unclear, it is a formal C–H/C–H cross-coupling, possibly involving the following steps: 1) anions are generated from both indole and carvone; 2) these anions are oxidized to their respective radical species and brought together in proximity by the copper (see **200**); 3) the cross-coupling of **200** provides coupling product **201**. After several steps, the total synthesis of (+)-hapalindole Q (**202**) was accomplished in 6 steps and in 22 % yield overall (from **199**). Using the same key reaction, a related family of alkaloids, such as fischerindole I, welwitindolinone A and ambiguine H, as well as other natural products, such as acremoauxin A and oxazinin 3, were synthesized.[109] Very recently, Zuo and Ma reported the total syntheses of communesins A and B by utilizing this method.[109e]

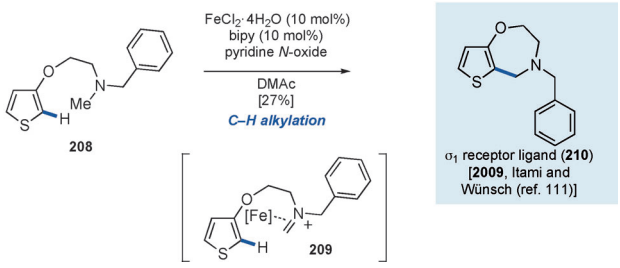
The oxidative cross-coupling strategy of indoles and carbonyl compounds can also be applied to the coupling of pyrroles. For example, Baran et al. demonstrated the enantioselective synthesis of (*S*)-ketorolac (**207**; Acular), a widely marketed pharmaceutical agent (Scheme 42).[110] Their synthesis commenced with the amidation of pyrrolecarboxylic acid **203** (which was readily prepared by the addition of



Scheme 42. C–H alkylation of pyrroles: Synthesis of (*S*)-ketorolac (**207**). TBAH = tetrabutylammonium hydroxide.

pyrrole to butyrolactone) with a chiral auxiliary to give **204**. Oxidative intramolecular C–H coupling of **204** proceeded by treatment with LHMDS, NEt$_3$, and ferrocenium hexafluorophosphate **205** to give the corresponding coupling product **206** as a 4.5:1 mixture of diastereomers. Bicyclic intermediate **206** was then benzoylated, and subsequent hydrolysis of the chiral auxiliary completed the synthesis of **207**.

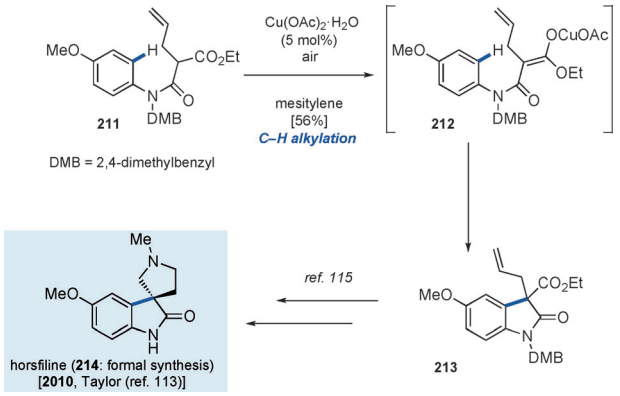
In 2009, Itami, Wünsh, and co-workers reported the iron-catalyzed oxidative coupling of heteroarenes with methylamines, and thereby created bicyclic heterocycle **210** (Scheme 43).[111] In the presence of a catalytic amount of $FeCl_2 \cdot 4H_2O$/2,2-bipyridine and pyridine *N*-oxide, thiophene



Scheme 43. Iron-catalyzed oxidative C–H alkylation of heteroarenes with methylamines.

208 was converted into **210** in 27 % yield. Although the reaction mechanism remains unknown, the reaction likely proceeds through a metal-bound iminium species **209**, which then undergoes electrophilic substitution of the thiophene moiety.[112] The coupling product **210** has a good binding affinity toward the σ_1 receptor protein. This new mode of oxidative C–H coupling can also be used for the intermolecular coupling of thiophenes, furans, and indoles with methylamines.

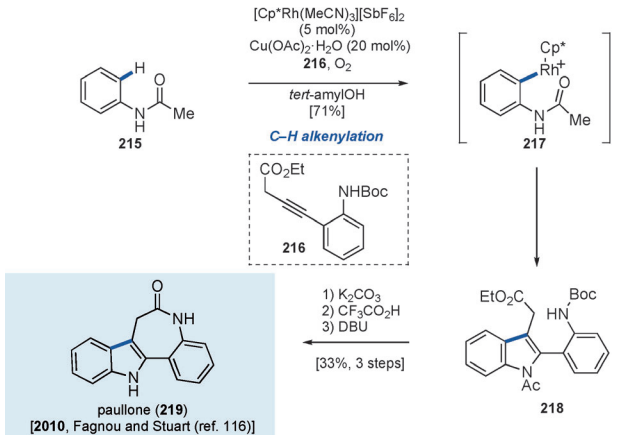
In 2010, Taylor and co-workers reported the formal synthesis of an anticancer and analgesic oxindole alkaloid, horsfiline (**214**), by using a copper-catalyzed intermolecular C–H coupling (Scheme 44).[113] They had already reported a stoichiometric approach to oxindoles through the use of 1.0 equiv of $Cu(OAc)_2 \cdot H_2O$ and 1.1 equiv of KO*t*Bu in DMF at 110 °C in air.[114] After a slight change in these conditions (without base, in mesitylene, and heating at 165 °C), the



Scheme 44. Copper-catalyzed oxidative coupling for the synthesis of oxindoles: Formal synthesis of horsfiline (**214**).

reaction was rendered catalytic (5 mol% $Cu(OAc)_2{\cdot}H_2O$). With this catalyst system in hand, they targeted spirooxindole **214**. Intramolecular C–H/C–H coupling of amide **211** afforded the resulting coupling product **213** in 56% yield. The transformation from oxindole **213** to horsfiline (**214**) was achieved following previously reported procedures.[115] This C–H alkylation is an effective method for constructing quaternary centers without prefunctionalization.

Recently, Stuart, Fagnou et al. reported an oxidative Larock-type heterocycle synthesis by rhodium catalysis and applied it to the synthesis of paullone (**219**) (Scheme 45).[116] The Larock heterocycle synthesis is a state-of-the-art, transition-metal-catalyzed intermolecular approach for the synthesis of indoles, pyrroles, and other heterocycles.[117] However, the starting materials for this reaction must be prefunctionalized as aryl and alkenyl halides. In the system developed by Stuart, Fagnou et al., a direct access to the indole framework was realized through a rhodium-catalyzed C–H functionalization of acetanilide derivatives with alkynes. For the synthesis of **219**, acetanilide (**215**) was coupled with alkyne **216** in the presence of a rhodium catalyst and $Cu(OAc)_2{\cdot}H_2O$ as an oxidant under air to form disubstituted indole **218** in 71% yield. Removal of the acetyl and Boc

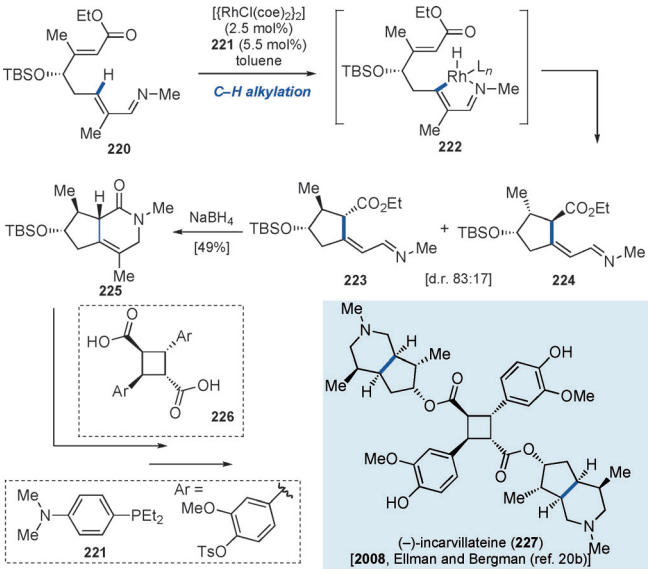


Scheme 45. Rhodium-catalyzed oxidative coupling of acetanilide and alkyne: Application to the synthesis of paullone (**219**). Cp* = C_5Me_5, DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

groups, followed by treatment with DBU afforded **219** in a total of 8 steps.

3.2.2. *Olefinic C–H Arylation, Alkenylation, and Alkylation*

In 2008, Tsai, Bergman, and Ellman reported an asymmetric synthesis of (−)-incarvillateine (**227**), in which they used an intramolecular olefinic C–H alkylation with rhodium catalysis (Scheme 46).[20b] Monoterpene alkaloid **227** and its analogues had already been synthesized by Kibayashi and co-

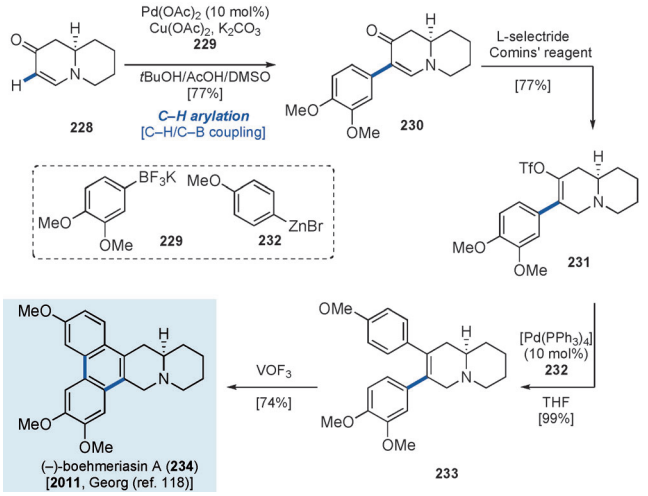


Scheme 46. Enantioselective total synthesis of (−)-incarvillateine (**227**) by rhodium-catalyzed olefinic C–H alkylation. coe = cyclooctene.

workers in over 20 synthetic steps.[20a] Ellman and Bergman applied their own C–H activation method with a rhodium catalyst (see other examples in Section 3.2.1) to accomplish the concise synthesis of (−)-incarvillateine (**227**) in 11 steps. The $C(sp^2)$–H alkylation of imine **220** was carried out using $[\{RhCl(coe)_2\}_2]$ and various ligands in toluene. The use of 5 mol% Rh catalyst and 11 mol% $FcPCy_2$ (this catalyst system was previously known for C–H alkylation, see Scheme 39) led to C–H activation and cyclization through intermediate **222**, to give the corresponding products **223** and **224** as a mixture of diastereomers (d.r. = 53:47). Further screening of ligands showed that the diastereoselectivity could be increased to 83:17 by using 2.5 mol% Rh catalyst and 5.5 mol% $(DMAPh)PEt_2$ **221** as the ligand. Treatment of the crude mixture of **223** and **224** with $NaBH_4$, followed by cyclization, afforded lactam **225** in 49% overall yield from **220** after separation of the undesired isomer by chromatography. After reduction of lactam **225** and removal of the TBS group, Mitsunobu inversion using cyclobutanedicarboxylic acid **226** followed by deprotection led to the completion of (−)-incarvillateine (**227**).

In 2011, Leighty and Georg reported the total synthesis of both *R* and *S* enantiomers of boehmeriasin A (**234**) by using olefinic C–H arylation as the key step (Scheme 47).[118] They

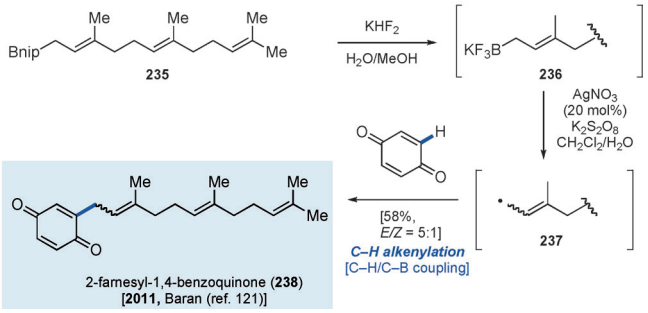
had previously reported a palladium-catalyzed C–H arylation of enaminones with organotrifluoroborates.[119] When $Pd(OAc)_2$, $Cu(OAc)_2$, and an appropriate base were used, enaminone **228** coupled with potassium organotrifluoroborate **229** to deliver the corresponding coupling product **230** in 77% yield. Treatment of **230** with L-selectride followed by trapping of the resulting enolate with Comins' reagent[120] led to triflate **231**. Negishi coupling of triflate **231** with organozinc reagent **232** gave coupling product **233** in excellent yield. A



Scheme 47. Olefinic C–H arylation: Total synthesis of boehmeriasin A (**234**).

final oxidative biaryl coupling of **233** with VOF_3 accomplished the total synthesis of boehmeriasin A (**234**). This concise synthetic strategy showcases the power of late-stage C–H arylations to rapidly access a chiral tetrahydroindolizinone framework.

In 2011, Baran and co-workers reported that an arylation/alkenylation of the $C(sp^2)$–H bond of benzoquinone derivatives can be accomplished with aryl/alkenyl boronic acids or boronates under silver catalysis (Scheme 48).[121] They also demonstrated that this olefinic C–H arylation/alkenylation can be applied to the synthesis of 2-farnesyl-1,4-benzoquinone (**238**). The pinacolboronate of farnesol (**235**) was



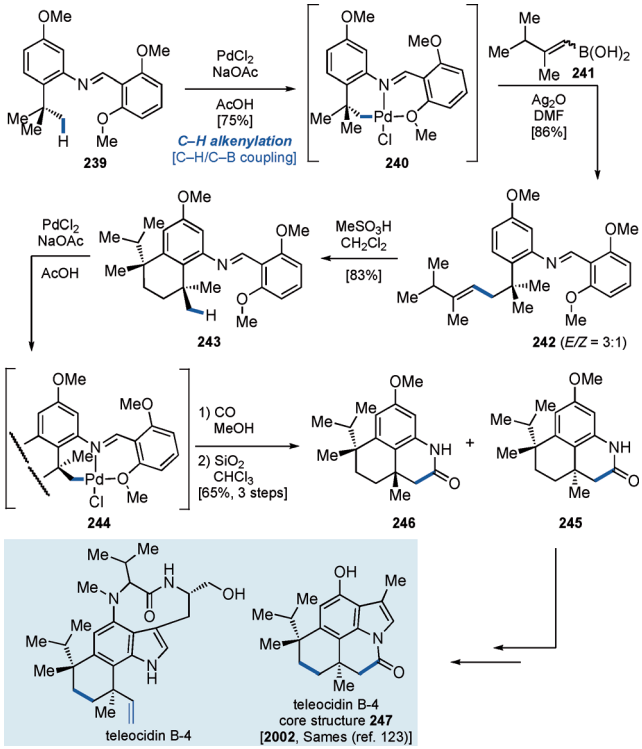
Scheme 48. Olefinic C–H alkenylation under Minisci conditions: Synthesis of 2-farnesyl-1,4-benzoquinone (**238**).

converted into potassium trifluoroborate **236** and was then coupled with benzoquinone in the presence of 20 mol% $AgNO_3$ and 3.0 equiv of $K_2S_2O_8$ (Minisci reaction conditions)[122] to deliver 2-farnesyl-1,4-benzoquinone (**238**) in 58% yield. It is presumed that allyl radical intermediate **237** is involved in this catalytic formation of a C–C bond.

Although the application of olefinic C–H functionalization to the synthesis of biologically active compounds is still rare, it has the potential to be useful in more complex natural product synthesis.

3.3. $C(sp^3)$–H Functionalization

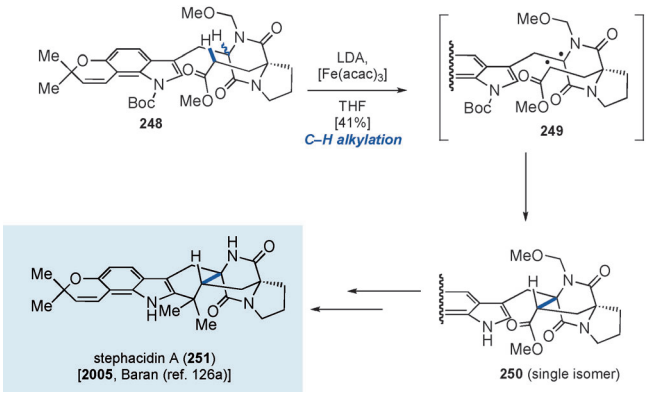
One of the early remarkable applications of $C(sp^3)$–H functionalization in natural product synthesis is found in the synthesis of teleocidin B-4 (bearing core structure **247**) by the Sames research group (Scheme 49).[123] They envisioned first that one of the methyl groups in the *tert*-butyl group of compound **239** could be alkenylated directly by C–H activation. Chelated palladacycle intermediates such as **240** had been known to undergo direct functionalization reactions;[124] however, transmetalation with boronic acids had not been reported. Treatment of palladium complex **240** with vinylboronic acid **241** in the presence of Ag_2O furnished alkenylated product **242** in 65% overall yield from **239**. Friedel–Crafts alkylation of **242** was then induced by treatment with methanesulfonic acid to yield cyclized product **243**. Imine **243** was again treated with stoichiometric amounts of $PdCl_2$ and NaOAc to deliver a diastereomeric mixture of palladacycle **244**, which was treated with gaseous CO and MeOH, before cyclizing with SiO_2 to afford lactams **245** and



Scheme 49. Synthesis of the core structure **247** of teleocidin B-4.

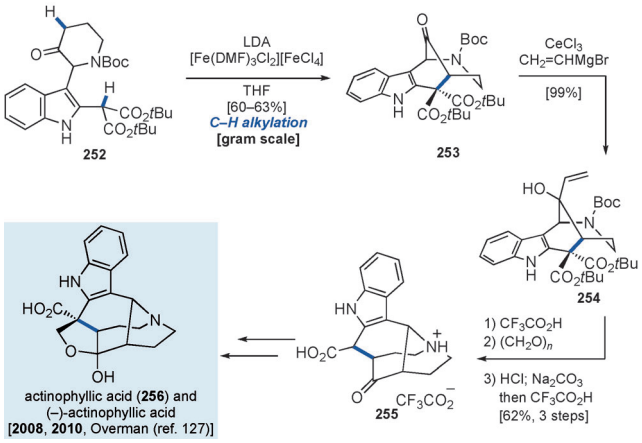
246 (65% yield over 3 steps; d.r. = 6:1). The construction of an indole moiety completed the synthesis of the core structure of teleocidin B-4.[125] This synthesis demonstrates the power of C–H functionalization in complex molecular settings, thus offering new modes of retrosynthetic analysis in natural product synthesis.

In 2005, Baran et al. achieved the first synthesis of the heptacyclic alkaloid stephacidin A (**251**) by a key oxidative coupling of two C(sp^3)–H bonds α to carbonyl groups (Scheme 50).[126a] They had already reported a copper-catalyzed oxidative coupling of indoles/pyrroles and carbonyl compounds for the synthesis of complex natural products (see details in Section 3.2.1, Schemes 41 and 42). Slightly modifying their previous coupling conditions, 2.2 equiv of LDA and [Fe(acac)$_3$] (instead of a copper complex), were used to cyclize compound **248** into **250** as a single isomer. The mechanism of this coupling reaction was proposed as follows: 1) deprotonation of the two C–H bonds; 2) oxidation by the iron complex to form radical intermediate **249**; and 3) stereoselective C–C bond formation to deliver **250**. The observed stereoselectivity was suggested to arise from a "head-to-head" orientation of the two carbonyl groups involved.[126c] Baran et al. also achieved the total synthesis of avrainvillamide (an analogue of stephacidin A) and stephacidin B (the dimer of stephacidin A).[126b] This remarkable enolate coupling reaction has thus been shown to be a simplifying disconnection strategy for the synthesis of natural products.



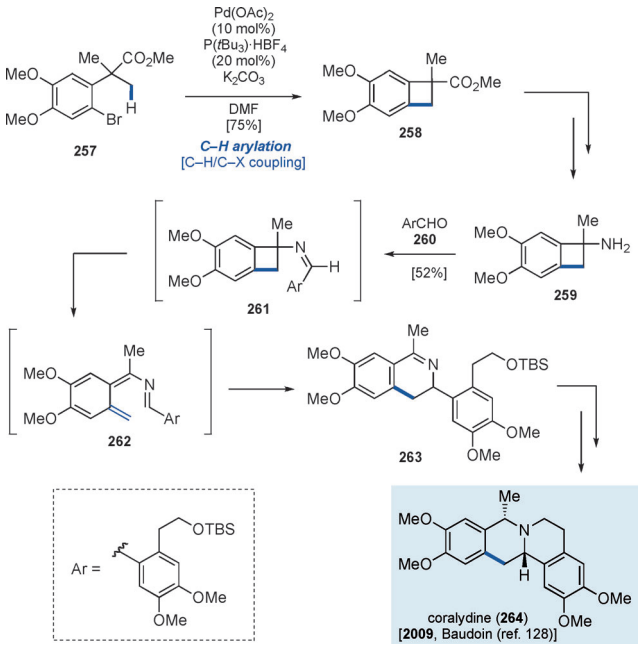
Scheme 50. Total synthesis of stephacidin A (**251**) by Baran and co-workers. LDA = lithium diisopropylamide, acac = acetylacetonate.

In 2008, Overman and co-workers reported the first total synthesis of actinophyllic acid (**256**) by utilizing Baran's oxidative coupling method described above (Scheme 51).[127a] Treatment of indole **252** with LDA and a stoichiometric amount of an iron(III) complex as oxidant promoted a C–H/C–H coupling to afford the keto-bridged hexahydro-1,5-methanoazocino[4,3-*b*]indole ring system **253** in 60–63% yield with complete regioselectivity. This oxidative coupling reaction can be scaled up to 10 g. The introduction of a vinyl moiety through vinylmagnesium bromide in the presence of $CeCl_3$ yielded **254**. After cleavage of the Boc group by trifluoroacetic acid, followed by addition of paraformaldehyde with a catalytic amount of camphorsulfonic acid, promoted an aza-Cope–Mannich rearrangement. The resulting diester was then hydrolyzed, decarboxylated, and treated with trifluoroacetic acid to generate ammonium trifluoroacetate **255**. After a final two-step sequence, the total synthesis of racemic actinophyllic acid (**256**) was completed in an overall yield of 8% (Scheme 51). Two years later, Overman and co-workers also reported a second-generation total synthesis of racemic **256** in 22% overall yield, along with an enantioselective synthesis of (−)-**256**.[127b]



Scheme 51. Total synthesis of actinophyllic acid (**256**).

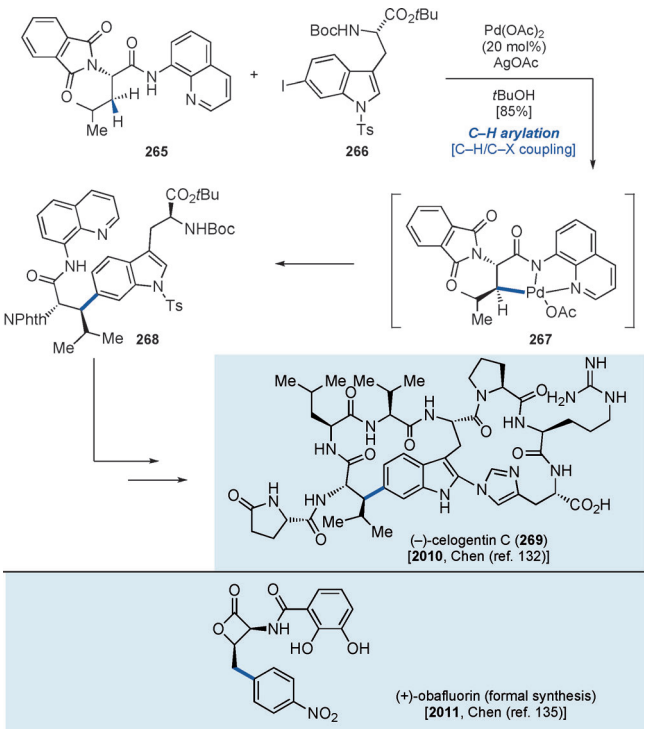
In 2009, the Baudoin research group reported the synthesis of the tetrahydroisoquinoline alkaloid coralydine (**264**) by an intramolecular C(sp^3)–H arylation/electrocyclization strategy (Scheme 52).[128] They previously developed a concise synthesis of benzocyclobutenes by a palladium-catalyzed C–H activation of methyl groups.[129] They then envisioned that an iminobenzocyclobutene such as **261** could be converted



Scheme 52. Intramolecular C(sp^3)–H arylation: Total synthesis of coralydine (**264**).

into dihydroisoquinoline **263** by a tandem electrocyclic 4π opening/6π closure via *o*-quinodimethane intermediate **262**.[130] Thus, bromobenzene derivative **257** was treated with a catalytic amount of $Pd(OAc)_2/P(tBu)_3$, HBF_4, and K_2CO_3 in DMF to effect intramolecular C(sp^3)–H arylation, thereby providing benzocyclobutene **258** in 75% yield.[131] After hydrolysis of the ester moiety of **258**, the resulting carboxylic acid was transformed into amine **259** by a Curtius rearrangement. Treatment of **259** with an aryl aldehyde **260** provided imine **261**, which underwent a ring-opening/closing electrocyclization sequence to set the core structure of coralydine (**263**).

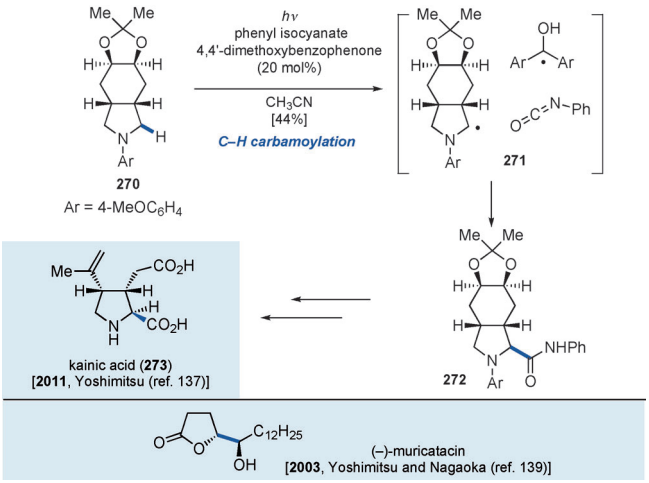
In 2010, Feng and Chen achieved the total synthesis of (−)-celogentin C (**269**) by intermolecular C(sp^3)–H arylation (Scheme 53).[132] Corey had discovered earlier that the C–H



Scheme 53. Total synthesis of (−)-celogentin C (**269**) by stereoselective C(sp^3)–H arylation.

bond at the β position of *N*-(8-quinolinyl)-α-phthalamido amides such as **265** can be arylated with aryl iodides with catalytic amounts of $Pd(OAc)_2$.[133a] Daugulis and co-workers also reported a procedure for the functionalization of related unactivated C(sp^3)–H bonds.[133b,c] He and Chen took advantage of these directing-group-assisted methods for their synthesis. Treatment of compound **265** with a $Pd(OAc)_2$ catalyst and 1.5 equiv of AgOAc as an oxidant formed the Pd^{II} intermediate **267**. This palladacycle reacted further with iodoindole **266** to afford coupling product **268** in excellent yield. After several steps,[134] the total synthesis of celogentin C (**269**) was accomplished in a total of 23 steps. This is the first application of a palladium-catalyzed intermolecular C(sp^3)–H arylation to natural product synthesis. They also achieved a formal synthesis of obafluorin by using a similar strategy.[135]

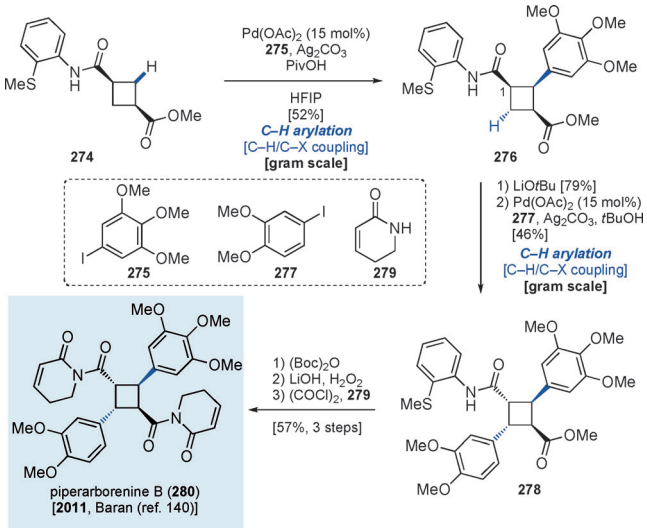
Inspired by pioneering studies in photochemical transformations of tertiary amines,[136] Yoshimitsu and co-workers developed a C–H carbamoylation reaction and applied it to the synthesis of kainic acid (**273**; Scheme 54).[137] Their synthesis of **273** commenced with the photolysis of amine



Scheme 54. C–H carbamoylation under photolytic conditions: Total synthesis of kainic acid (**273**).

270 with phenyl isocyanate in the presence of a sensitizer (20 mol% 4,4′-dimethoxybenzophenone) to generate amide **272** in 44% yield. The presumed mechanism involves the generation of α-aminoalkyl radical **271** by a photochemical reaction of **270** and the excited sensitizer (Scheme 54); a subsequent radical addition of **271** to phenyl isocyanate, followed by hydrogen atom abstraction can then produce **272**. After several transformations, the total synthesis of kainic acid (**273**) was achieved. This natural product has received particular attention as a synthetic target, and more than 20 total syntheses have been reported to date.[138] Although Yoshimitsu's synthesis may not be the most efficient one, it contains new and interesting features compared to other syntheses. Yoshimitsu, Makino, and Nagaoka also reported the synthesis of muricatacin by a radical-mediated C(sp^3)–H addition to an aldehyde.[139]

Most recently, Gutekunst and Baran reported the total synthesis of piperarborenine B (**280**), a dimeric cyclobutane-containing natural product, by sequential C(sp^3)–H arylation (Scheme 55).[140] In the presence of the catalyst $Pd(OAc)_2$, Ag_2CO_3, and PivOH, cyclobutane **274** underwent C(sp^3)–H arylation with 5-iodo-1,2,3-trimethoxybenzene (**275**) in hexafluoroisopropanol (HFIP) to yield **276** in 52% yield, with complete regio- and stereoselectivity, and on a gram scale. The use of [2-(methylthio)phenyl]carbamoyl[141] as the chelating unit was critical in this transformation. After epimerization of the C1 stereocenter of **276**, the second C(sp^3)–H arylation took place with 4-iodo-1,2-dimethoxybenzene (**277**) under similar conditions to provide coupling product **278** with complete stereoselectivity. Removal of the chelating group under Evans' conditions,[142] followed by condensation with



Scheme 55. Total synthesis of piperarborenine B (**280**) by sequential C–H arylation of two C(sp^3)–H bonds. HFIP = hexafluoroisopropanol.

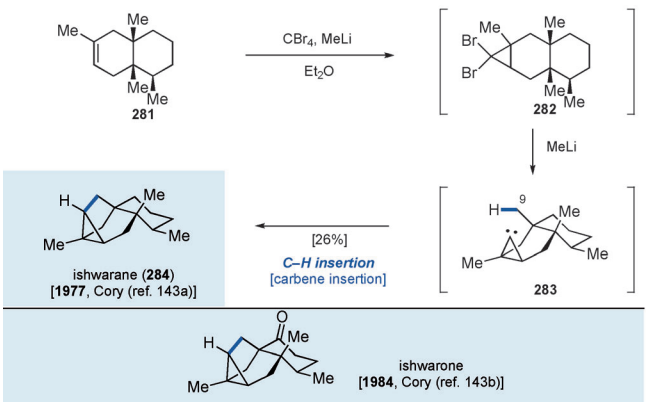
dihydropyridone **279**, completed the total synthesis of piperarborenine B (**280**). Although a [2+2] photocycloaddition of two alkenes is a representative route to build cyclobutane-containing compounds, this C–H functionalization method clearly offers a new strategy in cyclobutane synthesis, thus circumventing problems in cross-dimerization such as the production of homodimers or poor regio- and stereoselectivity.

3.4. C–H Insertion of Carbenes and Metal Carbenoids

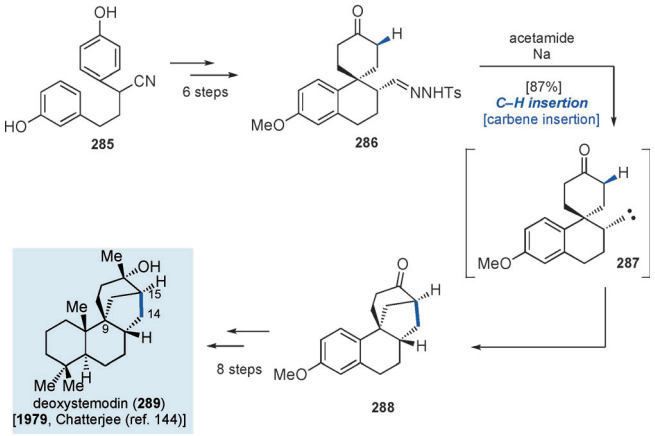
3.4.1. Early Examples of C–H Insertion of Carbenes (Non-Transition Metal-Catalyzed Reactions)

In 1977, an early contribution of non-transition-metal-catalyzed C–H insertion for the synthesis of natural products was reported by Cory et al.[143a] When targeting the tetracyclic sesquiterpene ishwarane (**284**), they envisioned that C–H insertion could occur from cyclopropylcarbene **283** into a specific C–H bond (the C9-position) to form the requisite six-membered ring (Scheme 56). To effectuate this key step, carbene **283** was prepared by dibromocyclopropanation of **281** with CBr_4 and base, followed by addition of MeLi. The insertion reaction on carbene **283** indeed provided ishwarane (**284**) in 26% yield, successfully providing a new form of "chemical logic" in natural product synthesis. Seven years later, the Cory research group also accomplished the total synthesis of ishwarone, a more oxidized version of **284**.[143b]

In 1979, Chatterjee also applied a C–H insertion method to the synthesis of deoxystemodin (**289**),[144] with the vision that the tetracyclic framework of **288** can be constructed by an intramolecular oxidative phenol coupling from bisphenol **285** and carbene insertion to forge the C14–C15 bond (Scheme 57). Thus, bisphenol **285** was converted into tosylhydrazone **286** in 6 steps, which involved an intramolecular oxidative phenol-coupling step.[145] Treatment of tosylhydrazone **286** with sodium in acetamide at 140 °C generated



Scheme 56. Early contribution using a carbene insertion reaction: The concise total synthesis of ishwarane (**284**).

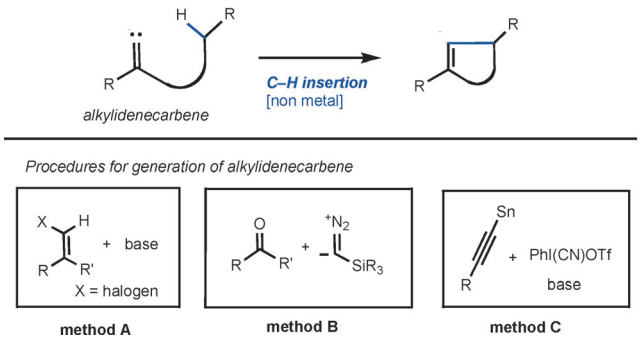


Scheme 57. Total synthesis of deoxystemodin (**289**) by C–H insertion.

tetracyclic compound **288** by a C–H insertion of carbene intermediate **287**. After several more steps, the synthesis of deoxystemodin (**289**) was completed.

3.4.2. C–H Insertion of Alkylidenecarbenes

Alkylidenecarbenes are versatile intermediates that can be used for C–H functionalization.[146] In general, alkylidenecarbenes undergo insertion into primary, secondary, and benzylic C–H bonds, as well as tertiary C–H bonds in a stereocontrolled fashion to form five-membered carbocyclic (i.e., cyclopentene) or heterocyclic systems (i.e., furan). Although many approaches for the generation of alkylidenecarbene species have been reported,[147] three particular methods have been frequently utilized in the synthesis of natural products: 1) α-elimination from terminal 1-haloalkenes (Scheme 58, method A), achieved by treating vinyl halides with strong bases (KO*t*Bu, KHMDS);[148] 2) the generation of diazoalkenes from carbonyl compounds (method B), accomplished by condensing the anion of (trimethylsilyl)diazomethane ($TMSCN_2^-$) with carbonyl compounds;[149] 3) the formation of alkynyliodonium salts from alkynes (method C), realized by combining alkynylstannanes and PhI(CN)OTf then adding an appropriate base (e.g., sodium *p*-



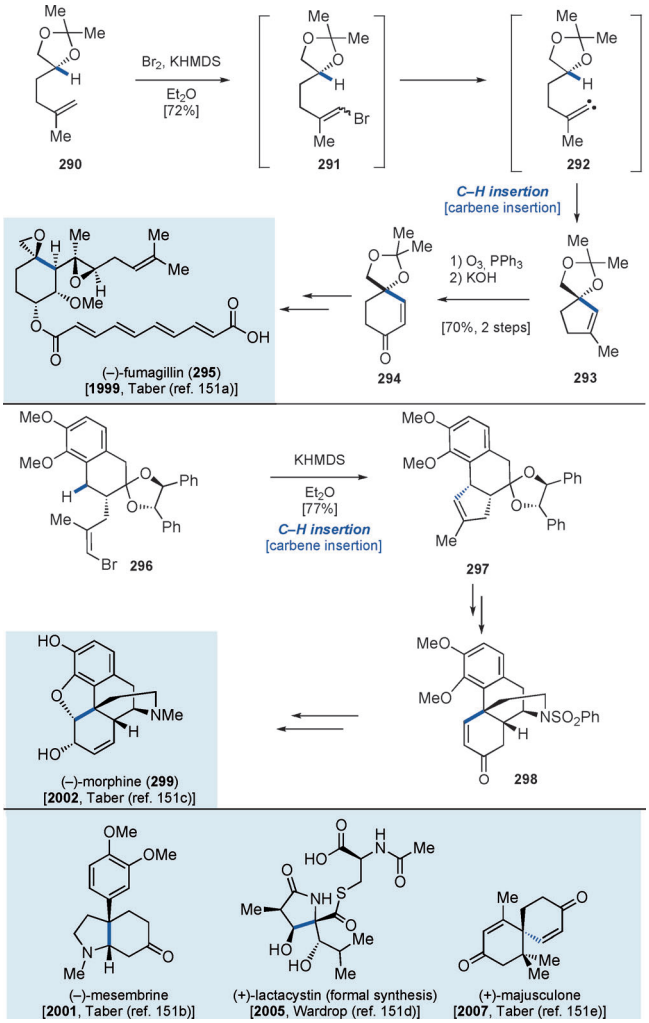
Scheme 58. An overview of C–H insertion of alkylidenecarbenes and representative procedures for the generation of alkylidenecarbenes.

toluenesulfinate or sodium benzenesulfinate).[150] In this section, we describe the syntheses of natural products that involve the C–H insertion of alkylidenecarbenes.

The generation of alkylidenecarbenes by α-elimination from terminal 1-haloalkenes (Scheme 58, method A) has led to a few applications in the total synthesis of natural products, particularly by Taber and co-workers.[151] For example, in 1999, the total synthesis of (−)-fumagillin (**295**), a well-known angiogenesis inhibitor, was reported (Scheme 59). This natural product has been a popular synthetic target in the organic chemistry community because of its interesting biological activity and structural features.[152] Taber et al. reported the second enantioselective total synthesis of **295**, which involved a stereoselective carbene insertion as one of their key steps. Alkylidenecarbene **292**, which was generated in situ from alkene **290**, afforded the C–H insertion product **293**. Ozonolysis of **293** and recyclization gave cyclohexenone **294**. After several steps from **294**, the synthesis of (−)-fumagillin (**295**) was achieved.

Morphine (**299**) is also a popular target that has been synthesized by a number of organic chemists.[153] In 2002, Taber et al. utilized a C–H insertion strategy for the construction of the tricyclic carbon framework of **299**.[151c] The sequence involved was similar to that used in the synthesis of fumagillin: bromoalkene **296** was treated with KHMDS to afford cyclopentene **297** in 77% yield. This key intermediate (**297**) was transformed into (−)-morphine (**299**) after a number of steps. Although their achievement might not classify as the best morphine synthesis, their disconnection strategy helped inspire new ideas in synthesis. Thereafter, the synthesis of (−)-mesembrine and (+)-majusculone by Taber et al. and the formal synthesis of (+)-lactacystin by Wardrop and Bowen were reported, based on similar C–H insertion strategies (Scheme 56).[151b,d,e]

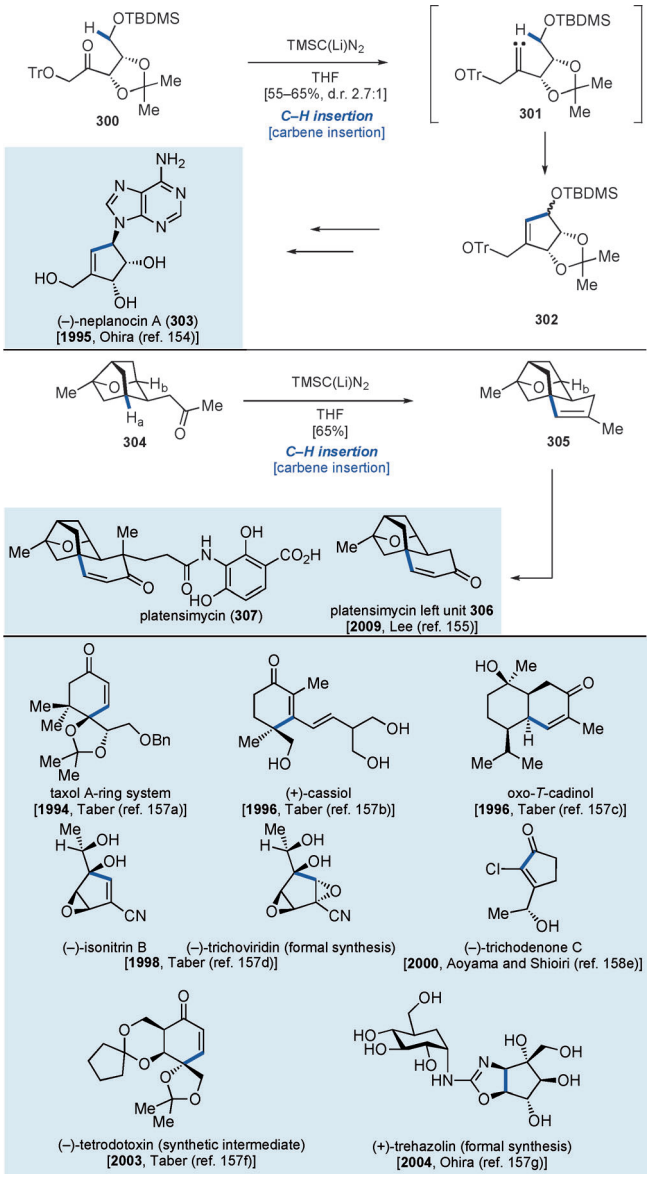
In 1995, Ohira et al. demonstrated the synthesis of neplanocin A (**303**)[154] by applying their own method in the generation of alkylidenecarbenes (Scheme 58, method B). Treatment of ketone **300** with Li-TMSCN$_2$ generated alkylidenecarbene **301**, which inserted into the C(sp^3)–H bond geminal to the silyloxy group to afford cyclopentene **302**. After a few functional-group transformations, followed by introduction of the adenine unit under Mitsunobu conditions and removal of the trityl protecting group, the total synthesis of neplanocin A (**303**) was completed (Scheme 60).



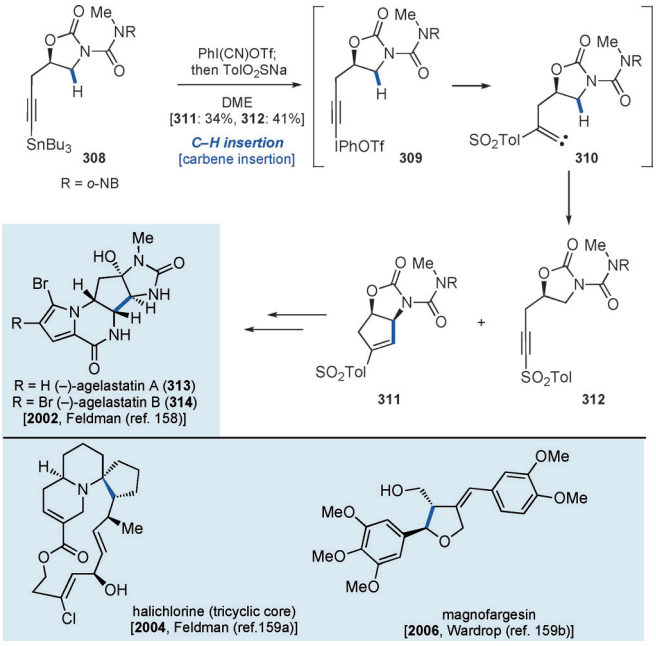
Scheme 59. C–H insertion of alkylidene carbenes in total synthesis I.

In 2009, a formal synthesis of platensimycin (**307**) was reported by the Lee research group.[155] Ketone **304** was treated with Li-TMSCN$_2$ to afford caged tetracycle **305** in 65% yield. Although two C–H bonds (H$_a$ and H$_b$) were adjacent to the reactive alkylidenecarbene generated from **304**, the reaction showed high regioselectivity in favor of C–H$_a$ insertion. After a few more steps, the non-aromatic portion of platensimycin (**306**) was synthesized. Thanks to existing procedures by the Nicolaou research group,[156] a formal synthesis of platensimycin (**307**) was completed. Other examples of natural product synthesis involving C–H insertion of alkylidenecarbenes generated from ketones and lithiated trimethylsilyldiazomethanes are listed in Scheme 60.[157]

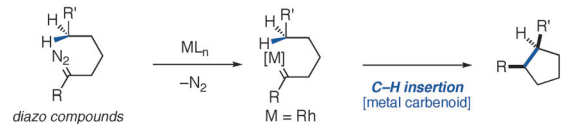
In the synthesis of agelastatin A (**313**) and B (**314**), Feldman et al. demonstrated the first use of carbenes generated from alkynyliodonium salts (see Scheme 58, method C) in the synthesis of natural products (Scheme 61).[158] Treatment of alkynyliodonium salt **309**, which was produced from oxazolidinone **308** and Stang's reagent (PhI(CN)OTf),[150] with sodium toluenesulfinate in DME at reflux provided the desired C–H insertion product **311** in 34% yield.



Scheme 60. C–H insertion of alkylidenecarbenes in total synthesis II. TBDMS = *tert*-butyldimethylsilyl.



Scheme 61. Alkylidene carbene insertion reactions in total synthesis III.



Scheme 62. General Scheme for metal-catalyzed C–H insertion from diazo compounds.

The Feldman research group proceeded to complete the synthesis of agelastatin A (**313**) and B (**314**) from this bicyclic product.

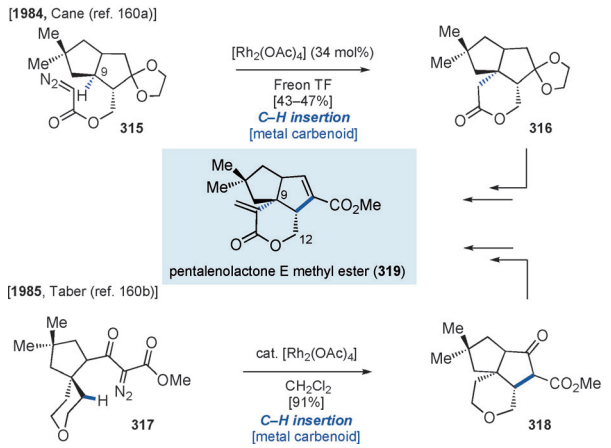
Feldman et al. also reported the synthesis of the tricyclic core of halichlorine, and Wardrop and Fritz accomplished the total synthesis of magnofargesin by using a similar method.[159]

3.4.3. C–H Insertion of Metal Carbenoids

Another frequently used mode of C(sp^3)–H functionalization is C–H insertion using a diazo compound and a transition-metal catalyst (Scheme 62). When diazo compounds are treated under the action of certain metal complexes, such as binuclear rhodium(II), metal carbenoids are produced. Such metal carbenoids often collapse by inserting into nearby C–H bonds intramolecularly to afford cyclic molecules (mostly five- or six-membered rings).

This C–H insertion through metal carbenoids is now well established in terms of chemo-, regio-, and stereoselectivity, and is remarkable for its low catalyst loading and high reactivity. Numerous methods and syntheses of natural products that utilize metal carbenoid C–H insertions have been reported, and a number of excellent reviews and books have been published.[4] Therefore, this Review focuses solely on topics that represent early contributions and landmark achievements in this field.

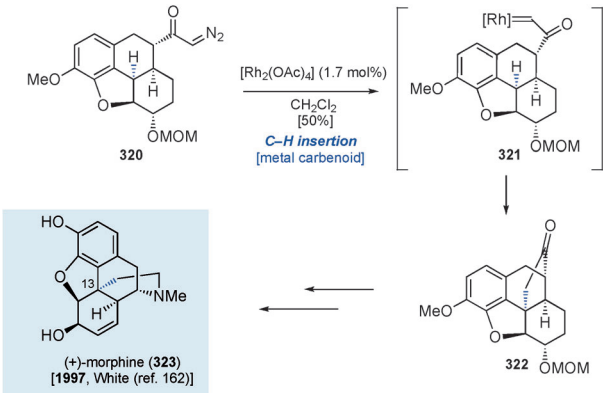
In 1984 and 1985, the Cane and Taber research groups independently reported total syntheses of pentalenolactone E methyl ester (**319**), by utilizing intramolecular C–H insertion of metal carbenoids (Scheme 63).[160] The key step in the synthesis of Cane and Thomas was performed on diazo compound **315**: the use of a $[Rh_2(OAc)_4]$ catalyst in Freon TF (1,1,2-trichloro-1,2,2-trifluoromethane)[161] under reflux conditions formed a rhodium carbenoid, which inserted into the C–H bond at the tertiary carbon atom C9 to afford tricyclic compound **316** in 43–47% yield.[160a] In contrast, Taber and Schuchardt used a different disconnection strategy to synthesize a similar tricyclic compound:[160b] the exposure of diazo ketoester **317** to a catalytic amount of $[Rh_2(OAc)_4]$ in dichloromethane at room temperature allowed the C–H insertion to occur smoothly at the secondary carbon atom C12 to provide **318** in 91% yield. These early examples both



Scheme 63. Early contributions in metal-catalyzed C–H insertion: Application to the synthesis of pentalenolactone E methyl ester (**319**).

showcased the utility of metal carbenoid C–H insertion for the synthesis of natural products.

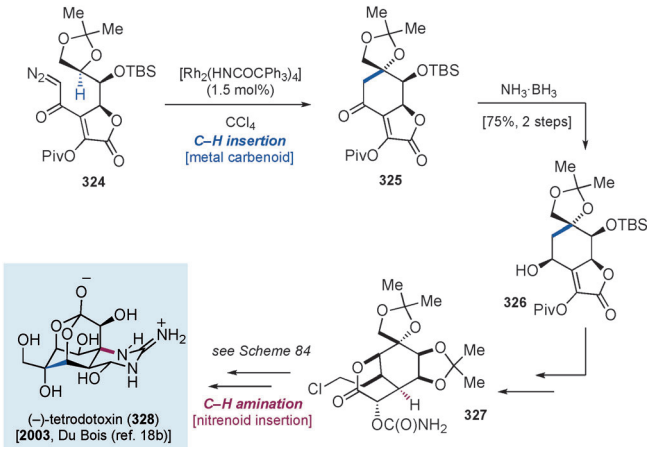
In 1997, White et al. described the total synthesis of (+)-morphine (**323**; Scheme 64).[162] They envisaged a C–H insertion strategy involving a metal carbenoid to construct the



Scheme 64. Total synthesis of (+)-morphine (**323**) by C–H insertion.

quaternary carbon atom C13 in **323**. After preparing diazo ketone **320**, C–H insertion in the presence of a rhodium catalyst occurred to give **322** in a regio- and stereoselective fashion. After a few more transformations, the synthesis of (+)-morphine (**323**), the unnatural enantiomer of morphine, was completed in a total of 28 steps. Morphine has been a popular synthetic target over the last 60 years (see another synthesis in Section 3.4.2), but this synthesis only represents the second asymmetric synthesis of this celebrated molecule.

Tetrodotoxin (**328**) is known to be one of the most structurally complex natural products, and therefore its synthesis, even in racemic form, is an extremely demanding task. In 1972, the landmark synthesis of racemic tetrodotoxin (**328**) was successfully achieved by Kishi et al. (29 steps),[19d] but nobody took up the challenge for a second synthesis, let alone an asymmetric synthesis, until the 21st century. In 2003, Isobe and co-workers reported the first asymmetric synthesis of (−)-**328**.[19a] However, it took 67 steps synthetic steps for its completion, thus highlighting the difficulty in assembling such molecular complexity. Impressively, a 32-step asymmetric synthesis of (−)-**328** was reported in the same year by the Du Bois research group, who utilized a state-of-the-art C–H functionalization method (Scheme 65).[19b] One of their key reactions was a rhodium-catalyzed intramolecular C–H



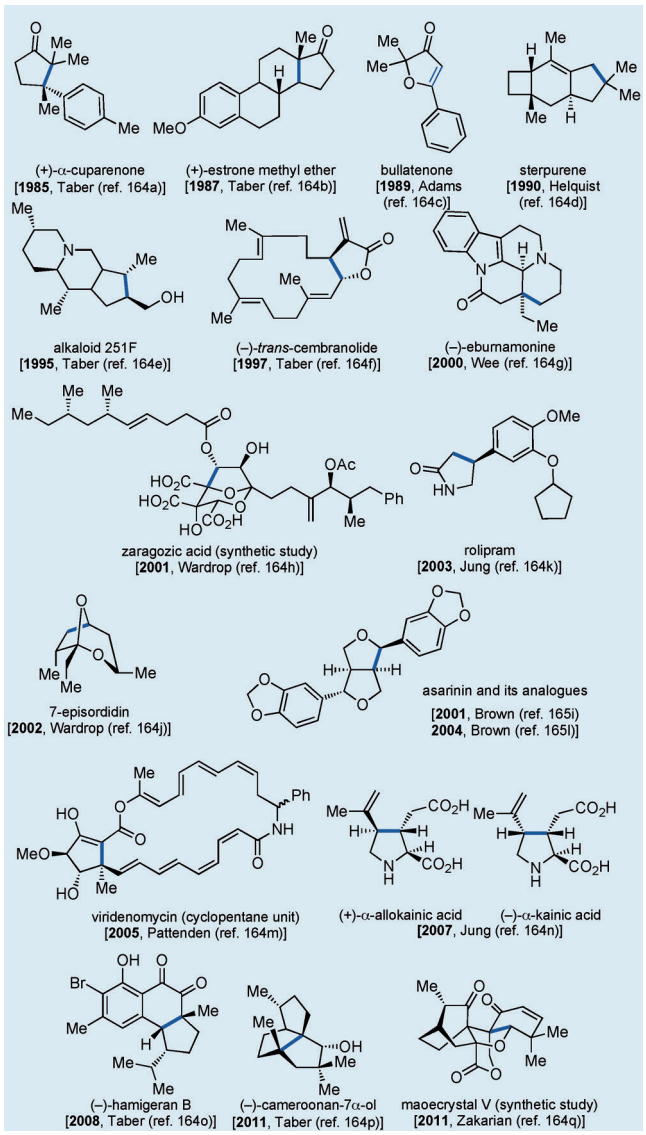
Scheme 65. Synthesis of (−)-tetrodotoxin (**328**).

insertion, which transformed diazoketone **324** into cyclohexanone **325** in the presence of 1.5 mol% [Rh_2-(HNCOCPh$_3$)$_4$].[163] Ketone **325** was then stereoselectively reduced to afford compound **326**. After several steps, it was elaborated into carbamate **327**, and the second key step, a C–H amination from **327**, is described later in Section 4.1.3.

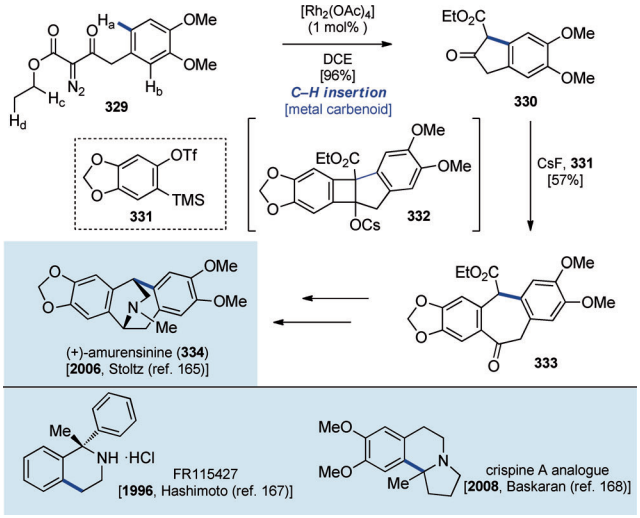
Other targets of total synthesis, formal synthesis, and partial synthesis that have involved C–H insertion are listed in Scheme 66.[164]

The catalytic C–H insertion of metal carbenoids is also applicable to aromatic C–H bonds. In 2006, Stoltz and co-workers demonstrated a selective aromatic C–H insertion reaction in the total synthesis of (+)-amurensinine (**334**; Scheme 67).[165] Four C–H bonds (H_a–H_d)in diazoketoester **329** are capable of insertion; however, treating **329** with a rhodium catalyst provided β-ketoester **330** with complete regioselectivity in 96% yield. The subsequent coupling of β-ketoester **330** and arene **331** in the presence of CsF gave seven-membered ring **333**. The proposed reaction mechanism involves the generation of a benzyne intermediate from **331**,[166] followed by two nucleophilic addition processes (a formal [2+2] reaction) to form **332**, then ring expansion. After installing a nitrogen-containing moiety, the synthesis of (+)-amurensinine (**334**) was completed.

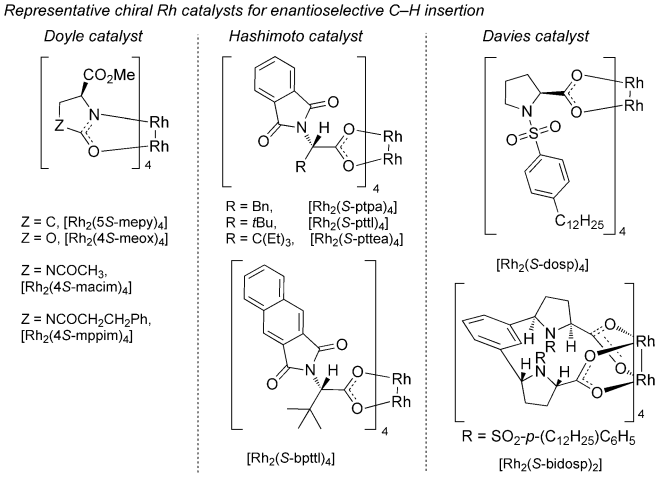
A synthesis of FR115427 was accomplished by Hashimoto and co-workers in 1996[167] by using a similar type of aromatic C–H insertion, and a synthesis of a methyl analogue of crispine A was achieved by the Baskaran research group in 2008.[168]



Scheme 66. Synthesis of natural products by C–H insertion of metal carbenoids.



Scheme 67. Total synthesis of (+)-amurensinine (**334**) by catalytic aromatic C–H insertion. DCE = 1,2-dichloroethane.



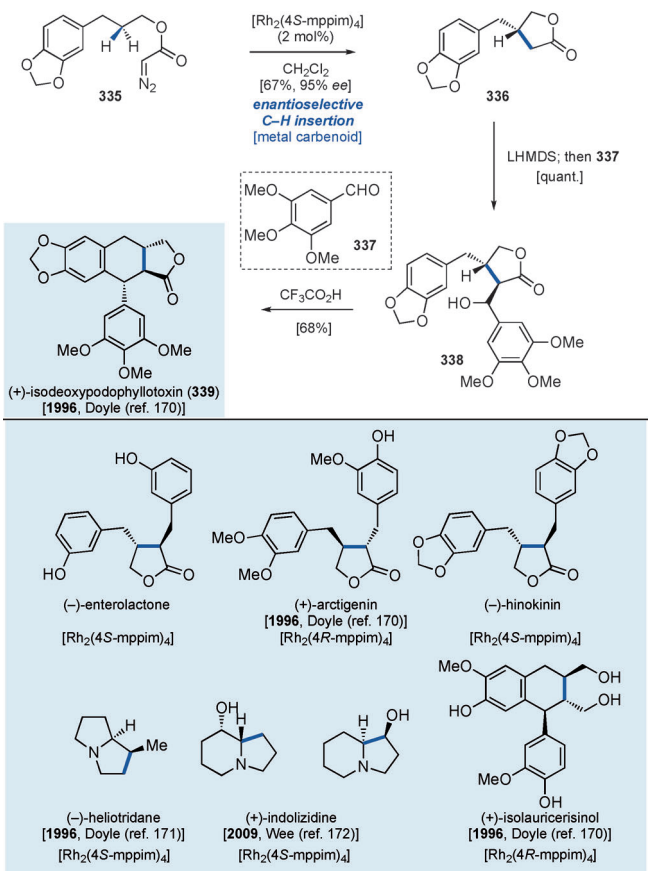
Scheme 68. Chiral rhodium catalysts for enantioselective C–H insertion.

3.4.4. ***Enantioselective C–H Insertion by Rhodium Catalysis***

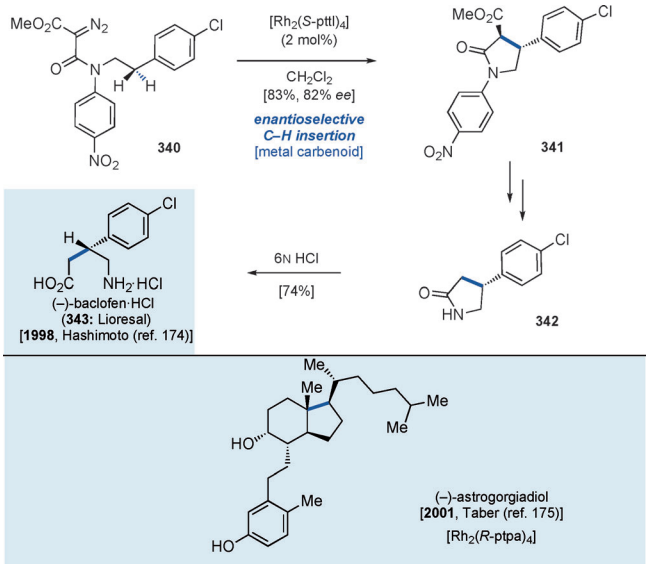
Rhodium-based chiral catalysts for asymmetric C–H insertion have been developed by the research groups of Doyle, Hashimoto, and Davies. Their representative catalysts are shown in Scheme 68. In this section, the synthesis of natural products and pharmaceuticals through enantioselective C–H insertion by rhodium catalysis is described.

In 1991, Doyle et al. developed [Rh_2(5*S*-mepy)$_4$] as a C–H insertion catalyst[169] and modified it to [Rh_2(4*S*-meox)$_4$], [Rh_2(4*S*-macim}$_4$], and [Rh_2(4*S*-mppim)$_4$] in 1996.[170] These catalysts were subsequently applied to the total synthesis of lignan lactones (Scheme 69).[171] The synthesis of isodeoxypodophyllotoxin (**339**) commenced with the reaction of diazoketone **335** with the [Rh_2(4*S*-mppim)$_4$] catalyst to produce lactone **336** with excellent enantioselectivity (95% *ee*) in 67% yield. The aldol reaction of **336** with 3,4,5-trimethoxybenzaldehyde (**337**) in the presence of LHMDS led to **338**, and addition of CF_3CO_2H afforded (+)-isodeoxypodophyllotoxin (**339**) in 36% overall yield from commercial starting materials. Doyle and co-workers synthesized other lignan lactones such as (−)-enterolactone, (+)-arctigenin, (−)-hinokinin, and (+)-isolauricerisinol were synthesized by the using the same procedure,[170] while imidazolidine alkaloids were reported by the research groups of Doyle (1996)[171] and Wee (2009).[172]

In 1994, Anada and Hashimoto developed the [Rh_2(*S*-pttl)$_4$] catalyst[173] for enantioselective C–H insertion. In 1998, they applied this catalyst to the synthesis of (−)-baclofen·HCl (**343**; Lioresal), a typical $GABA_B$ receptor (Scheme 70).[174] Diazo β-ketoester **340** was treated with 2 mol% [Rh_2(*S*-pttl)$_4$] (a modified [Rh_2(*S*-ptpa)$_4$] catalyst) at room temperature to afford C–H insertion product **341** in 83% yield and 82% *ee*. Subsequent decarboxylation of **341**, removal of the N-



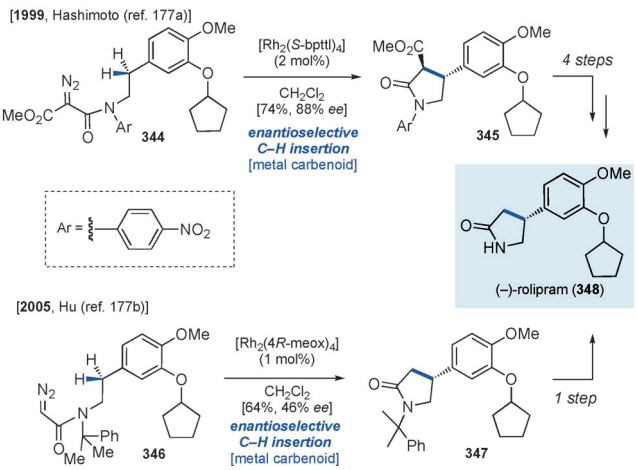
Scheme 69. Doyle's catalyst: Application to the synthesis of the lignan lactones (–)-heliotridane and indolizidine.



Scheme 70. Hashimoto's catalyst: Total synthesis of (–)-baclofen·HCl (**343**) and (–)-astrogorgiadiol.

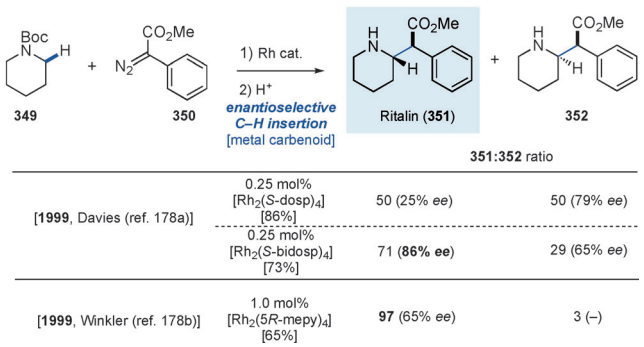
protecting group, and acid hydrolysis of the resulting lactam **342** completed the synthesis of (–)-baclofen·HCl (**343**). Taber and Malcolm also reported the total synthesis of (–)-astrogorgiadiol using $[Rh_2(R\text{-ptpa})_4]$ as catalyst.[175]

In 1999, the Hashimoto research group applied their own catalyst, $[Rh_2(S\text{-bpttl})_4]$,[176] to the enantioselective synthesis of (–)-rolipram (**348**).[177a] Treatment of β-diazoketoester **344** with 2 mol% $[Rh_2(S\text{-bpttl})_4]$ in CH_2Cl_2 at room temperature resulted in the formation of cyclized product **345** in 74% yield and 88% *ee*. After a four-step sequence, the synthesis of (–)-rolipram (**348**) was accomplished in a total of nine steps. In 2005, Hu and co-workers also employed an asymmetric C–H insertion with a rhodium catalyst for the synthesis of **348**.[177b] In general, β-diazoketoesters are less reactive than diazoketones toward rhodium catalysts because of the presence of the extra electron-withdrawing group. Nevertheless, they utilized diazoketone **346** as a C–H insertion substrate to achieve a more-step-economical synthesis, and also used a cumyl (2,2-dimethylbenzyl) unit as the N-protecting group to enhance the reactivity and regioselectivity.[177c] After investigating various catalysts, $[Rh_2(4R\text{-meox})_4]$ (Doyle catalyst)[170] was selected for the key transformation: the desired C–H insertion took place to provide cyclized product **347** in 64% yield and 46% *ee*. Although the enantiomeric excess was lower than that of Hashimoto's synthesis, a single-step transformation of **347** to rolipram (**348**) is notable (Scheme 71).



Scheme 71. Enantioselective syntheses of (–)-rolipram (**348**).

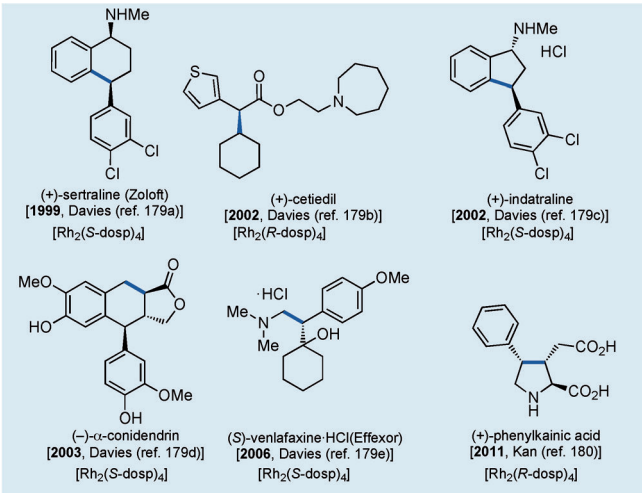
In 1997, the Davies research group reported the first intermolecular enantioselective C–H insertion into cyclohexanes and tetrahydrofurans by using their own $[Rh_2(S\text{-dosp})_4]$ catalyst (Davies catalyst).[105] Shortly thereafter, in 1999, Davies et al. applied it to the synthesis of *threo*-methylphenidate (**351**; Ritalin).[178a] Meanwhile, Winkler and co-workers independently synthesized **351** by using the same coupling partner but with a different rhodium catalyst (Scheme 72).[178b] In both syntheses, Boc-piperidine (**349**) was treated with diazoester **350** in the presence of rhodium catalysts, and removal of the Boc group yielded **351** and its diastereomer. When $[Rh_2(S\text{-dosp})_4]$ was used as the catalyst, the reaction afforded desired product **351** as well as the undesired diastereomer (d.r. = 50:50) with 25% *ee* and 79% *ee*, respectively. After ligand screening, they found that $[Rh_2(S\text{-bidosp})_4]$ was effective, thus giving the desired product



Scheme 72. Enantioselective synthesis of Ritalin (**351**) by intermolecular asymmetric C–H insertion.

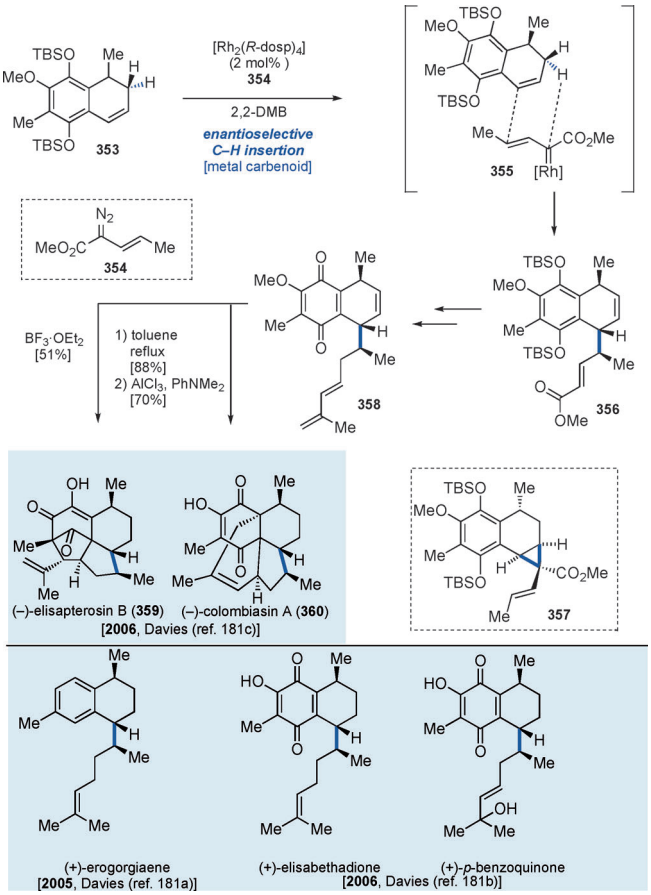
351 as the major diastereomer (d.r. = 71:29) with good enantioselectivity (86% *ee*). In contrast, when the Doyle catalyst [Rh_2(5*R*-mepy)$_4$] was used, the desired product was formed with high diastereoselectivity (d.r. = 97:3) with moderate enantioselectivity (65% *ee*). These pioneering studies in intermolecular enantioselective C–H insertion greatly influenced and motivated the synthetic chemists.

The Davies research group thereafter expanded the utility of their catalyst [Rh_2(*S*-dosp)$_4$], by showcasing it in the synthesis of numerous biologically active compounds (Scheme 73).[179] Very recently, Kan and co-workers also reported the enantioselective synthesis of (+)-phenylkainic acid by using the Davies catalyst (Scheme 73).[180]



Scheme 73. Enantioselective C–H insertion in the synthesis of biologically active compounds.

In 2005 and 2006, Davies et al. successfully synthesized diterpenes (+)-erogorgiaene,[181a] (+)-elisabethadione, (+)-*p*-benzoquinone,[181b] (–)-elisapterosin B (**359**), and (–)-colombiasin A (**360**), by a rhodium-catalyzed enantioselective C–H insertion/Cope rearrangement strategy (Scheme 74). A biomimetic approach from common precursor **358** to both **359** and **360** had already been known at the time.[182] They envisioned that quinone **358** could be formed regio- and stereoselectively with a C–H insertion of a rhodium carbe-

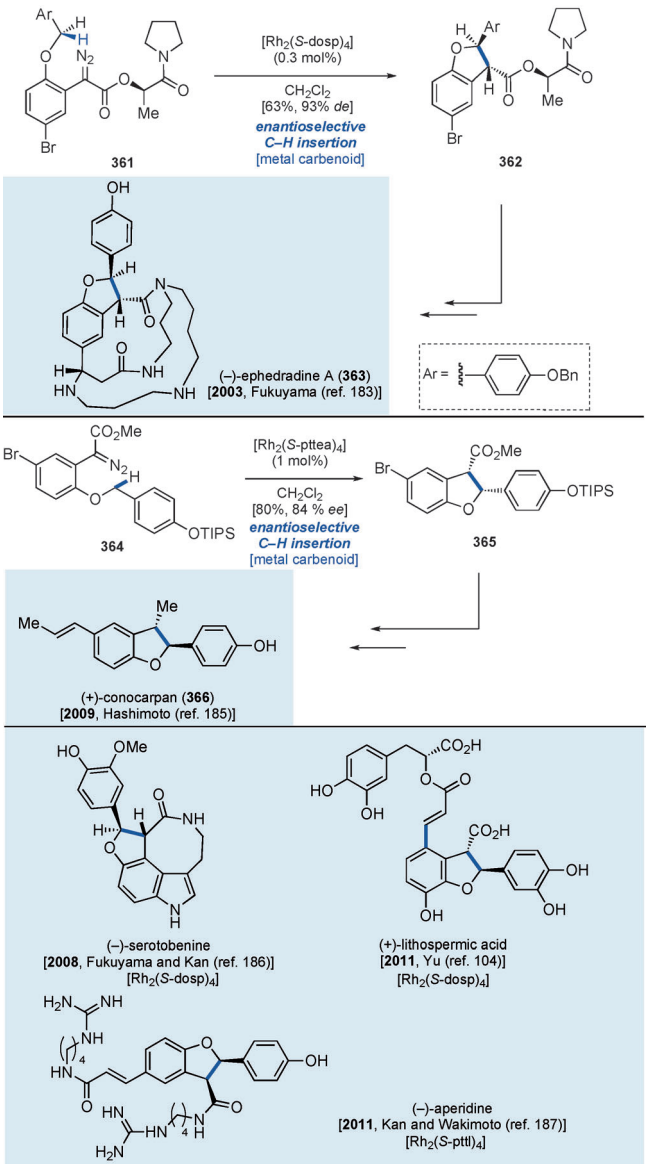


Scheme 74. Enantioselective synthesis of elisapterosin B (**359**) and (–)-colombiasin A (**360**) by C–H insertion/Cope rearrangement.

noid and Cope rearrangement. Indeed, treatment of **353** with the [Rh_2(*R*-dosp)$_4$] catalyst afforded the desired product **356** as well as by-product **357**, which was formed by cyclopropanation of the olefin with the rhodium carbenoid. After conversion of **356** into **358**, the enantioselective total synthesis of (–)-elisapterosin B (**359**) and (–)-colombiasin A (**360**) was achieved.[181c]

The enantioselective C–H insertion using chiral rhodium catalysts has been used not only to generate cyclopentanes, but also to forge dihydrobenzofurans. The examples below describe intramolecular C–H insertions as a strategy to create natural products containing dihydrobenzofuran units (Scheme 75).

In 2003, the Fukuyama research group completed a total synthesis of (–)-ephedradine A (**363**) by utilizing an intramolecular enantioselective C–H insertion as the key step.[183] They first attempted the C–H insertion of diazoester **361**, but the enantiomeric excess of the resulting dihydrobenzofuran **362** was low (32% *ee*).[184] After extensive investigation, a stereoselective C–H insertion was achieved by appending an α-alkoxyamide chiral auxiliary, by which **362** was produced in high diastereoselectivity (93% *de*) using 0.3 mol% of the Davies catalyst. The chiral induction strongly depended on the auxiliary rather than the catalyst. After 13 more steps, they completed the synthesis of (–)-ephedradine A (**363**).



Scheme 75. Intramolecular enantioselective C–H insertion: Syntheses of natural products that contain benzofuran moieties.

In 2009, Hashimoto and co-workers synthesized the dibenzofuran compound (+)-conocarpan (**366**) by using their own catalyst.[185] Treatment of diazoester **364** with 1 mol% $[Rh_2(S\text{-pttea})_4]$ (modified $[Rh_2(S\text{-pttl})_4]$ catalyst) in CH_2Cl_2 at −60 °C afforded dihydrobenzofuran **365** in 80% yield and 84% *ee*. Recently, the synthesis of (−)-serotobenine by Fukuyama, Kan, and co-workers,[186] the synthesis of (+)-lithospermic acid by Wang and Yu (see Scheme 40 in Section 3.2.1),[104] and the synthesis of (−)-aperidine by Kan, Wakimoto, and co-workers[187] have been reported by using chiral rhodium catalysts.

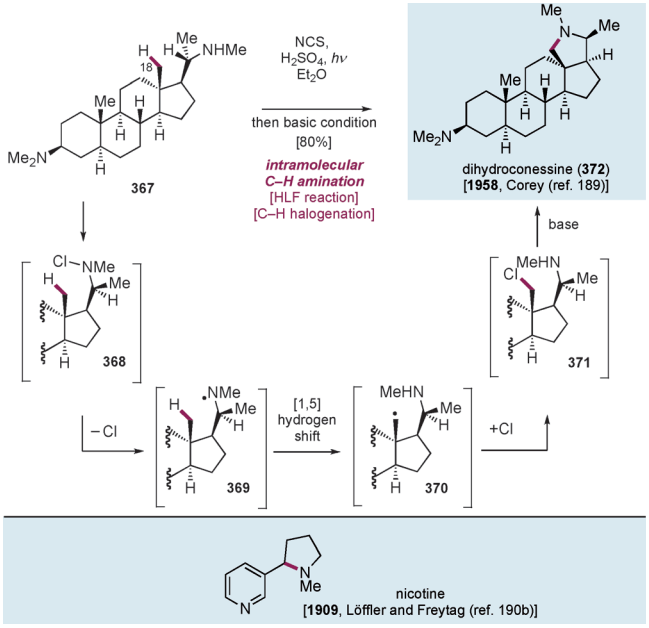
Although this Review focuses on catalysts that were employed in the synthesis of polyfunctionalized biologically active compounds, many other catalysts have been reported, and catalyst development is still ongoing for the insertion of metal carbenoids into C–H bonds and the C–H amination of metal nitrenoids.[188]

4. Carbon–Heteroatom Bond Formation

4.1. Carbon–Heteroatom Bond Formation by "Classical" C–H Functionalization

Recently, various types of nitrogen-, oxygen-, and halogen-containing natural products and pharmaceuticals have been synthesized by using amination, oxidation, and halogenation of C–H bonds. It should be noted, however, that pioneering discoveries showcasing methods for C–H functionalization in the synthesis of complex natural products were first reported more than 50 years ago.

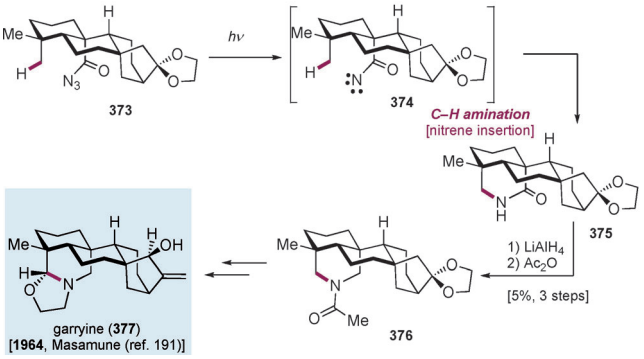
In 1958, Corey and Hertler reported the synthesis of dihydroconessine (**377**), by making use of intramolecular C–H halogenation (Scheme 76).[189] The C–H halogenation



Scheme 76. Formal C–H amination sequence: Synthesis of dihydroconessine (**372**) by the Hofmann–Löffler–Freytag (HLF) reaction (Corey and co-workers). NCS = N-chlorosuccinimide.

method (which is actually a net C–H amination method) in question is called the Hofmann–Löffler–Freytag reaction (HLF reaction). The original reaction was developed by Hofmann in 1879,[190a] and was expanded in terms of substrate scope by Löffler and Freytag in 1909;[190b] Löffler and Freytag and Kober also achieved the synthesis of nicotine by using this method.[190c] In the synthesis by Corey and Hertler, treatment of steroid derivative **367** with *N*-chlorosuccinimide (NCS) and H_2SO_4 resulted in the formation of *N*-chloro intermediate **368**, which then underwent a net chlorine atom transfer under irradiation of light to afford C18-chlorinated compound **371**. Concomitant cyclization of the amine onto the alkyl chloride upon basic work-up formed dihydroconessine (**372**; see related examples in Section 4.4).

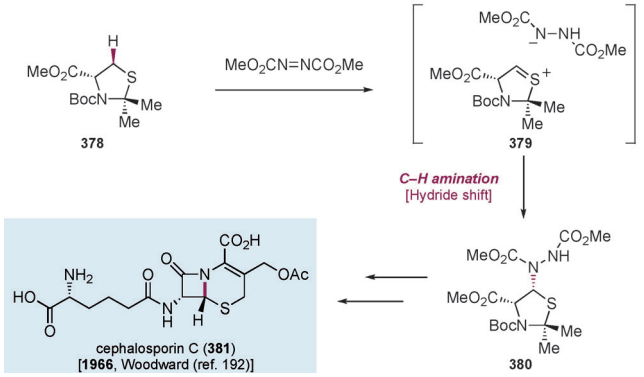
In 1964, Masamune demonstrated the total synthesis of garryine (**377**) by nitrene insertion (Scheme 77).[191] Acyl



Scheme 77. Total synthesis of garryine (**377**) by Masamune and co-workers.

nitrene **374**, which was prepared from unstable acyl azide **373** by irradiation with light, underwent direct amination into the C(methyl)–H bond to afford lactam **375**. Treatment of **375** with $LiAlH_4$, followed by acetylation of the resulting amine, provided piperidine **376** in 5% yield over 3 steps. After a few more steps, the synthesis of garryine (**377**) was accomplished. Although the direct amination step suffers from a poor yield, it is still a spectacular result from the early days of C–H amination (see further examples in Section 4.2).

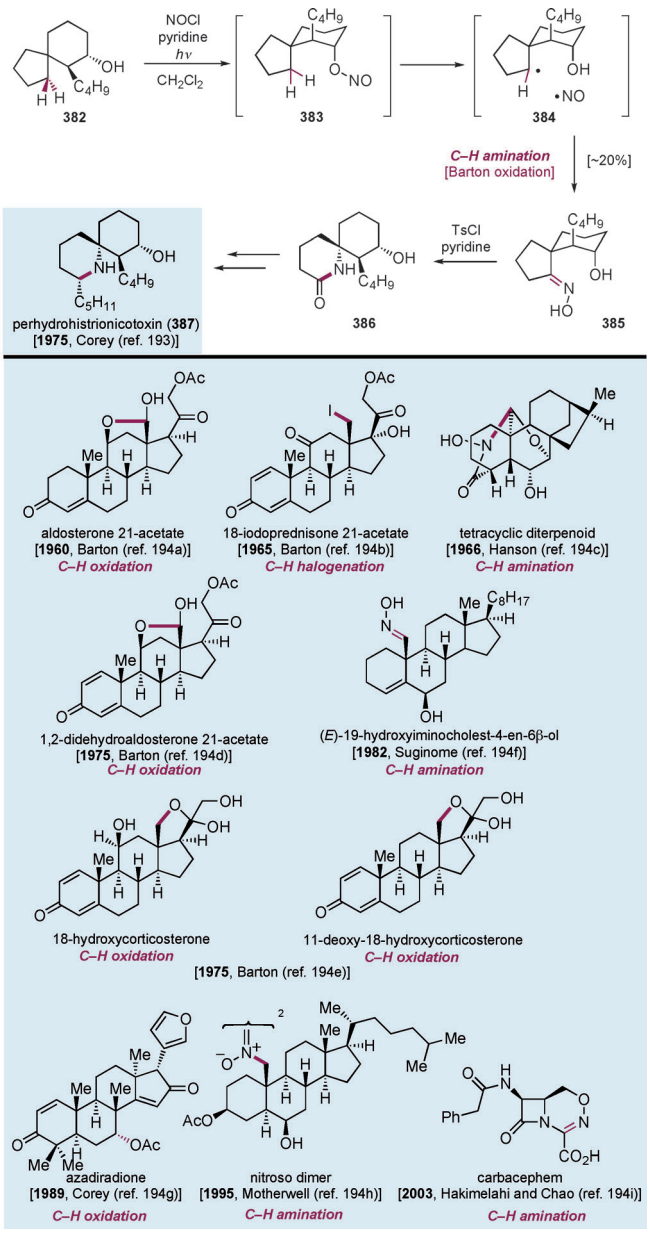
In 1966, Woodward and co-workers reported the total synthesis of cephalosporin C (**381**) through a classic C–H amination step (Scheme 78).[192] In their synthetic strategy, it was necessary to oxidize the C(methylene)–H bond adjacent



Scheme 78. Synthesis of cephalosporin C (**381**) through a classic C–H amination reaction.

to the sulfur atom of cysteine derivative **378**. To this end, they simply heated **378** in the presence of dimethyl azodicarboxylate (DMAD) to deliver product **380** with complete chemo- and stereoselectivity. This unusual amination reaction likely proceeded by the following mechanism: hydride shift from **378** to DMAD to give a nitrogen anion followed by nucleophilic attack of the nitrogen anion onto the resulting sulfonium cation **379**. Although the formation of this C–N bond is substrate-specific, it represents a landmark example in the synthesis of complex natural products by C–H amination.

In 1975, Corey et al. completed the total synthesis of perhydrohistrionicotoxin (**387**) by utilizing the Barton oxidation (i.e., the photomediated direct oxime formation of an $C(sp^3)$–H bond) as shown in Scheme 79.[193] Oxime **385** was prepared from alcohol **382** by treatment with nitrosyl chloride



Scheme 79. "Formal" C–H amination (C–H oxidation) sequence: Total synthesis of perhydrohistrionicotoxin (**387**) by Corey and co-workers, and related C–H functionalization of steroids.[194]

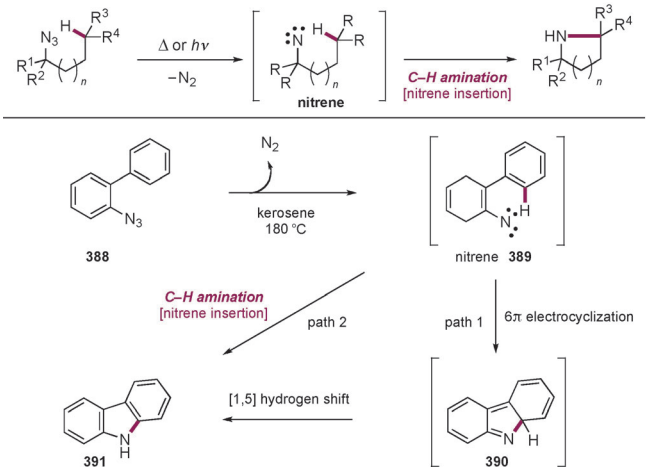
and pyridine under irradiation by light. Mechanistically, **382** might be converted into nitrite **383**, which can subsequently generate radical intermediate **384** through the cleavage of an O–N bond, followed by site-selective 1,5-hydrogen abstraction from an $C(sp^3)$–H bond; intermediate **384** can then couple with the nitroxyl radical and isomerized to give oxime **385**. The Beckmann rearrangement of **385** formed lactam **386**, which was then functionalized further to give perhydrohistrionicotoxin (**387**). This reaction sequence is both a C–H

amination method and a formal insertion of a nitrogen atom into a C–C bond.

Although the four examples above, which involve the formation of carbon–heteroatom bonds by "classic" C–H functionalization methods, have long been recognized, most chemists did not consider them to be useful for the construction of complex molecules. These reactions had been regarded as being "unusual" and that they could only be applied to specific substrates. However, in recent years, they have been revisited and improved in the context of both method development and natural product synthesis.

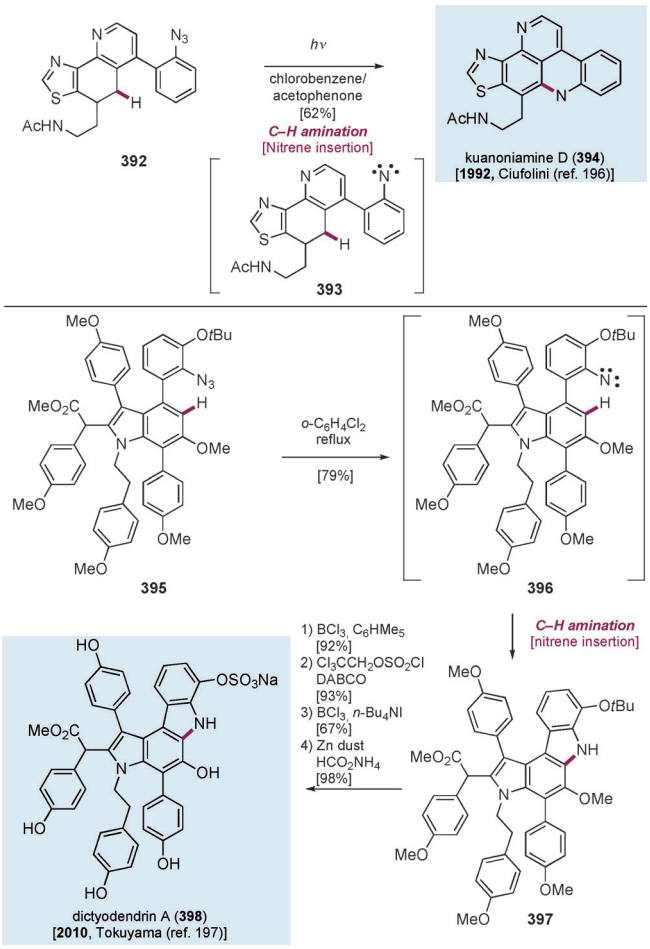
4.2. C–H Insertion of Nitrenes (C–H Amination)

The C–H insertion of nitrenes has received much attention because nitrenes are highly reactive and can be readily prepared from azides by irradiation with light or heating. In 1951, Smith and Brown synthesized carbazole (**391**) from 2-azidobiphenyl (**388**) by utilizing a nitrene insertion reaction (Scheme 80).[195] Azide **388** expelled nitrogen gas when heated at 180 °C in kerosene to give nitrene intermediate **389**. One mechanistic pathway to **391** involves a 6π electrocyclization to form **390**, followed by a 1,5-hydrogen shift; the second mechanistic scenario is a C–H insertion of nitrene **389** (C–H amination) to directly afford **391**. Regardless of the reaction mechanism, numerous complex molecules have been synthesized by using this type of reaction. In this section, three representative syntheses of biologically active molecules involving nitrenes are highlighted.



Scheme 80. C–H insertion of nitrene intermediate (C–H amination).

In 1991, Bishop and Ciufolini reported the synthesis of kuanoniamine D (**394**) by utilizing a nitrene insertion reaction (Scheme 81).[196] Azide **392** released nitrogen gas under irradiation with light to produce nitrene **393**, and the subsequent C–H amination step proceeded not on the pyridine but on the cyclohexane to deliver **394** in 62% yield. In 2010, Tokuyama and co-workers reported the concise synthesis of dictyodendrin A (**398**), which is known to possess



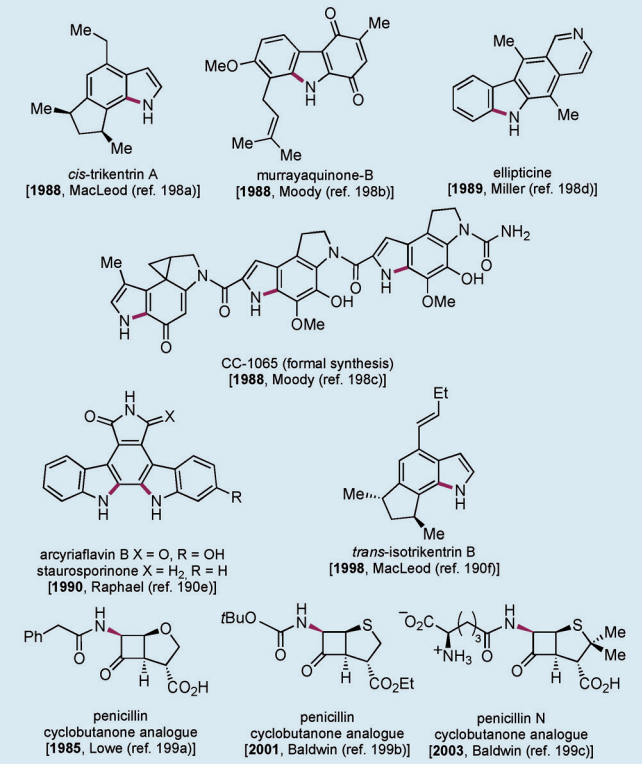
Scheme 81. Syntheses of kuanoniamine D (**394**) and dictyodendrin A (**398**) through nitrene insertion.

inhibitory activity against telomerase, by using nitrene insertion as the key step.[197] Azide **395** was heated in dichlorobenzene at reflux to thermally generate the corresponding nitrene **396**, which then inserted into the C–H bond of the benzene ring to afford **397** in 79% yield. After selective deprotection of a *tert*-butyl group and conversion of the resulting phenol into a trichloroethyl sulfate, all the methyl groups and the trichloroethyl group were removed to give **398**.

The nitrene insertion reaction has been utilized in total or formal syntheses of natural products such as *cis*-trikentrin A, murrayaquinone-B, CC-1065, ellipticine (**61**), arcyriaflavin B (**36**), staurosporinone and *trans*-isotrikentrin B (Scheme 82).[198] Although it does not constitute a total synthesis, the nitrene insertion reaction was also used for the synthesis of penicillin analogues (Scheme 82).[199]

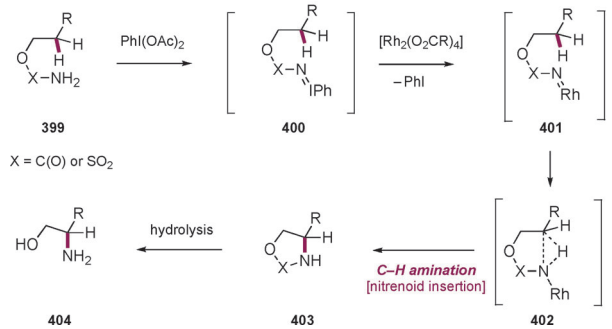
4.3. C–H Insertion of Metal Nitrenoids (C–H Amination)

The pioneering work of Breslow in 1983 showed that a rhodium(II) complex can be used for the intramolecular C–H amination of 2,5-diisopropylbenzenesulfonamide into its C(sp^3)–H bond in the presence of stoichiometric amount of



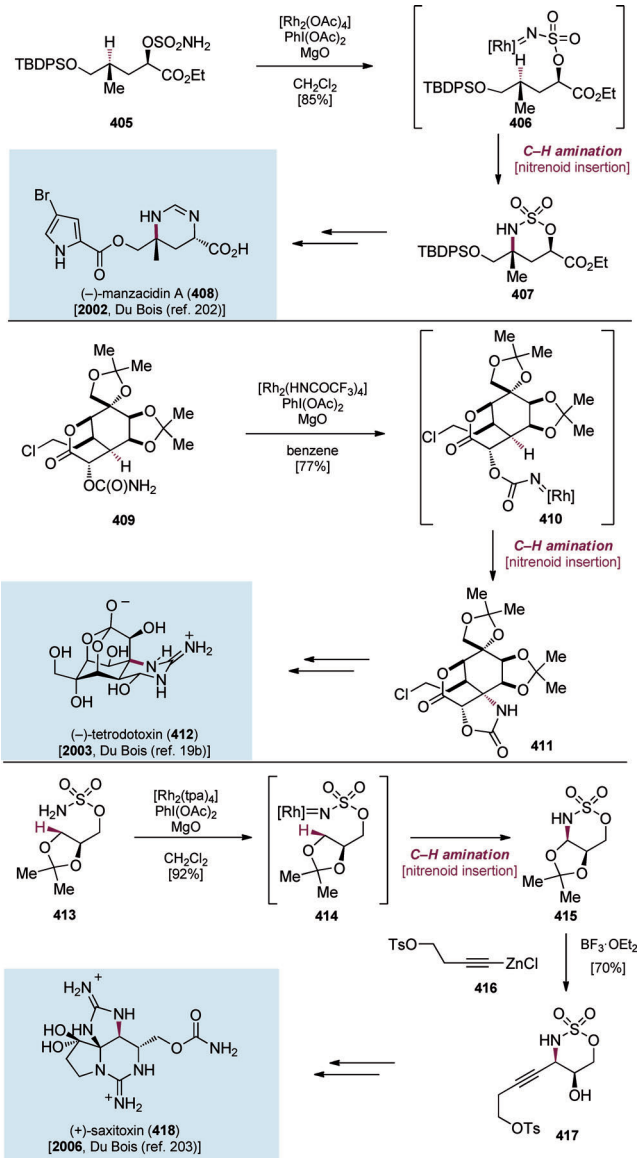
Scheme 82. The nitrene insertion reaction, featured in complex molecule synthesis.

iodobenzene diacetate ($PhI(OAc)_2$).[200] About two decades later, in 2001, Du Bois and co-workers extensively studied this reaction and discovered that carbamates (or sulfamate esters) react with $PhI(OAc)_2$ in the presence of a Rh^{II} catalyst to afford oxazolidinones (or oxathiazinanes) in high yield. A plausible mechanism of this reaction is shown in Scheme 83.[201a,b] Iminoiodinane **400** can be produced from **399** and $PhI(OAc)_2$, and then treated with a Rh^{II} complex to generate Rh nitrenoid **401**; this can be followed by $C(sp^3)$–H insertion to deliver **403**. Oxazolidinones (X = C=O) and oxathiazinanes ($X = SO_2$) can be used to make 1,3-difunctionalized amines **404** after hydrolysis. This reaction can even proceed at room temperature, and, additionally, it is possible to conduct enantioselective versions of this reaction by using chiral ligands.[200c]



Scheme 83. C–H amination with metal nitrenoids by Du Bois and coworkers.

With such advantages for synthetic utility, many total syntheses of complex natural products have been reported, including the three representative syntheses by the Du Bois research group previously introduced in this section (Scheme 84).



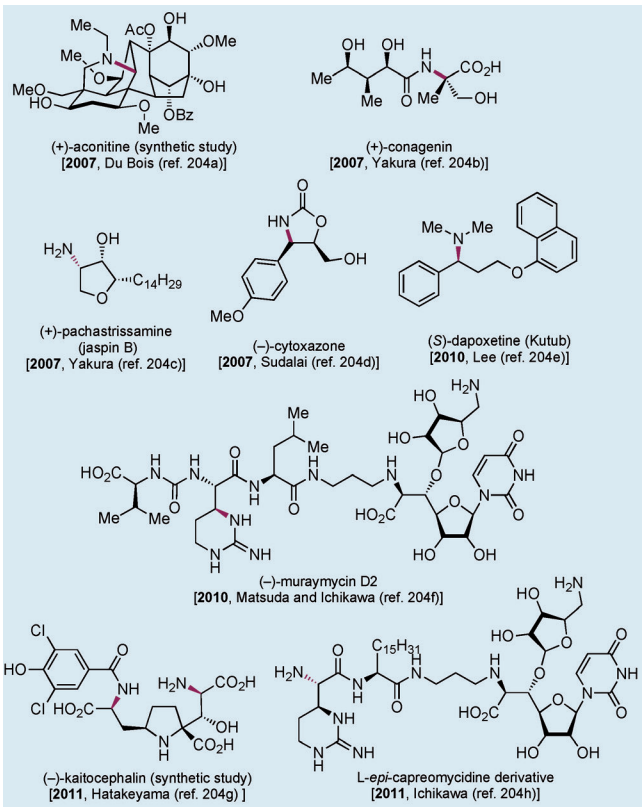
Scheme 84. Total syntheses of (–)-manzacidin A (**408**), (–)-tetrodotoxin (**412**), and (+)-saxitoxin (**418**). TBDPS = *tert*-butyldiphenylsilyl.

In 2002, Du Bois and co-workers demonstrated the total synthesis of (–)-manzacidin A (**408**), a bromopyrrole alkaloid, by first applying their own C–H amination method.[202] Sulfamate **405**, which was prepared from ethyl glyoxylate, was treated with $[Rh_2(OAc)_4]$, $PhI(OAc)_2$, and magnesium oxide as base to form rhodium nitrenoid **406**. Stereospecific insertion of the nitrenoid into the methine C–H bond afforded oxathiazinane **407** in 85% yield. Six more steps led to the total synthesis of (–)-manzacidin A (**408**) in an overall

yield of 28% from commercial starting materials. They also synthesized (+)-manzacidin C, which differs from **408** in its C2 stereocenter (i.e., it is a diastereomer of **408**).

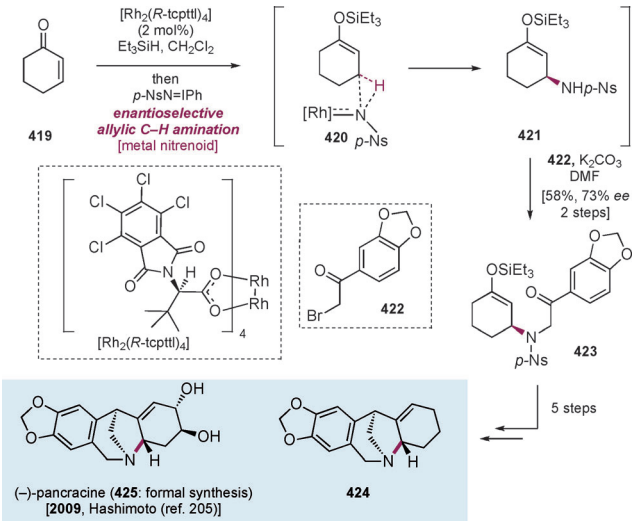
In the following year, the same research group successfully synthesized (−)-tetrodotoxin (**412**) through two types of C–H bond functionalizations (C–H insertion reactions of a metal carbenoid and a metal nitrenoid).[19b] Even when using a highly functionalized cyclohexane derivative such as **409** (which was constructed using carbene insertion; see Section 3.4.3), intramolecular C–H amination between the carbamate and a tertiary C(sp^3)–H bond on the cyclohexane ring proceeded smoothly via Rh nitrenoid **410** to deliver carbamate **411**. The total synthesis of (−)-tetrodotoxin (**412**) was accomplished after a few more steps from **411**. Such a late-stage C–H functionalization (particularly involving highly reactive heteroatom groups such as amines) in complex natural product synthesis is an impressive application of this method. In 2006, Fleming and Du Bois also achieved the total synthesis of (+)-saxitoxin (**418**) by utilizing their established C–H amination reaction (**413**→**415**), followed by diastereoselective alkenylation with zinc acetylide **416**.[203]

The C–H amination developed by Du Bois and co-workers has also been applied to synthetic studies of (−)-aconitine, (−)-kaitocephalin, and to the syntheses of (+)-conagenin, (+)-pachastrissamine, (−)-cytoxazone, (*S*)-dapoxetine, (−)-muraymycin D2, and L-*epi*-capreomycidine derivatives. This C–H amination reaction has wide substrate scope and functional-group tolerance, and has been demonstrated to be reliable as a key step in complex natural product synthesis (Scheme 85).[204]



Scheme 85. Rhodium-catalyzed nitrene insertion in natural product synthesis.

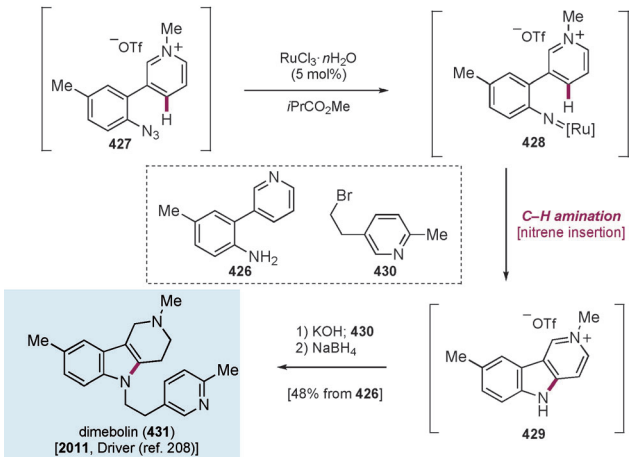
In 2009, Hashimoto and co-workers developed an enantioselective allylic C–H amination involving a chiral rhodium nitrenoid and utilized it in a formal synthesis of (−)-pancracine (**425**; Scheme 86).[205] They had already disclosed the modification of their original catalyst [Rh_2(*S*-pttl)$_4$] (see Section 3.4.4) to [Rh_2(*S*-tcpttl)$_4$], which involved a switch of four hydrogen atoms with four chlorine atoms on the phthalimido unit.[206] Treatment of cyclohexenone **419** with Et_3SiH in the presence of 2 mol% [Rh_2(*R*-tcpttl)$_4$], followed by addition of [(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN=IPh), provided amine **421** through rhodium nitrenoid intermediate **420**. N-Alkylation of amine **421** with bromoketone **422** provided **423** over two steps in 58% yield and 73% *ee*. After five more steps, **423** was transformed into compound **424**, which matched the intermediate described by Overman and Shim[207] in the total synthesis of (−)-(**425**), thereby constituting a formal synthesis of (−)-**425**.



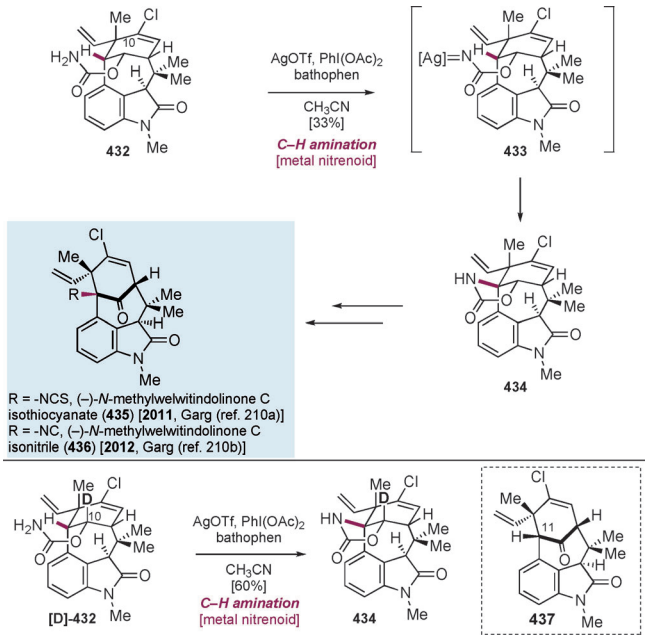
Scheme 86. Intermolecular enantioselective nitrene insertion: Formal synthesis of (−)-pancracine (**425**).

In 2011, Driver and co-workers synthesized dimebolin (**431**) by utilizing their own ruthenium-catalyzed nitrenoid insertion reaction (Scheme 87).[208] Azide **427** was readily prepared from **426** by a two-step sequence consisting of treatment with sodium nitrite and sodium azide followed by alkylation of pyridine. Addition of a catalytic amount of ruthenium trichloride hydrate to **427** most likely formed ruthenium nitrenoid **428**,[209] which then underwent regioselective C–H amination at the C4-position of the pyridinium ion to give γ-carbolinium **429** in 91% yield. Deprotonation of the N–H bond of **429**, followed by alkylation with **430**, appended the requisite pyridine side chain. Finally, treatment of the resulting compound with sodium borohydride completed the synthesis of target **431** in 48% yield from **426**.

In 2011, Garg and co-workers reported the total synthesis of (−)-*N*-methylwelwitindolinone C isothiocyanate (**435**), as well as its isonitrile (**436**) and analogues, by using a late-stage C–H amination (Scheme 88).[210a] Although indole-containing carbamate **432** had been treated with various rhodium complexes to achieve nitrene insertion at the C11-position,



Scheme 87. Ruthenium-catalyzed nitrene insertion: Synthesis of dimebolin (**431**). Tf = trifluoromethanesulfonyl.

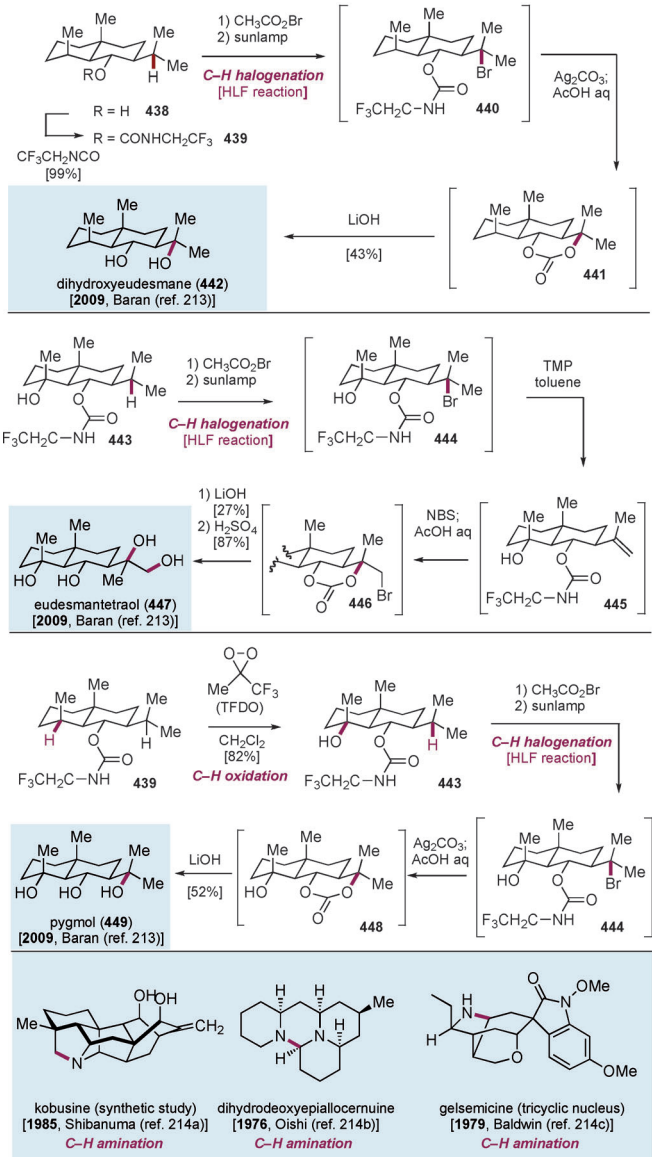


Scheme 88. Total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**435**) and (–)-*N*-methylwelwitindolinone C isonitrile (**436**).

the resulting product was ketone **437** rather than the desired product **434**. It was noted that by-product **437** presumably forms by a pathway involving initial insertion into the C10–H bond. After further investigation, they found that silver catalysis[211] was effective. Thus, the treatment of carbamate **432** with AgOTf, $PhI(OAc)_2$, and bathophenanthroline (bathophene) furnished amination product **434** in 33% yield via a silver nitrenoid intermediate **433**. After a three-step sequence, the total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate (**435**) was achieved. In 2012, this research group modified several steps in the synthesis of (–)-**435** and also accomplished the total synthesis of (–)-*N*-methylwelwitindolinone C isonitrile (**436**).[210b] One of the modifications involved the C–H amination step, where they envisioned that the use of C10-deuterated carbamate [D]-**432** would prevent the direct amination of the C10–H bond by a deuterium kinetic isotope effect. Indeed, when [D]-**432** was used, the C–H amination successfully provided the desired product **434** in up to 60% yield.

4.4. HLF- and Suárez-Type C–H Oxidation

In 2008, Baran and co-workers expanded the utility of HLF chemistry to synthesis by developing a 1,3-diol synthesis method (a net C–H oxidation),[212] and subsequently reported the total synthesis of eudesmane terpenes by site-selective C–H oxidations (Scheme 89).[213] They proposed a "two-phase" approach to the synthesis of terpenes, inspired by terpene biosynthesis, which proceeds in two separate phases: a "cyclase phase" and an "oxidase phase". Their synthesis began by building the carbon framework of a specific terpene

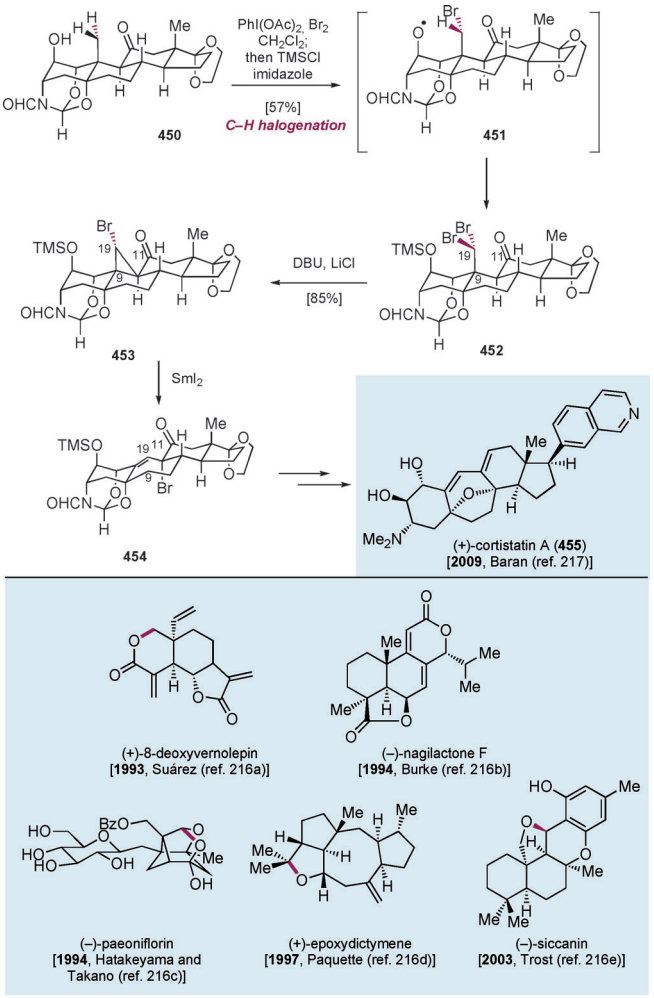


Scheme 89. HLF-type C–H hydroxylation: Application to the synthesis of natural products.[214] TMP = 2,2,6,6-tetramethylpiperidine.

family (cyclase phase), and then functionalizing the framework by consecutive C–H oxidations to access more highly oxidized members of the family (oxidase phase). For example, in the synthesis of dihydroxyeudesmane (**442**), readily synthesized dihydrojunenol (**438**) was transformed to carbamate **439**, which was subjected to N-bromination and photoirradiation to give intermediate **440** through an HLF reaction (C–H halogenation). Bromide **440** was then treated with Ag_2CO_3 to induce cyclization to form carbonate **441**. After hydrolysis of **441**, dihydroxyeudesmane (**442**) was obtained, and a net C–H hydroxylation was achieved. By using this "oxidase-phase" approach, the synthesis of four terpenes that differ in oxidation states was completed, including eudesmantetraol (**447**) and pygmol (**449**; Scheme 89).

In 1985, Suárez and co-workers modified the HLF reaction to enable the use of more neutral conditions by using $PhI(OAc)_2$ in the presence of iodine under the irradiation of a tungsten lamp.[215] This modification of the HLF reaction (also called the Suárez reaction) demonstrated its utility in a number of steroid syntheses. The Suárez reaction can also be used to generate alkoxyl radicals from alcohols, and this reaction extension has been applied numerous times in natural product synthesis (Scheme 90).[216]

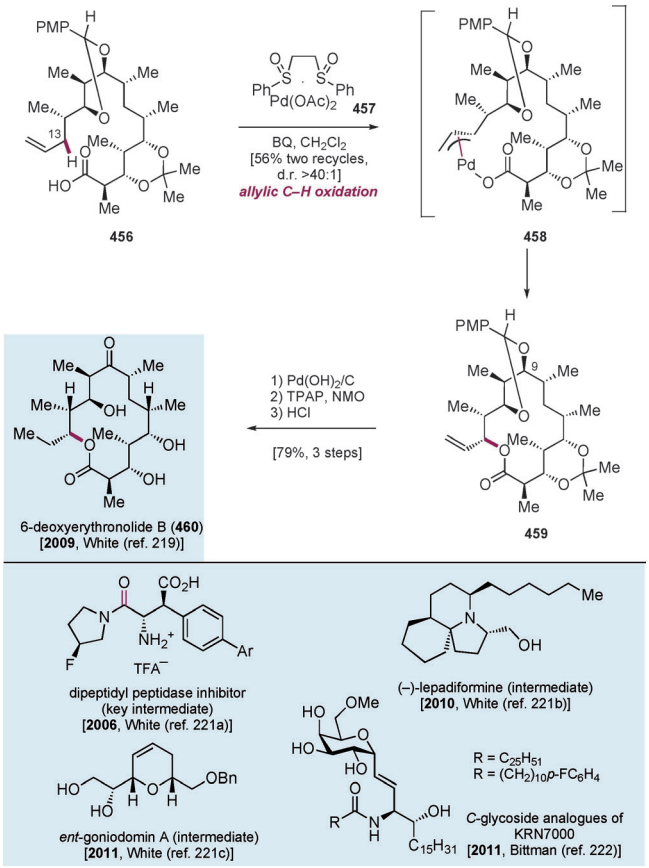
In 2008, the Baran research group demonstrated the utility of the Suárez reaction in the total synthesis of (+)-cortistatin A (**455**), which is a potent angiogenesis inhibitor.[217] To date, a number of chemists have synthesized this compound,[218] because of its intriguing structure and interesting biological activity. Baran and co-workers envisioned that the seven-membered ring of **455** could be constructed by a ring expansion of a six-membered ring found in an inexpensive steroid, followed by functional group manipulations. Alcohol **450**, which was prepared from commercially available prednisone in seven steps, was treated with $PhI(OAc)_2$, Br_2, TMSCl, and imidazole under photoirradiation to give dibromide **452** in 57% yield through double C–H bromination (Suárez reaction). Treatment of **452** with DBU and LiCl afforded cyclopropane **453**, and subsequent ring-opening isomerization of **453** to cycloheptyl α-bromoketone **454** was achieved using SmI_2. After several steps from **454**, the semisynthesis of cortistatin A (**455**) was completed.



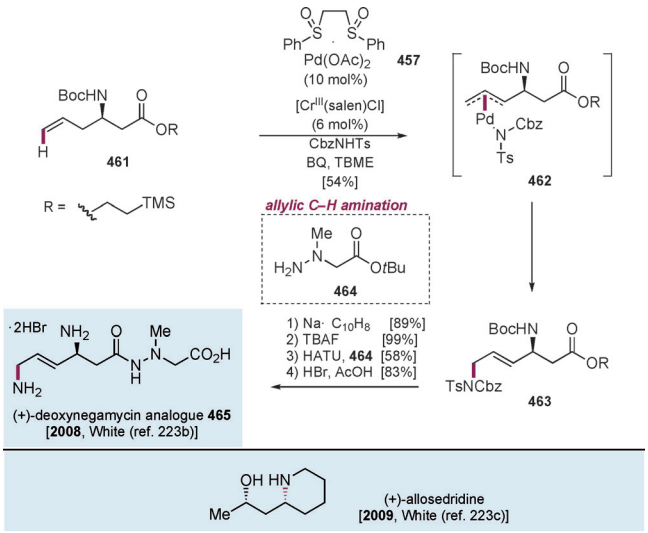
Scheme 90. The Suárez reaction in natural product synthesis.

4.5. Metal-Catalyzed Allylic C–H Amination and C–H Oxidation

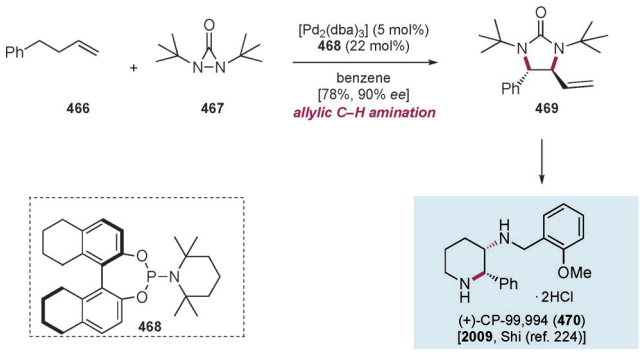
In 2009, Stang and White demonstrated the utility of their own allylic C–H oxidation method in the synthesis of 6-deoxyerythronolide B (**460**; Scheme 91).[219] Such polyketide macrolide antibiotics have garnered attention from the synthetic community because they contain a large number of stereocenters and a macrocycle, both of which have been important targets of method development. Numerous total syntheses of these types of macrolides have been reported;[220] however, existing strategies mostly relied on the synthesis of ω-hydroxy acids, which were macrocyclized at a late stage. Instead, Stang and White disconnected macrolide **460** to an alkenoic acid, which would necessitate a late-stage intramolecular C–H oxidation. Firstly, the C–H oxidation precursor **456** was prepared by well-known methods for polyketide synthesis (such as the Evans aldol reaction and diastereoselective reduction of ketone groups) in 18 steps. Then, an intramolecular C–H oxidation/macrocyclization of this linear precursor was achieved using their robust palladium catalyst **457**. In the presence of **457** and benzoquinone as an oxidant, 14-membered macrolide **459** was formed via π-allylpalladium carboxylate **458** in 56% yield with nearly complete chemo-, regio-, and stereoselectivity after two recycled reactions. Hydrogenation of the terminal alkene and removal of the *p*-methoxyphenylmethyl (PMP) acetal group with $Pd(OH)_2/C$, followed by selective oxidation of the C9 alcohol and acetonide removal, completed the synthesis of (−)-6-deoxyerythronolide B (**460**) in 22 steps and 7.8% yield overall. This synthesis provided a novel approach for macrolide formation, as well as a late-stage C–H functionalization in a complex setting. White and co-workers also reported the synthesis of a key intermediate of a dipeptidyl peptidase inhibitor, the formal synthesis of lepadiformine and *ent*-goniodomin A by using the allylic C–H oxidation strategy.[221] In 2011, Liu and Bittman also reported the synthesis of KRN7000 C-glycoside analogues by using allylic C–H oxidation.[222]



Scheme 91. Application of allylic C–H oxidation to the total synthesis of natural products. PMP = *p*-methoxyphenyl, BQ = benzoquinone, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide.



Scheme 92. Allylic C–H amination: Application to the synthesis of the (+)-deoxynegamycin analogue (**465**) and (+)-allosedridine. TBME = methyl *tert*-butyl ether, HATU = *O*-(7-azabenzotriazol-1-yl)-tetramethyluronium hexafluorophosphate.



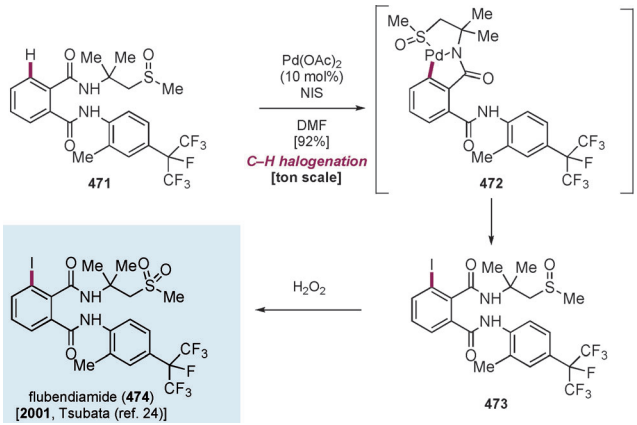
Scheme 93. Enantioselective allylic C–H amination: Synthesis of (+)-CP-99,994 (**470**) by Shi and co-workers. dba = dibenzylideneacetone.

The allylic C–H oxidation system presented above is also useful for C–H amination. In 2008, White and co-workers developed a catalytic intermolecular linear allylic C–H amination[223a] and applied it to the synthesis of (+)-deoxynegamycin analogue (**465**; Scheme 92). Treatment of ester **461** with *N*-(benzyloxycarbonyl)-*p*-toluenesulfonamide (CbzNHTs) in the presence of 10 mol% bissulfoxide/Pd(OAc)$_2$, 6 mol% of the [Cr^{III}(salen)Cl] complex and 2.0 equiv benzoquinone in *tert*-butyl methyl ether (TBME) gave amine **463** in 54% yield. Removal of the tosyl and trimethylsilylethyl groups, followed by condensation with **464** and treatment with acid, completed the synthesis of (+)-deoxynegamycin analogue **465**.[223b]

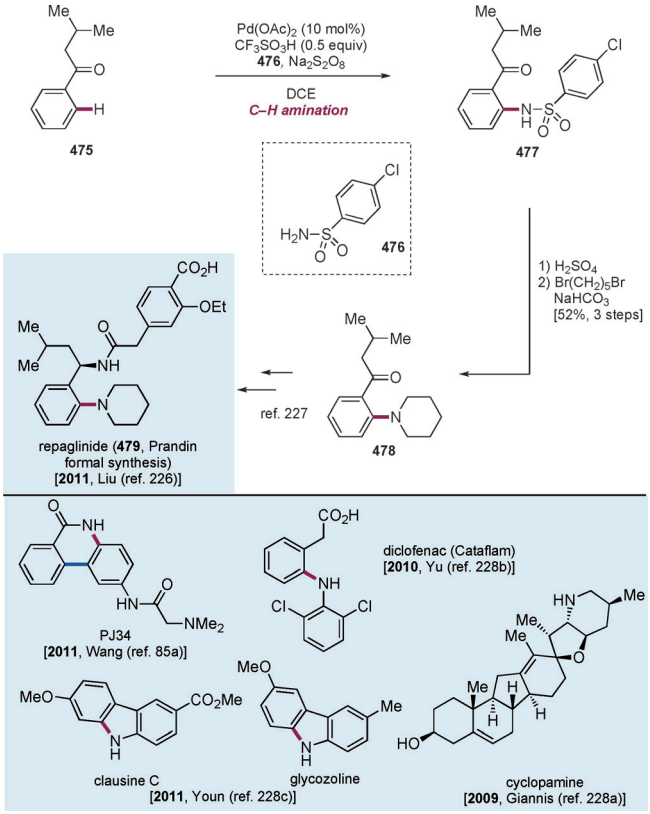
In 2009, Shi and co-workers reported an enantioselective synthesis of (+)-CP-99,994 (**470**) by allylic C–H amination (C–H diamination).[224] They found that terminal alkenes can be aminated at both the allylic *and* homoallylic carbon atoms to form vicinal diamine **469** (Scheme 93).[225] Additionally, in the presence of chiral phosphoramidite **468**, the C–H amination product **469** was produced with high enantioselectivity. This urea derivative was then further functionalized to furnish (+)-CP-99,994 (**470**) in 13 steps and in 20% overall yield.

4.6. Metal-Catalyzed C–H Halogenation and C–H Amination

In 2001, Tsubata and co-workers at Nihon Nohyaku synthesized flubendiamide (**474**), a novel benzenedicarbamide insecticide, by utilizing an aromatic C–H iodination as the key step (Scheme 94).[24] The original route to **474** suffered from difficulties in scale-up because of its lengthy and hazardous steps (involving a Sandmeyer reaction to introduce iodine onto the aromatic system), but was overcome by late-stage C–H iodination. Treatment of phthalamide **471** with *N*-iodosuccinimide in the presence of catalytic Pd(OAc)$_2$ in DMF successfully afforded the desired product **473** in moderate yield. The obtained regioselectivity can be explained by assuming that the chelation of sulfoxide and amide moieties to palladium forces the C–H palladation to occur at the desired position. The sulfoxide in **473** was then converted into the corresponding sulfone by the action of



Scheme 94. Industrial synthesis of flubendiamide (**474**) through palladium-catalyzed C–H halogenation.



Scheme 95. Palladium-catalyzed intramolecular C–H amination: Application to the synthesis of biologically active compounds.

hydrogen peroxide to complete the short, concise synthesis of flubendiamide (**474**). The synthetic route of **474** was later industrialized and the insecticide came on the market in 2007. In 2010, it was produced on the hundred-ton scale, and was ranked within the top 10 insecticides in terms of worldwide sales. Although this compound is not a pharmaceutical, it is included in this Review as a landmark achievement in the field of C–H functionalization.

In 2011, Liu and co-workers reported a palladium-catalyzed *ortho*-C–H amination (amidation) procedure for aromatic ketones, and applied it to the synthesis of repaglinide (**479**; Prandin; Scheme 95), the drug used for type II diabetes.[226] Ketone **475** was coupled with sulfonamide **476** in the presence of a $Pd(OAc)_2$ catalyst, trifluoromethanesulfonic acid, and $Na_2S_2O_8$ to furnish *ortho*-amidation product **477**. Removal of the 4-chlorobenzenesulfonamide group, followed by alkylation with 1,5-dibromopentane, afforded amine **478** in 52% yield over 3 steps. The synthesis of repaglinide (**479**) was completed following a previously reported route.[227]

Other research groups also applied similar palladium-catalyzed intermolecular aminations to the synthesis of PJ34 (see Sections 3 and 3.1.4, Scheme 28),[85a] carbazole alkaloids clausine C and glycozoline, diclofenac, and cyclopamine.[228]

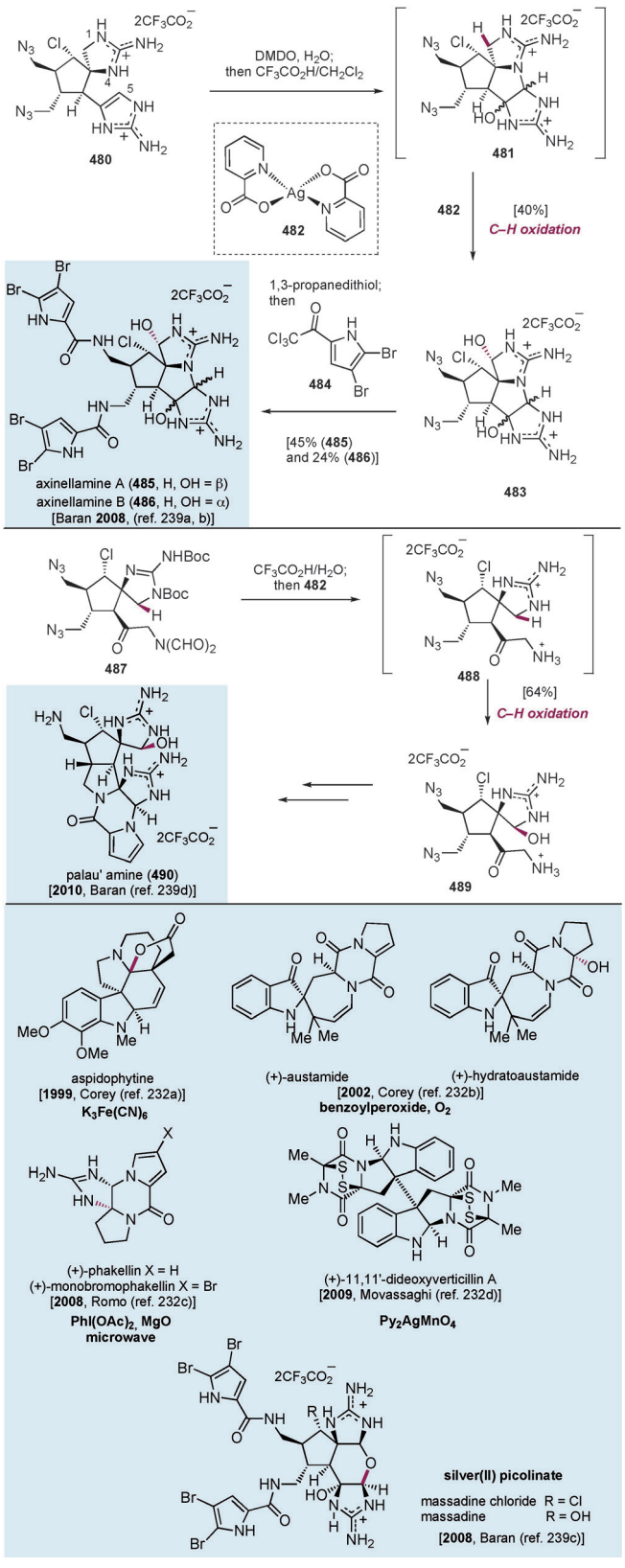
4.7. C–H Oxidation on a Carbon Atom Bearing a Nitrogen Atom

Between 2008 and 2010 the Baran research group reported the first synthesis of axinellamines A (**485**) and B (**486**), massadine chloride, massadine, and palau'amine (**490**), which are all dimeric pyrrole-imidazole alkaloids (Scheme 96).[229] Palau'amine (**490**), isolated by Sheuer et al. in 1993, has received significant attention from the synthetic chemistry community because of its structural complexity. Despite extensive efforts by many research groups,[230] however, the total synthesis of **490** or its congeners had not been previously been reported. Although there are many synthetic puzzles and interesting steps in their synthesis of the pyrrole-imidazole alkaloid family, this Review focuses on one key step in these syntheses, a C–H oxidation on a carbon atom bearing a nitrogen atom (Scheme 96).

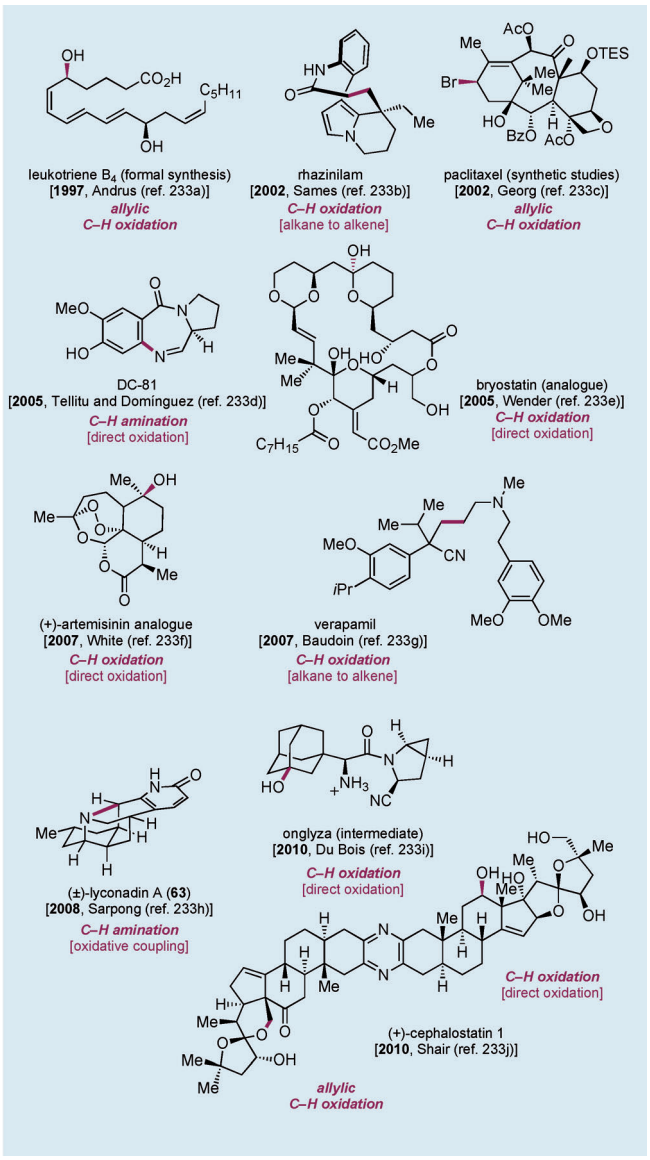
Spirocyclic guanidinium intermediate **480** had to be increased in oxidation state at both the C1- and C5-positions to access natural products **485** and **486**. Oxidation of the aminoimidazole moiety was achieved by the use of dimethyldioxirane (DMDO), followed by nucleophilic attack from the guanidine nitrogen atom, to form tetracycle **481** as a mixture of two diastereomers. After extensive investigation, the use of excess silver(II) picolinate (**482**)[231] led to C–H oxidation of the C1 methylene unit to provide a mixture of the desired compounds **483** in 40% yield from **480**. After reduction of the azides and condensation of two bromopyrrole units, the total synthesis of axinellamines A (**485**) and B (**486**) was achieved.[239a,b] In the case of palau'amine (**490**), the C1 methylene unit of spirocycle **487** was hydroxylated with the same oxidant to give **489**, which eventually led to the first total synthesis of palau'amine (**490**).[239d]

Other examples of C–H oxidation on a carbon atom bearing a nitrogen atom in natural product synthesis by using a stoichiometric amount of an oxidant (except chromium oxidants) are shown in Scheme 96.[232]

In many other complex-molecule syntheses, C–H oxidation or C–H amination were used as key C–H bond-functionalizing transformations. Some examples are shown in Scheme 97.[233]



Scheme 96. C–H oxidation on a carbon atom bearing a nitrogen atom in natural product synthesis. DMDO = dimethyldioxirane.



Scheme 97. Molecules that were synthesized using C–H oxidation or amination as key steps.

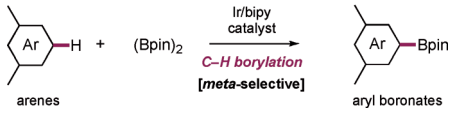
4.8. C–H Borylation

The direct borylation of C–H bonds[234] is a straightforward and valuable method in synthetic organic chemistry, since the reaction product can be used in the versatile palladium-catalyzed Suzuki–Miyaura cross-coupling reaction. The net effect is thus a C–H to C–C bond transformation. Although numerous types of C–H bonds (such as arenes, alkenes, and alkanes) have been shown to undergo C–H borylation, there is an increasing demand to introduce boron atoms into C–H bonds for complex natural products and pharmaceuticals, for which mild reaction conditions, functional group tolerance, and site-selectivity are of crucial importance. Thus far, the most widely used type of C–H to C–B bond transformation is the aromatic C–H borylation and, in part, olefinic C–H borylation using iridium catalysts. Early studies on this reaction were reported in 1999, when Smith

and co-workers discovered an iridium-catalyzed C–H borylation of benzene with pinacolborane.[235] Subsequently, Chen and Hartwig reported a rhenium-catalyzed C–H borylation of alkanes and arenes.[236] In 2000, both research groups discovered similar borylation reactions using rhodium catalysts.[237] However, these early reaction conditions required: 1) excess amounts of substrates (≈60 equivalents); 2) the use of unstable catalysts with limited turnover; 3) high temperatures between 150 °C and 200 °C.

In 2002, the collaborative effort of the research groups of Hartwig, Miyaura, and Ishiyama resulted in a regioselective C–H borylation reaction of arenes by using an Ir/bipy catalyst system.[238] This reaction proceeded at 80 °C to afford borylated arenes in 58–95 % yield; furthermore, it provided products even at room temperature, with remarkably high turnover numbers (8000 turnovers) and with a decreased loading of arenes (≈2.0 equivalents) when using 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as the ligand. The selectivity of the borylation depended highly on the steric properties of the substrate, and hence the reaction generally provided mixtures of *para*- and *meta*-borylated arenes (*para*/*meta* = 1:2).

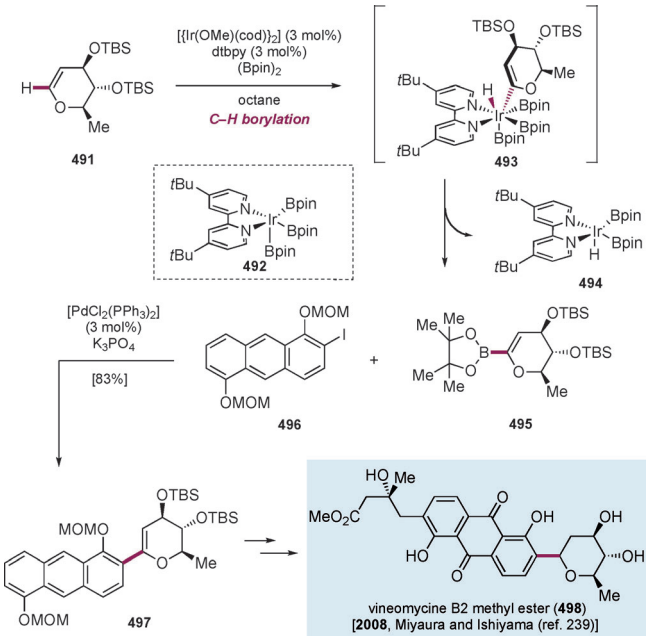
This aromatic C–H borylation method is synthetically useful, since *meta*-substituted benzene derivatives are difficult to synthesize by other methods, such as electrophilic aromatic substitution or directing-group-assisted C–H functionalization. Therefore, this Ir-catalyzed C–H borylation gained much attention from the synthetic community, and is now often referred to as the "Hartwig–Miyaura borylation" (Scheme 98). Very recently, several chemists reported the total synthesis of complex natural products by using this Ir-catalyzed reaction as their key step.



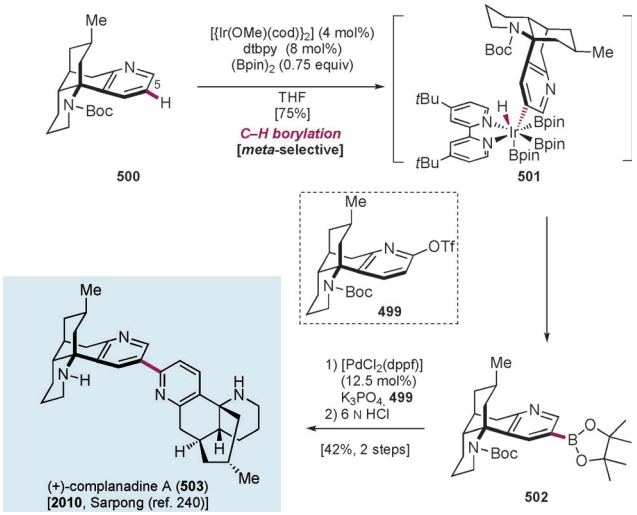
Scheme 98. Iridium-catalyzed aromatic C–H borylation.

In 2008, Miyaura, Ishiyama, and co-workers applied their own C–H borylation protocol to synthesize vineomycin B2 methyl ester (**498**; Scheme 99).[239] The C–H borylation of dihydropyran **491** occurred selectively at the γ position to afford boronate **495** in excellent yield when [{Ir(OMe)(cod)}$_2$]/dtbpy was used as the catalyst. It was proposed that Ir^V species **493** is generated from **491**, B_2pin_2, and [{Ir(OMe)(cod)}$_2$]/dtbpy, which then reductively eliminates vinylboronate **495**. Oxidative addition of $(Bpin)_2$ to iridium hydride **494** followed by reductive elimination of HBpin can regenerate active catalyst **492**. Boronate **495** (1.1 equiv) was then coupled with aryl iodide **496** under Suzuki–Miyaura cross-coupling conditions to deliver **497** in 83 % yield based on **496**. After several steps, the total synthesis of vineomycin B2 methyl ester (**498**) was achieved.

In 2010, Fischer and Sarpong demonstrated a skillful use of C–H borylation to synthesize (+)-complanadine A (**503**), an unsymmetrical lycodine dimer (Scheme 100).[240] Pyridine derivative **500**, which was readily prepared from **499** by removal of the triflate moiety, was treated under the standard



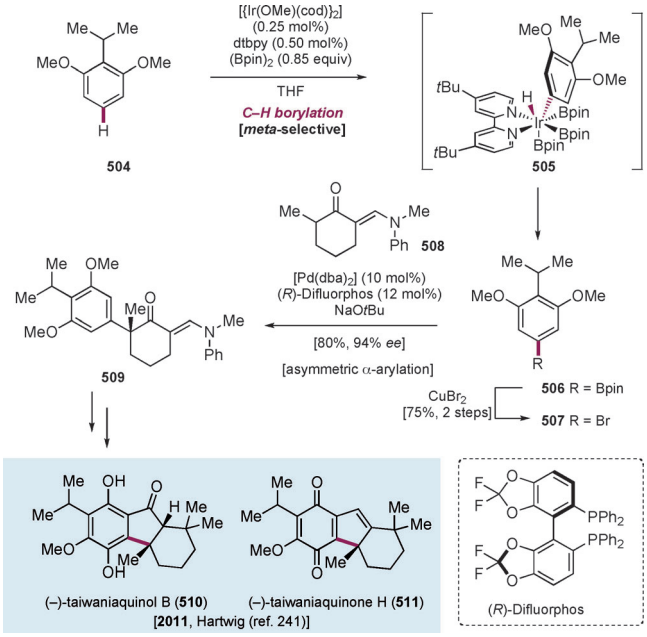
Scheme 99. Total synthesis of vineomycin B_2 methyl ester (**498**). cod = 1,5-cyclooctadiene.



Scheme 100. Total synthesis of (+)-complanadine A (**503**).

Hartwig–Miyaura C–H borylation conditions to afford boronate **502** as a single regioisomer (at the C3-position of the pyridine moiety) in 75 % yield. The observed regioselectivity was consistent with that noted by Miyaura and Hartwig for pyridine functionalization, and appeared to be guided mainly by steric factors. The Suzuki–Miyaura cross-coupling of **502** with triflate **499** led to complanadine A (**503**) in a total of eight steps. This strategy has the potential to be used for the synthesis of many lycodine analogues and derivatives, as well as to make symmetrical and unsymmetrical lycodine dimers.

Hartwig and co-workers applied the C–H borylation method to the synthesis of (−)-taiwaniaquinol B (**510**) and its analogue (−)-taiwaniaquinone H (**511**) by using their own

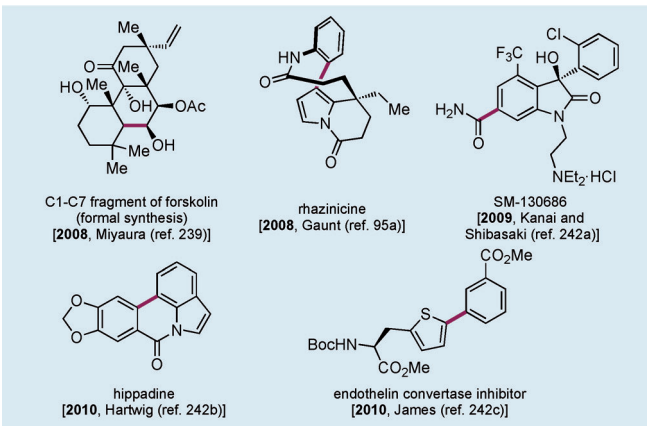


Scheme 101. Total syntheses of (−)-taiwaniaquinone H (**511**) and (−)-taiwaniaquinol B (**510**) by iridium-catalyzed C−H borylation and palladium-catalyzed asymmetric α-arylation.

protocols for iridium-catalyzed C−H borylation and palladium-catalyzed asymmetric α-arylation (Scheme 101). Their synthesis commenced with C−H borylation of arene **504**, followed by bromination of the resulting aryl boronate ester **506** with copper bromide. In general, electrophilic aromatic substitution undergoes bromination *ortho* to the two methoxy groups. To overcome this regioselectivity problem, they employed a two-step bromination sequence (75% yield in one pot, multigram scale). Then, enantioselective α-arylation of cyclohexanone **508** with aryl bromide **507** in the presence of $[Pd(dba)_2]$/(*R*)-difluorophos catalyst formed α-arylcyclohexanone **509** in 80% yield and 94% *ee*. From intermediate **509**, they completed the first enantioselective total synthesis of **510** and **511** in a total of 10 and 12 steps, respectively.[241]

Other notable achievements that utilized aromatic C−H borylation include the formal synthesis of forskolin by Miyaura and co-workers,[239] the total synthesis of rhazinicine by Gaunt and co-workers,[95a] the synthesis of SM-130686 by Kanai, Shibasaki and co-workers, the total synthesis of hippadine by Hartwig and co-workers, and the synthesis of endothelin convertase inhibitor by James and co-workers (Scheme 102).[242]

As such, the synthesis of complex natural products by using C−H borylation, particularly the iridium-catalyzed borylation of arenes, has been described. Further studies have been recently conducted by many research groups to develop more catalysts, to optimize reaction conditions, and to broaden the substrate scope (to include non-aromatic substrates as well). In the near future, we expect to see more elegant disconnections in retrosynthetic analysis based on this iridium-catalyzed transformation, or based on C−H borylation reactions that have yet to be discovered.



Scheme 102. Syntheses of bioactive compounds through C−H borylation.

5. Summary and Outlook

In this Review, we described syntheses of natural products and pharmaceuticals that were enabled by developments in C−H functionalization methods, from historical landmarks to recent achievements. We attempted to group these C−H functionalization methods into broad categories, however, it is highly probable that future developments in this field will defy the definitions, classifications, and concepts described herein. As such, the concepts and categories outlined in this Review do not need to serve a practical purpose, as long as C−H functionalization methods continue to provide an effective tool toward an ideal synthesis.

It is of note that this Review did not describe state-of-the-art C−H functionalization methods that are not target-oriented. Despite the fact that the field of transition-metal-catalyzed C−H activation has recently shown tremendous progress, and that it is of no doubt that these methods will be used in the synthesis of biologically active compounds in the near future, its true utility as a synthetic tool has yet to be demonstrated.

Pursuit of the "ideal synthesis" through C−H bond functionalization is a means for us to realize what is truly required of current synthetic methods. It is gradually becoming possible to propose an unconventional, yet direct, retrosynthetic analysis toward a specific target, one that we could otherwise not even dream of without the notion of C−H functionalization. The next generation of synthetic organic chemistry by C−H functionalization has just begun.

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