Recent Applications of Phosphane-based Palladium Catalysts in Suzuki-Miyaura Reactions Involved in Total Syntheses of Natural Products

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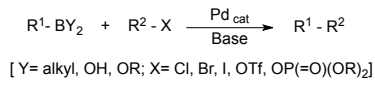
Abstract: This review with 800 references illustrates applications of Suzuki-Miyaura (S.-M.) reactions in the total syntheses of 147 natural products that were made in the period 2010–2013. The review has been organized on the basis of the seven classes of phosphane-based Pd catalysts that have been used in the reported total syntheses. Emphasis has been given to describe and discuss the experimental conditions of the Pd-catalyzed (S.-M.) cross-coupling reactions also outlining the methods used to prepare the reactants. A focus has also been set on the biological and pharmacological properties of the reported natural products as well as on the most significant steps of the reported total syntheses.

Keywords: *Chemoselectivity, Siteselectivity, Stereoselectivity, Carbon–carbon bond forming reactions, Transition metal catalyst*

1. INTRODUCTION

Over the past three decades the Pd-catalyzed Suzuki-Miyaura (S.-M.) cross-coupling reaction of organoboron reagents with organic halides or pseudohalides (Scheme 1) has become one of the most important methods for the construction of Csp^2–Csp^2 bonds.[1]



Scheme 1. The Suzuki–Miyaura cross-coupling reaction

The significant importance of this reaction in the areas of academia and industry was recognized awarding the 2010 Nobel Prize in Chemistry in part to Prof. Akira Suzuki. In fact, the reaction has proved of great utility in the synthesis of natural products,[2] biologically and pharmacologically active compounds[3] some of which have also been prepared on a large scale,[4] agrochemicals,5 and conjugated polymers useful in optoelectronic and electronic applications.[6] Several factors have contributed to the wide spread use of this reaction. They include: i) commercial availability of several organoboron reagents; ii) toleration of a broad range of functional groups; iii) water stability; iv) easy separation of the boron-containing by-products; v) environmentally benign nature of the organoboron reagents; and vi) the high regio- and stereoselectivity of the reaction. Moreover, during the last two decades many protocols have been developed that allow to carry out the reaction in mild conditions by using low loadings of the Pd catalyst precursors and make the reaction to proceed even with relatively inert electrophilic substrates such as unactivated aryl chlorides and very hindered aryl halides,1k alkyl tosylates,[7] aryl and alkenyl triflates,[8] alkenyl mesylates and tosylates,[9] (hetero)aryl sulfamates,[10] aryl

imidazolylsulfonates,[11] allylic phosphates,[12] heteroaryl mesylates[13] and carboxylates,[14] vinyl acetate,[15] and phosphonium salts.[16]

Most early work in the S.-M. reaction, including the seminal studies by Suzuki[17] and the first application of this cross-coupling reaction in the synthesis of a natural product[18] was accomplished by using $Pd(PPh_3)_4$ as the catalyst precursor. Nowadays, the ever-growing catalogue of the Pd catalysts for the S.-M. reaction include: i) systems composed of a Pd(0) or a Pd(II) derivative and phosphorus-based ligands;[19,20] ii) Pd(0) or Pd(II) catalyst precursors containing *N*-heterocyclic carbene (NHC) ligands;[21] iii) palladacycles;[22] iv) systems composed of Pd(0) or Pd(II) derivatives and ligands different from phosphanes and NHCs;[23] v) ligandless Pd catalyst precursors;[24] vi) supported Pd derivatives;[25] vii) Pd nanocatalysts[26] including those supported on conventional supports or polymers,[27] cyclodextrins,[28] metal oxides and double hydroxides,[29] carbon nanotubes,[30] magnetic materials,[31] and dendrimer-containing supports;[32] viii) fluorous media-based nanocatalysts;[33] and ix) Pd nanoparticles in ionic liquids.[34]

Nevertheless, despite the wide variety of homogeneous and heterogeneous Pd catalysts currently available, the vast majority of S.-M. cross-couplings, which have been employed in the total syntheses of natural products described to date, have been carried out by using phosphane-based Pd catalysts and only few examples of total syntheses involving the use of Pd-catalyzed S.-M. reactions under ligandless conditions have recently been reported.[35]

This critical review with 800 references is aimed to present a broad overview of recent applications of S.-M. cross-couplings, which have been performed by using phosphane-based Pd catalyst systems, in the total synthesis of natural products many of which are known to exhibit interesting biological or pharmacological properties. The literature on this topic, which covers the results described in the period January 2010–December 2013, for the sake of clarity has been subdivided in seven sections interposed between the introduction and conclusions: (i) total syntheses via $Pd(PPh_3)_4$-catalyzed S.-M. cross-couplings; (ii) total syntheses via S.-M. reactions promoted by $PdCl_2(PPh_3)_2$ or a combination of PPh_3 with $Pd(OAc)_2$ or $Pd_2(dba)_3$; (iii) total syntheses via *trans*-$PdBr(N\text{-Succ})(PPh_3)_2$-catalyzed S.-M. reactions; (iv) total syntheses via S.-M. reactions promoted by a combination of P(*o*Tol)$_3$ or a tri(cyclo)alkylphosphane with a Pd(II) or a Pd(0) derivative; (v) total syntheses via S.-M. reactions promoted by a combination of a dicycloalkylbiarylphosphane with a Pd(II) or a Pd(0) derivative; (vi) total syntheses via $PdCl_2$(dppf)- or $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. reactions; and (vii) total syntheses via S.-M. reactions promoted by a combination of $PdCl_2$(dppf) with $AsPh_3$. The specific aspects of some of these total syntheses have been discussed in detail.

It is also worth noting that the topics of these sections have not been covered in recent reviews and books on the S.-M. reaction, though a small number of applications of the S.-M. cross-coupling reaction in 20 total syntheses of natural products, which have been accomplished in the period 2010–2012 and involve the use of phosphane-based Pd catalysts, have been summarized in a review published in 2012 by Heravi and Hashemi.[2f] We wish also to point out that the present review shortly describes the origin and the biological and/or pharmacological properties of the examined natural compounds, but does not cover the use of the S.-M. reaction in the synthesis of fragments of natural products that have not yet been employed in the total synthesis of these natural products.

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1. TOTAL SYNTHESES VIA $Pd(PPh_3)_4$-CATALYZED SUZUKI-MIYAURA (S.-M.) CROSS-COUPLING REACTIONS

$Pd(PPh_3)_4$ is a commercially available compound, which is commonly used as catalyst precursor in S.-M. reactions, even it is an air- and moisture sensitive complex. Moreover, the products of $Pd(PPh_3)_4$-catalyzed S.-M. reactions involving the use of aryl halides as electrophiles sometimes have been found to be contaminated by biaryl products where an aryl group derives from the PPh_3 ligand of the catalyst precursor via an aryl–aryl exchange reaction between the Pd center and the phosphane ligand in the intermediates Pd(II) complexes.[36] It should also be noted that $Pd(PPh_3)_4$ exists in solution primarily as complex $Pd(PPh_3)_3$,[37] which unfortunately does not feature the optimal catalytic activity of PdL_2 species (L = tertiary phosphane) present in the most widely accepted catalytic cycle for the S.-M. reaction. However, despite these drawbacks, as illustrated in this section, $Pd(PPh_3)_4$ continues to be widely employed as a catalyst precursor in S.-M. reactions involved in total syntheses of natural products.

Table 1 lists the structures and the literature data on the isolation of the naturally-occurring compounds that have been synthesized in the period January 2010–December 2013 by using $Pd(PPh_3)_4$-catalyzed S.-M. reactions. These natural substances include: methyl (5*Z*,8*Z*,10*E*,12*E*,14*Z*)-eicosapentenoate (**1**), which was isolated from the red algae *Lithothamnion coralloides*;[38] protectin D1 (**2**), an anti-inflammatory and proresolving metabolite of docosahexaenoic acid (22:6, n = 3, DHA);[39]meridianins G (**3**) and A (**4**), two indole alkaloids isolated from the tunicate *Aplidium meridianum*;[40] the diterpene oxepane **5**, which was isolated from the leaves of *Montanoa tomentosa* (Asteraceae);[41] the pentacyclic pyrrolic alkaloid lamellarin S (**6**), which was isolated from the Australian tunicate *Didemnum* sp.;[42] (+)-vertine (**7**) an alkaloid isolated from the wild flowering shrub *Heimia* salicifolia (Lythraceae)[43a] and the plant *Decodon verticillatus* (Lythraceae);[43b] gymnopusin (**8**), a phenanthrene derivative isolated from the orchid *Bulbophyllum gymnopus* (Orchidaceae),[46a] whose revised structure[44b] is shown in Table 1; the cytotoxic quinoline alkaloid camptothecin (**9**), first isolated from the Chinese plant *Camptotheca acuminate* (Cornaceae);[45] camalexin (**10**), a cruciferous phytoalexin, which was first isolated from *Camelia sativa* and *Arabidopsis thaliana* (Brassicaceae);[46] the macrocyclic bis(bibenzyl) compound **11**, which was isolated in 1984 from the liverwort *Plagiochila acantophylla* subsp. *japonicas*;[47] rhuschalcone VI (**12**), a potent antiplasmodial bischalcone isolated for the first time from the root bark of *Rhus pyroides* (Anacardiaceae);[48] the marine alkaloid hyrtinadine A (**13**), a cytotoxic bisindole derivative isolated from the Okinawan marine sponge *Hyrtios* sp.;[49] lamellarin □-20-sulfate (**14**), isolated from an unidentified ascidian collected from the Arabian sea;[50] cassiarin F (**15**), a tetracyclic alkaloid, which was isolated from the flowers of *Cassia siamea* (Fabaceae);[51] arcyriarubin A (**16**) a bisindolyl maleimide isolated from the fruiting bodies of the slime mold;[52] arcyriaflavin A (**17**), a bisindole alkaloid isolated from the marine ascidian *Eudistoma* sp.;[53] clausines C (**18**) and R (**19**), two carbazole alkaloids isolated from the bark of *Clausena excavate* (Rutaceae);[54,55] the cytotoxic carbazole clauraila A (**20**) isolated from the roots of *Clausena harmandiana* (Rutaceae);[56]the antibiotic polyketide (-)-aurafuron A (**21**) isolated from the myxobacterium *Stigmatella aurantiaca* DW4/3-1;[57] (-)-hamigeran B (**22**), a tricyclic compound isolated from the poecilosclerid sponge *Hamigera tarangaensis*;[58] the rearranged diterpene microstegiol (**23**) isolated from *Salvia microstegia* (Lamiaceae);[59] (+)-herboxidiene (**24**), a potent phytotoxic polyketide isolated from *Streptomyces chromofuscus* A7847;[60] the marine ladder-frame polyether toxin (–)-brevenal (**25**), which was identified in a laboratory culture of the marine dinoflagellate *Karenia brevis*[61a] and was found to bind to a previously unreported site on mammalian sodium channels;[61b] amorphastilbol (**26**), a compound isolated from a *Robinia pseudoacacia* var. *umbraculifer* (Fabaceae) seed extract[62a] and from *Amorpha* nana (Fabaceae)[62b] and was shown to exhibit antimicrobial[62b] and antidiabetic properties;[62c] cladoacetals A (**27**) and B (**28**), two benzofused dioxabicyclo[4.2.1]nonene derivatives isolated from fermentation cultures of an unidentified fungicolous isolate;[63] oteromycin (**29**), a novel antagonist of endothelin receptor first isolated from fungus strains MF 5810 and MF 5811;[64] isobongkreic acid [(*E*)-**30**], a fatty triacid which was obtained from the fermentation of *Pseudomonas cocovenants*;[65] bongkreic acid [(*Z*)-**30**], an anti-apoptotic agent produced by *Burkholderia gladioli* pathovar *cocovenants* (formerly *Pseudomonas cocovenants*) (Burkhoderiaceae);[66] vialinin A (terrestrin A) (**31**), a terphenyl compound isolated from the dry fruiting bodies of the mushroom *Telephora vialis*, which was shown to possess potent inhibitory activity of TNF-α production from RBL-2113 cells;[67] sauristolactam (**32**), an alkaloid first isolated from the extracts of the aquatic weed *Saururus cernuus*,[68a] which was found to be active against a variety of tumor cells;[68b] carbazomadurin A (**33**) a polysubstituted carbazole alkaloid isolated from the microorganism *Actinomadura madurae* 2808–SV1;[69] (+)-carbazomadirin B (**40**), a neuronal cell-protecting carbazole alkaloid isolated from *A. madurae* 2808–SV1;[69,76] the potent antimitotic agent leiodermatolide (**34**), a macrolide isolated from the deep-water marine sponge *Leiodermatium* sp.;[70](*R*)-trichostatin (**35a**), an antibacterial metabolite isolated from strains of the bacterial species *Streptomyces hygroscopicus*;[71a] (*R*)-trichostatic acid (**35b**), a compound isolated from *S. sioyaensis*, which was reported to induce differentiation of leukemia cells;[71b] prekinamycin (**36**), a metabolite produced by *S. murayamensis* mutant MC2;[72] 3-methoxy-2,5-diphenylcyclohexa-2,5-dien-1,4-dione (**37**), an *ortho*-quinone isolated from common coelomycetous soil fungi *Phoma* sp., which is an inhibitor of parasite cyclic GMP-dependent protein kinase;[73] ecteinascidin 743 (**38**),

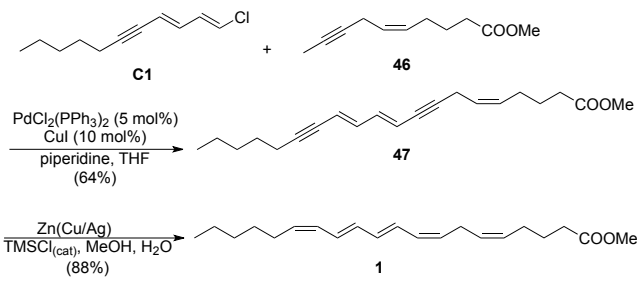
an extremely potent antitumor agent isolated from the Caribbean tunicate *Ectinascidia turbinata*;[74] (*S*,5*Z*,8*E*,10*E*)-12-hydroxyheptadeca-5,8,10-trienoic acid (**39**), a co-product of the pathway leading to thromboxane A_2 from PGH_2, a metabolite of cyclooxygenase;[75] (+)-gregatin B (**41**), a phytotoxic metabolite produced by the Deuteromycete fungus *Phialophora gregata adzukicola*, a causal agent of brown stem rot in adzuki beans;[77] rodgersinol (**42**), a 2-arylpropanol isolated from the aerial parts of *Rodgersia podophylla* (Saxifragaceae), which was found to exhibit significant inhibitory effect on iNOS and COX-2 expression in LPS-activated macrophages;[78] dictyodendrin B (**43**), a tyramine-based pyrrolocarbazole alkaloid isolated from the marine sponge *Dictyodendrilla verongiformis*, which was shown to completely inhibit telomerase;[79] benzo[*j*]fluoranthene-4,9-diol (**44**), a polyketide produced from the mantis-associated *Daldinia eschschlolzii* (Ascomycota, Xylariaceae);[80] and michellamine B (45), an axially chiral biaryl compound originally isolated from tropical liana *Ancistrocladus korupensis* (Ancystrocladaceae), which was shown to be a strong anti-HIV-1 and anti-HIV-2 agent.[8]

TABLE 1 HERE

Table 2 illustrates the $Pd(PPh_3)_4$-catalyzed S.-M. cross-coupling reactions employed in the total syntheses of the natural compounds listed in Table 1. In particular, Table 2 shows the experimental conditions and yields of these reactions.

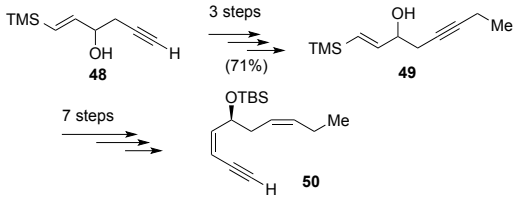
TABLE 2 HERE

The $Pd(PPh_3)_4$-catalyzed S.-M. reaction between (*E*)-1,2-dichloroethene (**B1**) and the boronic acid, which was obtained by mild hydrolysis of the MIDA-protected boronate ester **A1**[121] with 1 M aq. NaOH , was a step of a convergent synthesis of methyl (5*Z*,8*Z*,10*E*,12*E*,14*Z*)-5,8,10,12,14-eicosapentenoate (**1**) which was published in 2011.[82] The S.-M. cross-coupling reaction (entry 1, Table 2) provided compound **C1** in 70% yield.[82] A subsequent Sonogashira reaction between compound **C1**, which was obtained in 70% yield from the Suzuki reaction, and 1-alkyne **46** gave dienediyne **47**, which was converted into the target compound by stereoselective reduction with Zn(Cu/Ag)[122] in the presence of a catalytic amount of TMSCl in methanol (Scheme 2).[82]



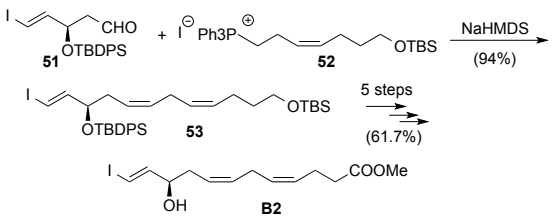
Scheme 2. Synthesis of compound **1** from dienyl chloride **C1**

In 2011, compound **C2**, an advanced intermediate in the total synthesis of the anti-inflammatory and proresolving agent protectin D1 (**2**), was synthesized in a satisfactory yield by $Pd(PPh_3)_4$-catalyzed S.-M. reaction between the disiamylborane derivative **A2** and vinyl iodide **B2** (entry 2, Table 2).[83] (*Z*)-Enyne **50**, the acetylenic precursor to **A2**, was prepared from alcohol **48** via a 10-step reaction sequence involving the asymmetric epoxydation of racemic alcohol **49** (Scheme 3).[83]



Scheme 3. Synthesis of enyne **50**

On the other hand, vinyl iodide **B2** was prepared by using a Wittig reaction between aldehyde **51** and the ylid obtained from phosphonium iodide **52**, which gave enantiomerically pure compound **53** in 94% yield (Scheme 4).[83]



Scheme 4. Synthesis of compound **53**, a precursor to **B2**

In the same year, Müller and co-workers employed the one-pot Masuda borylation-S.-M. coupling sequence for concise total syntheses of meridianins G (**3**) and A (**4**).[84] Remarkably, the typical catalyst for Masuda borylations, $PdCl_2$(dppf),[123] failed to give the required organoboron reagents **A3** and **A4** in a good yield. Nevertheless, these reagents, which were employed in the reactions of entries 3 and 4 of Table 2, were prepared in good yields by treatment of the corresponding 3-iodo-1*H*-indole-1-carboxylates, **54** and **55**, respectively (Figure 1), with 4,4,5,5-tetramethyldioxaborolane (**56**) (Figure 1) in dioxane in the presence of Et_3N and a catalytic amount of $Pd(PPh_3)_4$.

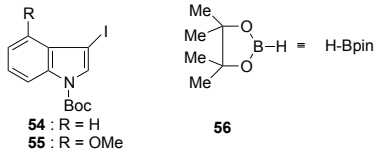
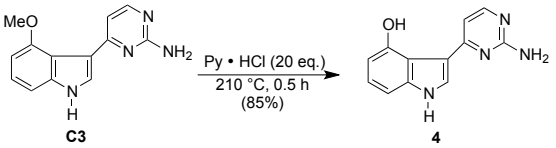


Figure 1. Structures of compounds **54–56**

Crude compounds **A3** and **A4** were then reacted with 2-amino-4-chloropyrimidine (**B3**) yielding meridianin G (**3**) and compound **C3** in 73 and 77% yield, respectively (entries 3 and 4, respectively, Table 2).[84] Demethylation of **C3** with pyridine hydrochloride[124] provided meridianin A (**4**) in 85% yield (Scheme 5).[84]



Scheme 5. Demethylation of compound **C3**

Still in 2011, compound **C4**, an early intermediate in the synthesis of (+)(2'*S*,3'*R*)-zoapatanol (**5**), was synthesized in 81% yield by Raghvan and Babu using the $Pd(PPh_3)_4$-catalyzed reaction between alkenyl triflate **B4** and the 9-alkyl-9-BBN derivative **A5** (entry 5, Table 2). The latter compound was prepared by hydroboration of 1-alkene **57** (Figure 2) with 9-borabicyclo[3.3.1]nonane (9-BBN-H) dimer.[85]

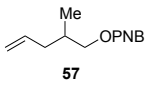
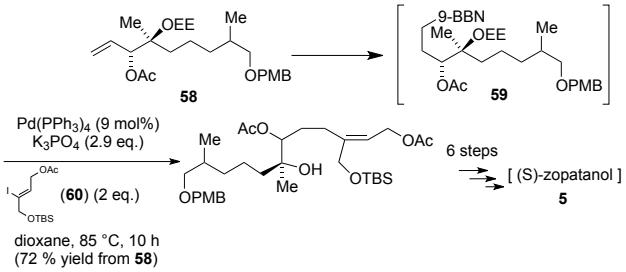


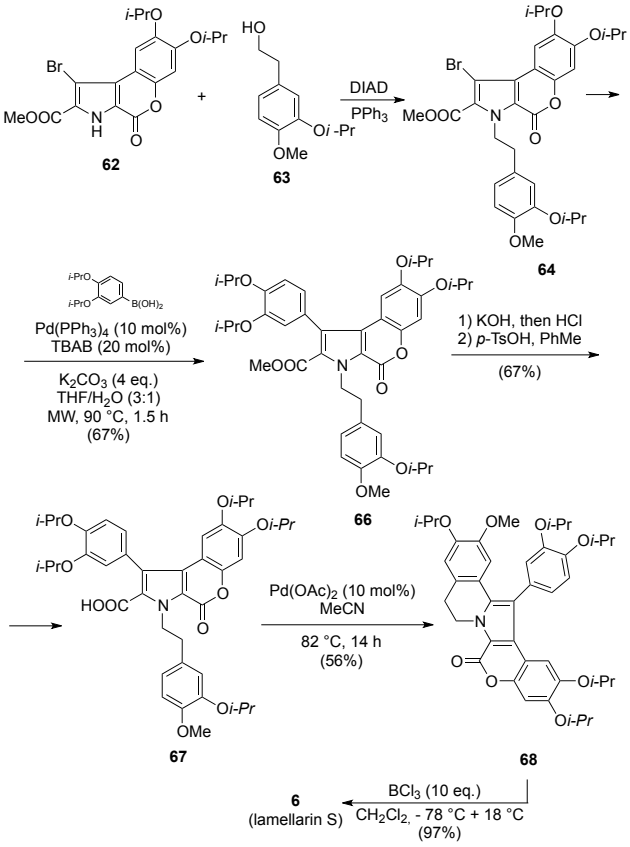
Figure 2. Structure of 1-alkene **57**

On the other hand, compound **61**, an advanced intermediate in the synthesis of **5**, was prepared in 72% yield by $Pd(PPh_3)_4$-catalyzed coupling of (*Z*)-alkenyl iodide **60** with organoborane **59** and concomitant deprotection of the ethoxyethyl ether protecting group (Scheme 6). Compound **59** was in turn obtained by hydroboration of 1-alkene **58** with (9-BBN-H) (Scheme 6).[85]



Scheme 6. Synthesis of (*S*)-zoapatanol (**5**) from compound **58**

The first total synthesis of lamellarin S (**6**) was accomplished in 2011 by Banwell and co-workers via a route in which compound **C5**, a key intermediate, was prepared in 92% yield by S.-M. cross-coupling of the key pyrrolic buiding block **B5** with boronate ester **A6** (entry 6, table 2).[86] Bromination of **C5** with NBS followed by a Mitsunobu reaction of the resulting compound **62** with β-phenethyl alcohol **63** gave compound **64** in a high yield. Microwave-assisted $Pd(PPh_3)_4$-catalyzed cross-coupling reaction of **64** with boronic acid **65** then gave pyrrole **66** in 67% yield (Scheme 7). Finally, a subsequent $Pd(OAc)_2$-catalyzed decarboxylative arylation of carboxylic acid **67**,[125] which was derived from **66**, provided the pentacyclic compound **68**, which by cleavage of all five isopropyl ether units gave lamellarin S (**6**) (Scheme 7).[86]



Scheme 7. Synthesis of lamellarin S (**6**) from compound **62**

Lamellarin L 20-sulfate (**14**) had previously been synthesized from compound **69** (Figure 3), which in turn was prepared via a six-step reaction sequence that commenced with the $Pd(PPh_3)_4$-catalyzed coupling of bistriflate **B6** with boronic acid **A7**. As shown in entry 7 of Table 2, this reaction occurred in 74% yield.[87]

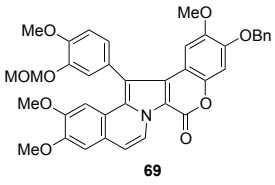
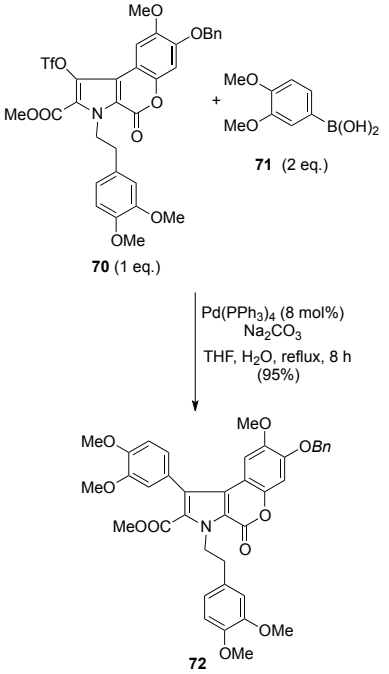


Figure 3. Structure of compound **69**

A more advanced intermediate in the synthesis of **69**, compound **72**, was prepared in 95% yield by the $Pd(PPh_3)_4$-

catalyzed cross-coupling reaction of triflate **70** with 2 equiv of boronic acid **71** (Scheme 8).[87]



Scheme 8. Synthesis of compound **72** from triflate **70**

In 2012, the S.-M. reaction between boronate **A8** and quinolizidone **B7** to give **C7** (entry 8, Table 2) was used as a key step of an asymmetric total synthesis of (+)-vertine (**7**).[88] Compound **B7** was obtained via a condensation reaction between pelletierine [(*R*)-**73**] and 6-iodoveratraldehyde (**74**) (Figure 4).[88]

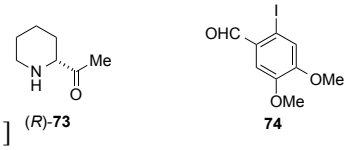
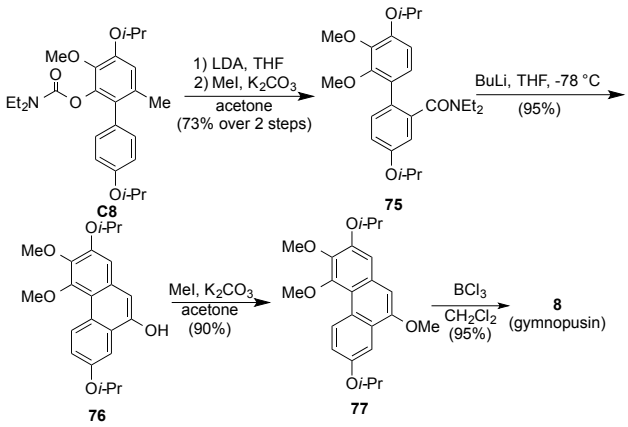


Figure 4. Structures of compounds (*R*)-**73** and **74A**

Again in 2012, Snieckus and co-workers demonstrated that the originally assigned structure for gymnopusin was incorrect and reported a total synthesis of this natural product possessing the revised structure **8** by using compound **C8** (Table 2) as a key intermediate.[89]Biaryl **C8** was prepared in 90% yield by S.-M. reaction of boronic acid **A9** with bromophenyl carbamate **B8** (entry 9, Table 2). The remote anionic Fries rearrangement of **C8** by using an excess of LDA in refluxing THF and the subsequent methylation of the resulting compound gave the biaryl amide **75**, which on treatment with BuLi provided phenanthrol **76** (Scheme 9). Methylation of **76** delivered compound **77**, which was found to be unstable and therefore was immediately treated with BCl_3 to afford gymnopusin (**8**) in an excellent yield (Scheme 9).[89]



Scheme 9. Synthesis of gymnopusin (**8**) from compound **C8**

In 2013, Zhang and co-workers described a concise formal synthesis of camptothecin (**9**) in which a key step was the S.-M. reaction illustrated in entry 10 of Table 2.[90] The crude organoboron derivative **A10** employed in this reaction was synthesized by $PdCl_2$(dppf)-catalyzed boronation of heteroaryl chloride **78** (Figure 5) with bis(pinacolato)diboron (**79**) in DME in the presence of KOAc. Compound **A10** was then converted to the corresponding boronic acid by treatment with 2 M Na_2CO_3 and this organoboron reagent was directly used in the $Pd(PPh_3)_4$-catalyzed reaction with chloride **B9**. A subsequent two-step reaction sequence allowed to convert the cross-coupling product **C9** into the cyclized derivative **80**, which, according to the literature,[126] was a precursor to camptothecin (**9**). Figure 5 shows the structures of compounds **78–80**.

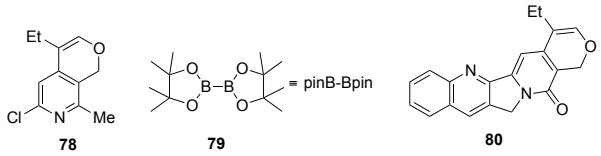
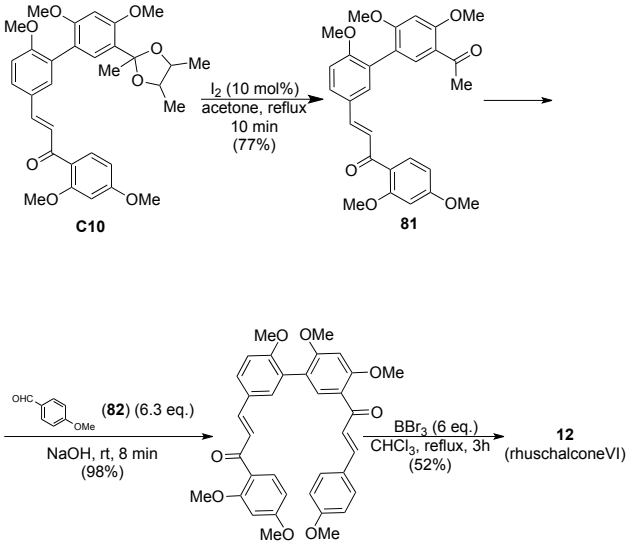


Figure 5. Structures of compounds **78–80**

In the same year, Müller and co-workers reported a one-pot, high-yielding synthesis of camalexin (**10**) that involved the cross-coupling reaction between crude boronate **A3** and 2-bromothiazole (**B10)** (entry 11, Table 2).[91] Interestingly, the reaction conditions of this reaction caused the conversion of **A3** into the corresponding boronic acid as well as the *N*-deprotection of the cross-coupling product.[91]

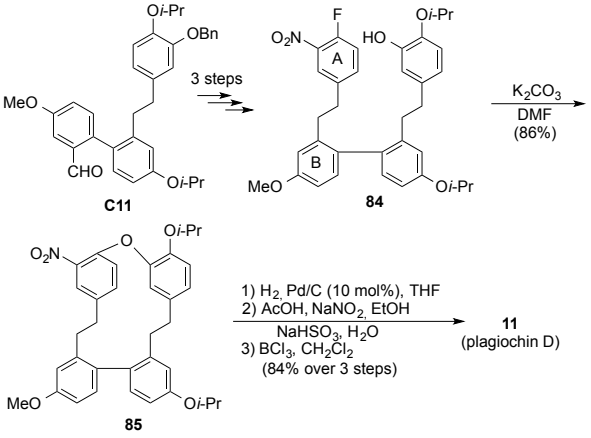
Abegaz and co-workers had previously synthesized compound **C10** by S.-M. reaction of boronate ester **A11** with bromochalcone **B11** (entry 12, Table 2).[92] Methyl ketone **81**, which was obtained by deprotection of **C10** was then converted into compound **83** by solvent-free aldol condensation with anisaldehyde (**82**) in the presence of NaOH. Finally, bichalcone **83** was demethylated by treatment with 6 equiv of BBr_3 in $CHCl_3$ to give

rhuschalcone VI (**12**) in 39.2% overall yield from **C10** (Scheme 10).[92]



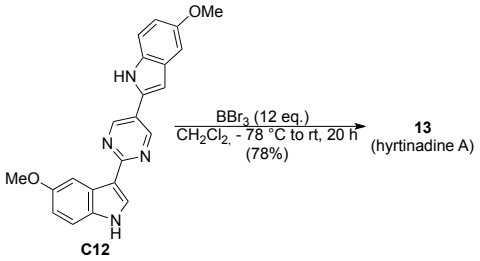
Scheme 10. Synthesis of rhuschalone VI (**12**) from compound **C10**

In 2011, González-Zamora and co-workers accomplished an interesting total synthesis of plagiochin D (**11**), a macrocyclic bis(bibenzyl) compound, in which compound **C11** containing rings B, D and C of the natural product, was obtained in 86% yield by $Pd(PPh_3)_4$ catalyzed reaction of boronic acid **A12** with 2-(benzyloxy)-4-(2-bromo-5-isopropoxyphenethyl)-1-isopropoxybenzene (**B12**) (entry 13, Table 2).[93] An intramolecular S_NAr reaction involving compound **84**, which was obtained from **C11** via a 3-step reaction sequence, provided the 16-membered ring derivative **85** in 86% yield (Scheme 11). Finally, reductive deamination of the amine derivative, which was obtained by catalytic reduction of **85**, followed by removal of the isopropyl groups furnished plagiochin D (**11**) in a good yield from **84** (Scheme 11).[93]



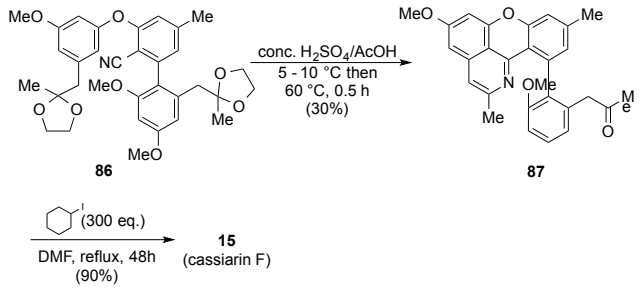
Scheme 11. Synthesis of of plagiochin D (**11**) from compound **C11**

In the same year, Müller and co-workers carried out a concise synthesis of the marine alkalod hyrtinadine A (**13**) which involved the preparation of compound **C12** by the Masuda borylation–S.-M. coupling illustrated in entry 14 of Table 2.[94] Demethylation of **C12** with 12 equiv of BBr_3 in CH_2Cl_2 provided hyrtinadine A in 78% yield (Scheme 12).[94]



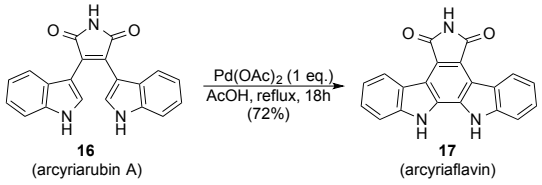
Scheme 12. Synthesis of hyrtinadine A (**13**) by demethylation of **C12**

Again in 2011, Morita and co–workers employed the S.-M. coupling illustrated in entry 15 of Table 2 for the construction of the biaryl unit of cassiarin F (**15**), an alkaloid showing potent antiplasmodial activity against *Plasmodium falciparum* in vitro.[95] Key steps of the total synthesis of **15**,[95] which involved 8 steps, were a nucleophilic aromatic substitution and a Houben-Hoesch type cyclization.[127] In the latter reaction compound **86** was treated with a 1: 1 mixture of sulfuric acid and AcOH at 60 °C to give the tetracyclic compound **87** in 30% yield (Scheme 13). The subsequent tris-*O*-demethylation of **87** by treatment with iodocyclohexane in refluxing DMF[128] gave **15** in 90% yield (Scheme 13).[95]



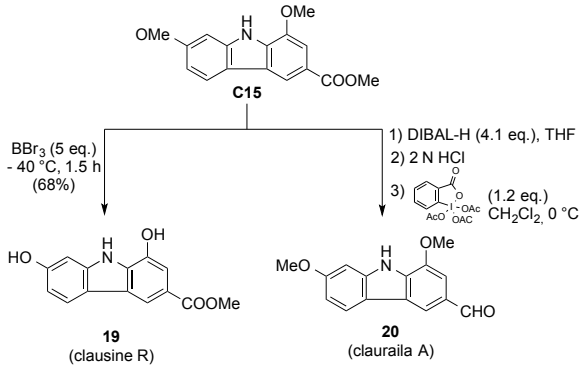
Scheme 13. Synthesis of cassarin F (**15**) from compound **86**

A year earlier, a synthesis of arcyriarubin A (**16**) was accomplished by Wang and Liu via $Pd(PPh_3)_4$-catalyzed S.-M. reaction of boronic acid **A15** with dibromomaleimide (**B15**) (entry 16, Table 2).[96] A 3-step reaction sequence allowed the conversion of the cross-coupling product, **C14**, into **16** in 66.8% yield. It was also established that treatment of **16** with 1 equiv of $Pd(OAc)_2$ in refluxing AcOH provided arcyriaflavin (**17**) in 72% yield (Scheme 14).[96]



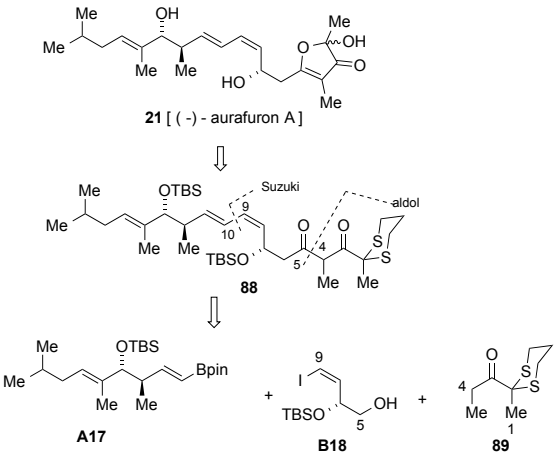
Scheme 14. Synthesis of arcyriaflavin (**17**) from arcyriarubin (**16**)

In 2011, Ren and co-workers synthesized clausine C (**18**) by S.-M. cross-coupling reaction of iodotriazene **B16** with triazene boronic acid **A16** followed by treatment of the resulting crude biaryl triazene with $BF_3{\cdot}Et_2O$ (entry 17, Table 2).[97] The same procedure was the employed to prepare the carbazole derivative **C15** in 90% yield from **A16** and **B17** (entry 18, Table 2). Demethyl of **C15** with BBr_3 afforded clausine R (**19**) in 68% yield (Scheme 15).[97] Moreover, treatment of **C15** with DIBAL-H followed by reaction of the resulting crude product with a solution of Dess-Martin periodinane in CH_2Cl_2 at 0 °C gave clauraila A (**20**) in 72% yield (Scheme 15).[97]



Scheme 15. Synthesis of clausine R (**19**) and clauraila A (**20**) from compound **C15**

In 2012, Hartmann and Kalesse reported the first total synthesis of (-)-aurafuron A (**21**).[98] As shown in the retrosynthetic analysis of this 3(2*H*)-furanone illustrated in Scheme 16, compound **88** was a key intermediate in which the C4–C5 bond was built via an aldol reaction between ethyl ketone **89** and an aldehyde generated at C5. On the other hand, the C9–C10 connection was established by using a $Pd(PPh_3)_4$-catalyzed S.-M. reaction between pinacol boronate **A17** and vinyl iodide **B18**. As shown in entry 19 of Table 2, this coupling, which was performed at room temperature in 2–5 h by using TlOEt as the base, gave the required compound **C16** in 68% yield. [98]

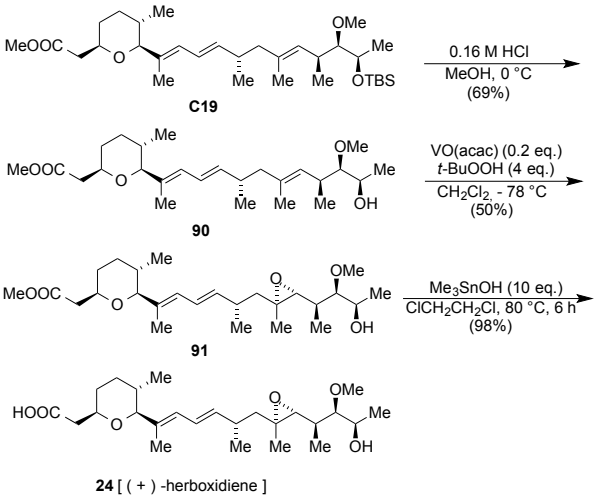


Scheme 16. Retrosynthetic analysis of (-)-aurafuron A (**21**)

More recently, Jiang and co-workers developed a concise, efficient and enantioselective formal synthesis of (-)-hamigeran B (**22**).[99] Compound **C17**, which had been previously converted to **22** in 5 steps,[129] was prepared almost in quantitative yield by $Pd(PPh_3)_4$-catalyzed coupling of isopropenyl boronate **A18** with alkenyl bromide **B19** in a mixture of EtOH, water and toluene at 90 °C in the presence of Na_2CO_3 as the base (entry 20, Table 2).[99] The key steps of this formal synthesis, which was free of protecting groups, involved an intermolecular Pauson-Kand reaction and a reductive Claisen rearrangement, which allowed the construction of the chiral quaternary carbon of the natural product.[99]

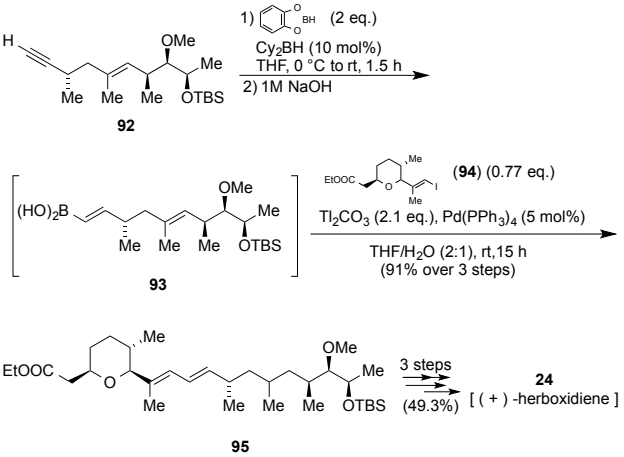
Taj and Green had previously employed the $Pd(PPh_3)_4$-catalyzed S.-M. reaction of alkenyl boronate **A18** with naphthyl bromide **B20** to prepare compound **C18**, an early precursor to racemic microstegiol (**23**).[100] The cross-coupling reaction, which was performed in a mixture of DME and water in the presence of LiCl and by using K_2CO_3 as the base, gave compound **C18** in 80% yield (entry 21, Table 2).[100]

In 2011, a stereoselective convergent synthesis of (+)-herboxidiene (**24**) was accomplished by Gosh and Li assembling the core structure of this natural compound by a S.-M. reaction between chiral pinacol boronate **A19** and (*E*,2*R*,5*S*,6*S*)-vinyl iodide **B21** in the presence of 5 mol% $Pd(PPh_3)_4$ (entry 22, Table 2).[101a] The Pd-catalyzed cross-coupling reaction provided compound **C19** in 71% yield, which was then converted into **24** via a 3-step reaction sequence involving treatment of **C19** with 0.16 M HCl in MeOH, epoxidation of the resulting alcohol **90** with *t*-BuOOH in CH_2Cl_2 at -78 °C in the presence of a catalytic amount of VO(acac) which gave oxirane **91** and subsequent reaction of this compound with 10 equiv of Me_3SnOH (Scheme 17).[101a]



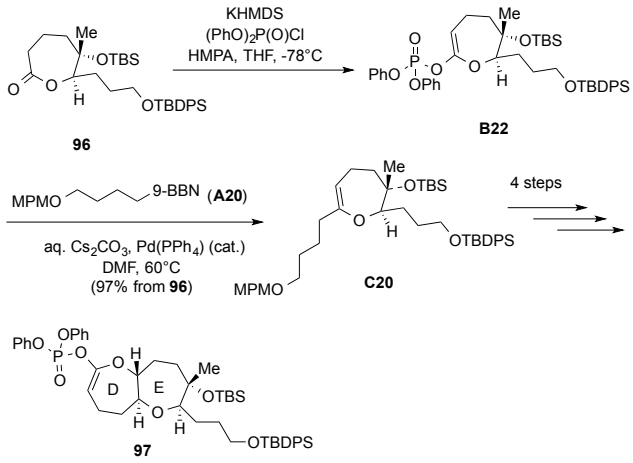
Scheme 17. Synthesis of (+)-herboxidiene (**24**) from compound **C19**

In the same year, Romea, Urpi and co-workers described a total synthesis of **24** via a multistep reaction sequence that involved hydroboration of alkyne **92** with catecholborane in the presence of a catalytic amount of dicyclohexylborane followed by hydrolysis of the resulting boronate.[101b] The $Pd(PPh_3)_4$-catalyzed coupling of the resulting boronic acid **93** with vinyl iodide **94** in a mixture of THF and water in the presence of Tl_2CO_3 as the base provided compound **95** in 91% yield. Finally, removal of the silyl protecting group and epoxidation of the resulting bis-homoallylic alcohol followed by saponification of the ethyl ester group furnished (+)-herboxidiene (**24**) in 49.3% yield from **95** (Scheme 18).[101b]



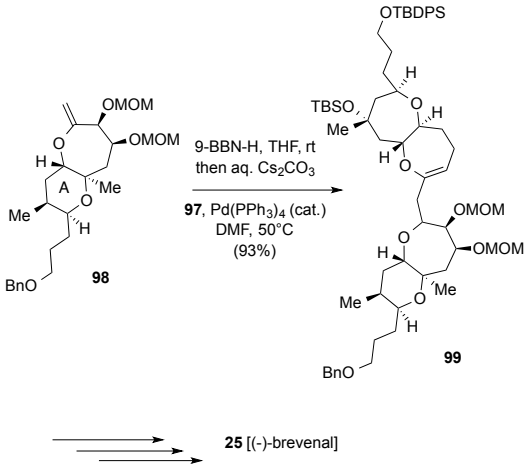
Scheme 18. Synthesis of (+)-herboxidiene (**24**) from 1-alkyne **92**

In the same year, Ebine, Fuwa and Sasaki described a concise total synthesis of (-)-brevenal (**25**) and accomplished the preparation of the DE-ring fragment **97** of this pentacyclic polyether through the $Pd(PPh_3)_4$-catalyzed S.-M. reaction illustrated in entry 23 of Table 2.[102] In particular, the DE-ring enol phosphate **97** was prepared from the cross-coupling product **C20** in 76.2% yield via a 4-step reaction sequence and enol phosphate **B22**, which was the electrophile used in the S.-M. reaction with alkylborane **A20**, was synthesized from lactone **96** as shown in Scheme 19.[102]



Scheme 19. Synthesis of compound **97** from lactone **96**

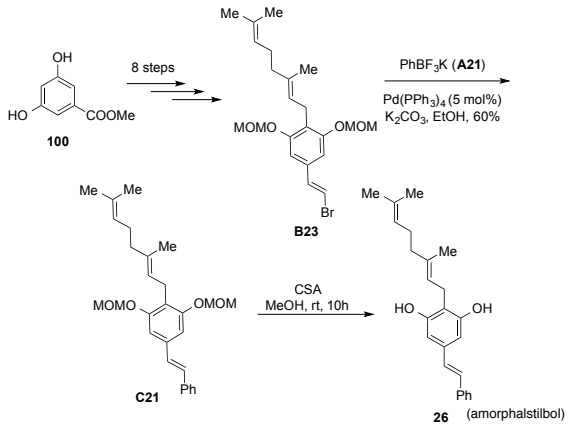
Compound **97** was then employed as the electrophile in the $Pd(PPh_3)_4$-catalyzed S.-M. reaction with the alkylborane generated by hydroboration of the AB-ring exocyclic ether **98** with 9-BBN-H. This reaction (Scheme 20) gave the endocyclic enol ether **100** in 93% yield as a single stereoisomer, which was an advanced precursor to **25**.[102]



Scheme 20. Synthesis of (-)-brevenal (**25**) via $Pd(PPh_3)_4$-catalyzed S.-M. reaction between compound **97** and the alkylborane generated from **98**

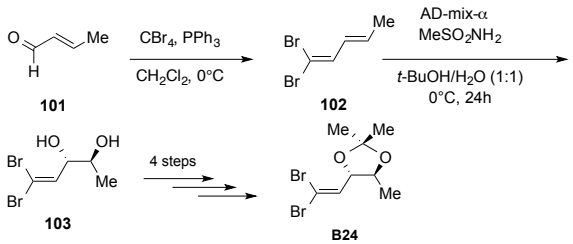
In 2012, Ham and co-workers synthesized (*E*)-styryl bromide **B23** starting from methyl 3,5-dihydroxybenzoate (**100**) and employed this bromo derivative as electrophile in a $Pd(PPh_3)_4$-catalyzed reaction with potassium phenyltrifluoroborate (**A21**).[103] The coupling, which was performed under the conditions reported in entry 24 of Table 2, gave compound **C21**, which was then converted

into amorphastilbol (**26**), a natural compound having a C-genarylated 4'-dihydroxyveratrol structure, by treatment with 10-camphorsulfonic acid (CSA) in methanol at room temperature (Scheme 21).[103]



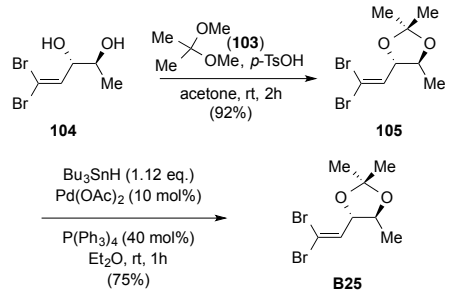
Scheme 21. Synthesis of amorphastilbol (**26**) from compound **100**

In the same year, Hsu and Lin described the first enantioselective syntheses of (+)-cladoacetal A (**27**) and (-)-cladoacetal B (**28**) in nine and seven steps, respectively.[104] A key feature of the synthesis of **27** was the $Pd(PPh_3)_4$-catalyzed reaction between boronic acid **A22** and (*Z*)-vinyl bromide **B24**, which produced compound **C22** in 81% yield (entry 25, Table 2). Compound **B24** was in turn prepared from crotonaldehyde (**101**) using a 6-step reaction sequence in which compound **103** was obtained by Sharpless asymmetric dihydroxylation of dibromoalkene **102** using AD-mix-α (Scheme 22).[104] The developed protocol also involved the selective protection of the hydroxyl group at C-2 in **103** followed by inversion of the configuration of the allylic hydroxyl group under Mitsunobu conditions.



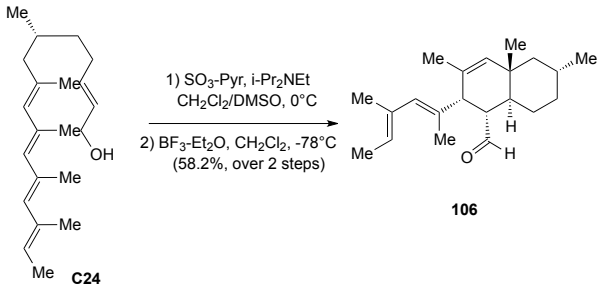
Scheme 22. Synthesis of compound **B24** from crotonaldehyde (**101**)

On the other hand, a key step in the total synthesis of (-)-cladoacetal B (**28**) was the S.-M. coupling of **A22** with *Z*)-vinyl bromide **B25** (entry 26, Table 2).[104] The latter compound was obtained by protection with 2,2-dimethoxypropane (**103**) of diol **104** as isopropylidene ketal **105** and subsequent hydrogenolysis of the resulting compound **105** by Pd-catalyzed reaction with Bu_3SnH (Scheme 23).[104]



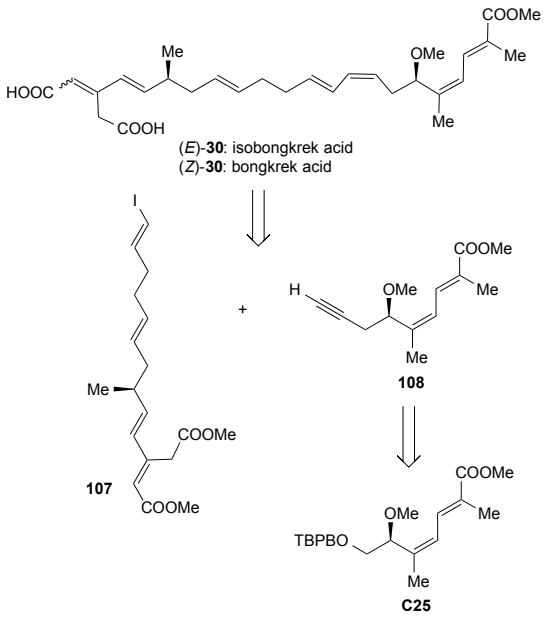
Scheme 23. Synthesis of compound **B25** from diol **104**

More recently, Uchiro and co-workers investigated the first total synthesis of oteromycin (**29**), an antagonist of the endothelian receptor,[105] and in this context they synthesized the conjugated tetraene **C24** in 72% yield by the $Pd(PPh_3)_4$-catalyzed S.-M. reaction of trienyl catecholborane **A23** with vinyl iodide **B26** (entry 27, Table 2). Oxidation of **C24** by using SO_3-pyridine complex gave the corresponding aldehyde, which by treatment with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at -78 °C, gave the *endo*-type cyclization product **106** with almost perfect stereoselectivity (Scheme 24). The decalin aldehyde **106** was then used as a key precursor to **29**.[105] In this study it was also established that the stereochemistry at C24 position of oteromycin (**29**) is the *S*-configuration.[105]



Scheme 24. Synthesis of the decalin aldehyde **106** from compound **C24**

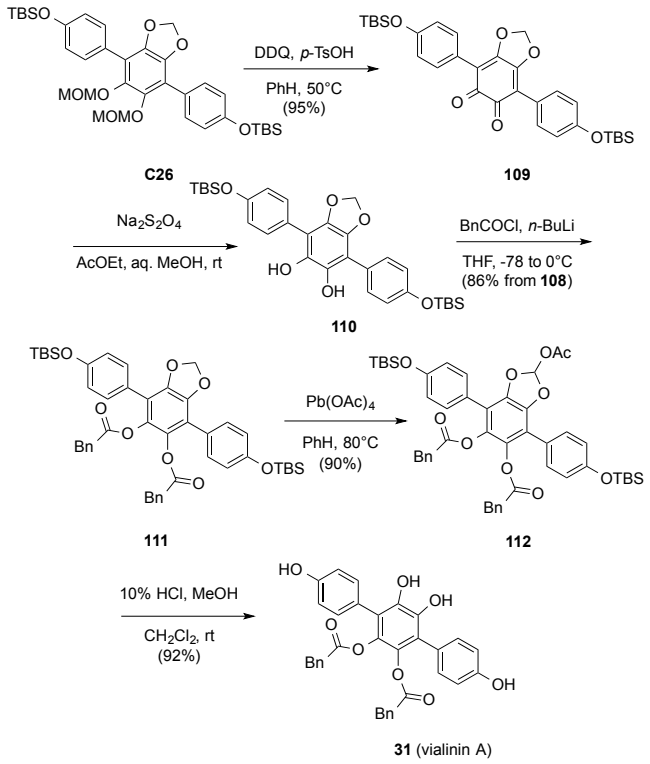
Ley and co-workers had previously carried out the total syntheses of isobongkreic acid [(*E*)-**30**] and bongkreic acid [(*Z*)-**30**] on the basis of the retrosynthetic analysis depicted in Scheme 25 in which the target compounds were obtained via a Sonogashira coupling of vinyl iodide **107** with 1-alkyne **108** and compound **C25** was an intermediate in the synthesis of the latter compound.[106a]



Scheme 25. Retrosynthesis of isobongkreic acid [(*E*)-**30**] and bongkreic acid [(*Z*)-**30**]

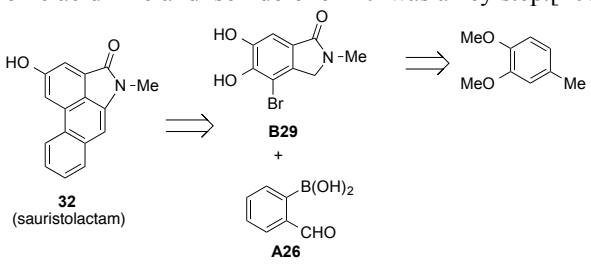
As shown in entry 28 of Table 2, compound **C25** was obtained in 92% yield by the S.-M. reaction of vinyl iodide **B27** with boronic ester **A24**, which was carried out under the modified Kishi conditions.[130] Remarkably, only when these conditions involving the use of TlOEt as the base were employed, a complete stereospecific coupling occurred.[106a] It is also likely that the thallium base was employed because of the reported acceleration the counter cation carries on transmetalation.[106b]

In 2010, vialinin A (**31**), a powerful inhibitor of TNF-α production, was synthesized by Takahashi and co-workers through a series of reactions involving the double S.-M. coupling of bis-triflate **B28** with boronic acid **A25**.[107] The reaction (entry 29, Table 2), which was carried out in the presence of 5.2 mol% $Pd(PPh_3)_4$, gave compound **C26** in an excellent yield. Treatment of **C26** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of *p*-TsOH in benzene at 50°C provided *o*-quinone **109**, which by reduction with $Na_2S_2O_4$ gave the corresponding catechol **110** (Scheme 26). Compound **111**, which was obtained by acylation of **110**, underwent reaction with 2.5 equiv of $Pb(OAc)_4$ in benzene at 80 °C to provide **112** in a high yield. Finally, exposure of **112** to mild acidic conditions gave vialinin A (**31**) (Scheme 26).[107]



Scheme 26. Synthesis of vialinin A (**31**) from compound **C26**

A year later, an efficient and practical synthesis of the naturally-occurring alkaloid sauristolactam (**32**) was accomplished by Heo and co-workers on the basis of the retrosynthesis shown in Scheme 27 in which a S.-M. coupling/aldol condensation cascade reaction involving boronic acid **A26** and isoindolone **B29** was a key step.[108]

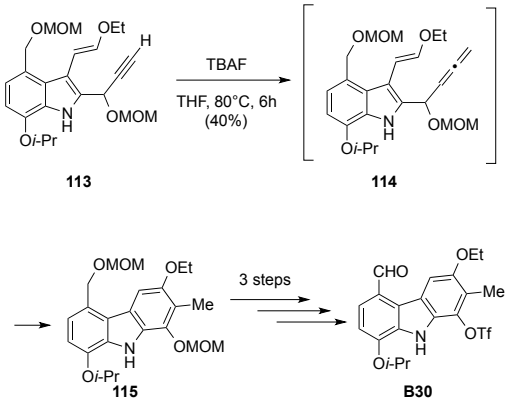


Scheme 27. Retrosynthesis of sauristolactam (**32**)

As shown in entry 30 of Table 2, the reaction of **B29** with **A26**, which was performed in a mixture of toluene and EtOH under microwave irradiation in the presence of 4 mol% $Pd(PPh_3)_4$ and 3 equiv of Cs_2CO_3, provided **32** in 80% yield.[108]

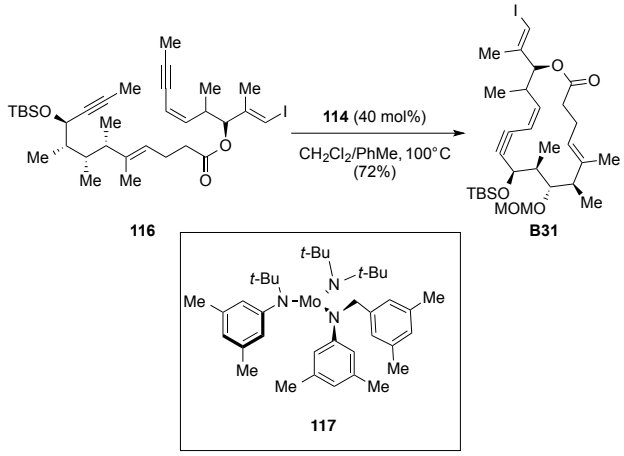
In 2010, Choshi, Hibino and co-workers described a total synthesis of the neuronal cell protecting carbazole alkaloid carbazomadurin A (**33**) in which the (*E*)-alkenyl side chain at the C1 position of carbazole was introduced by the $Pd(PPh_3)_4$-catalyzed reaction of pinacol boronate **A27** with triflate **B30** (entry 31, Table 2).[109] Unfortunately, the detailed experimental conditions of the coupling, which was carried out in DMF using Na_2CO_3 as base to provided compound **C27** in almost quantitative yield, were not

reported. Carbazole **115**, which was a precursor to **B30**, was obtained from the 2-allenyl indole intermediate **114** generated by treatment of propargyl indole **113** with TBAF in THF at 80 °C (Scheme 28).[109]



Scheme 28. Synthesis of carbazole triflate **B30** from compound **113**

In 2012, Fürstner and co-workers reported the first total synthesis of the structurally challenging and biologically highly promising antimitotic agent leiodermatolide (34).[110] Compound **C28**, an advanced intermediate to **34**, was synthesized in 56% yield by the $Pd(PPh_3)_4$-catalyzed reaction of boronate **A28** with vinyl iodide **B31** (entry 32, Table 2). The latter compound was obtained in 72% yield by intramolecular metathesis of compound **116** in the presence of 40 mol% of the molybdenum complex **117** activated with CH_2Cl_2 (Scheme 29).[131]



Scheme 29. Synthesis of vinyl iodide **B31**

Remarkably, this total synthesis allowed for a conclusive assignment of the stereostructure of leiodermatolide.[110

]More recently, Helquist and co-workers accomplished an enantioselective synthesis on a gram scale of the potent histone deacetylase inhibitor (*R*)-trichostatin A (**35a**).[111] The synthetic intermediate **C29** was synthesized by $Pd(PPh_3)_4$-catalyzed coupling of methyl (*E*)-3-bromopropenoate (**B32**) with the organoboron compound **A29** followed by saponification (entry 33, Table 2). Compound **A29** was in turn prepared by treatment of alkyne **118** (Figure 6) with (-)-Ipc_2BH in THF at 0 °C.[111]

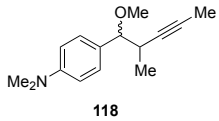
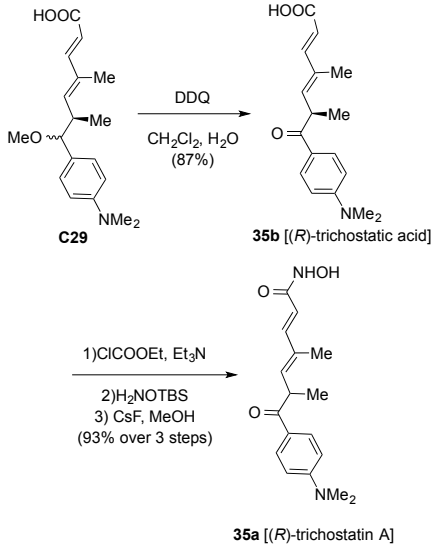


Figure 6. Structure of alkyne **118**

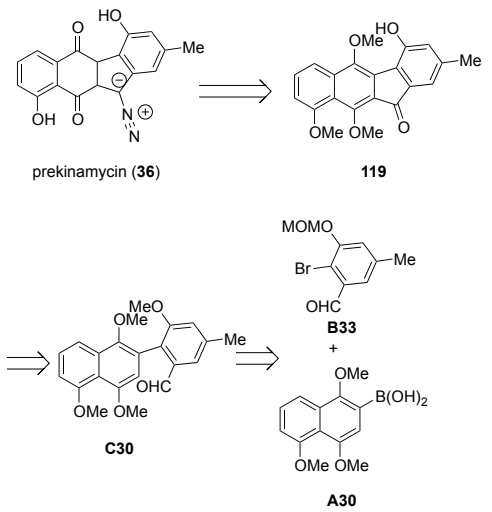
Compound **C29** was then treated with DDQ to give (*R*)-trichostatic acid (**35b**), which was converted to (*R*)-trichostatin (**35a**) by conversion to a mixed anhydride followed by reaction with *O*-*t*-butyldimethylsilyl (TBS) hydroxylamine and subsequent *O*-desilylation (Scheme 30).[111]



Scheme 30. Synthesis of (*R*)-trichostatic acid (**35b**) and (*R*)-trichostatin A (**35a**)

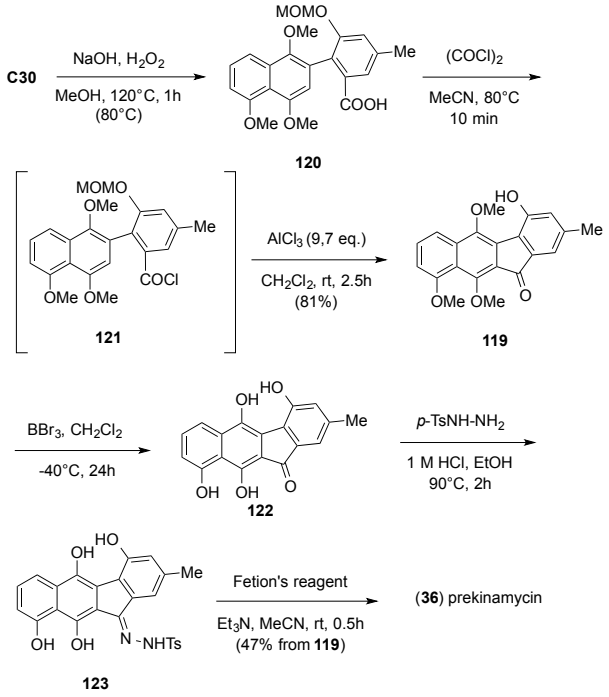
It should be noted that trichostatic acid of unknown absolute configuration is a natural product first isolated from *Streptomyces sioyaensis*, which was found to induce differentiation of leukemia cells.[132]

In 2011, Kumamoto and co-workers accomplished a total synthesis of the naturally-occurring diazoalkane prekinamycin (**36**) on the basis of the retrosynthetic analysis illustrated in Scheme 31.[112]



Scheme 31. Retrosynthesis of prekinamycin (**36**)

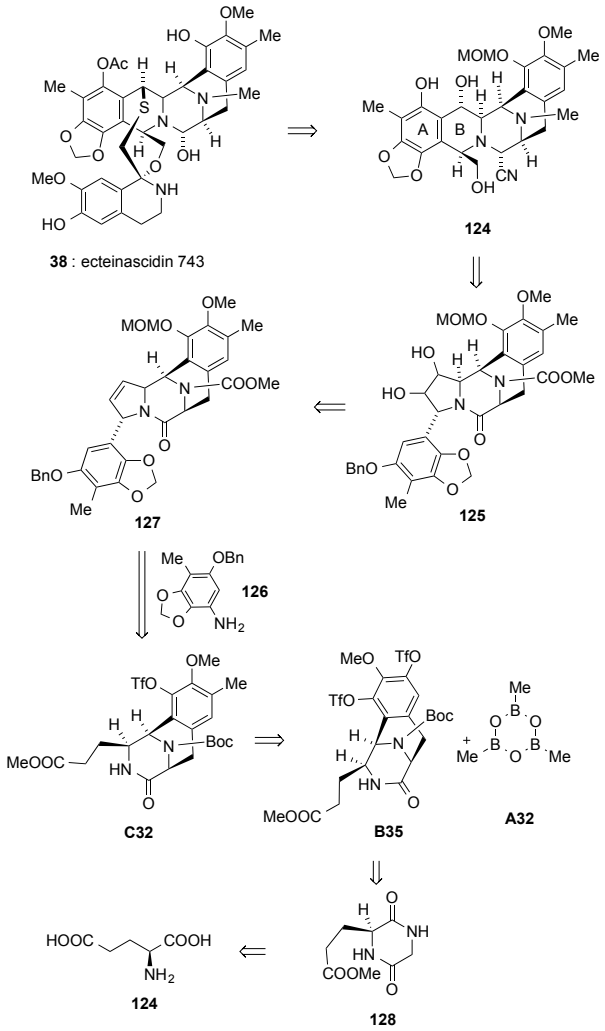
As shown in entry 34 of Table 2, compound **C30**, a precursor to **36**, was synthesized in an excellent yield by the reaction of boronic acid **A30** with aryl bromide **B33** in DME at 90 °C in the presence of Na_2CO_3 as base and 2.7 mol% $Pd(PPh_3)_4$. Aldehyde **C30** was then converted into the corresponding carboxylic acid **120** using the system H_2O_2/NaOH. Treatment of **120** with oxalyl chloride in MeCN at 80 °C gave crude **121**, which was reacted with 9.7 equiv of $AlCl_3$ in CH_2Cl_2 at room temperature providing **119** in 81% yield (Scheme 32). Demethylation of **119** with BBr_3 in CH_2Cl_2 at -40 °C gave tetraol **122**, which was converted into hydrazone **123** by treatment with $TsNHNH_2$. Finally, oxidation of **123** with Fetizon's reagent (Ag_2CO_3 on Celite®) provided prekinamycin (**36**) in 47% yield from **123** (Scheme 32).[112]



Scheme 32. Synthesis of prekinamycin (**36**) from compound **C30**

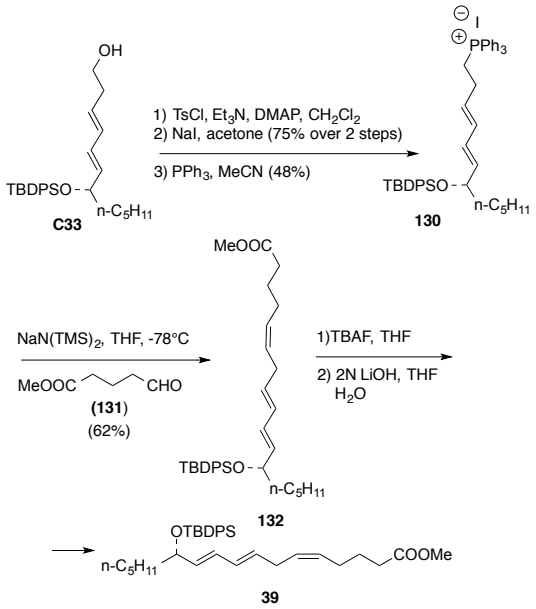
In 2013, Nishikawa and co-workers employed the S.-M. reaction illustrated in entry 35 of Table 2, involving boronic acid **A31** and the dibromo derivative **B34**,[73b] to accomplish the synthesis of 3-methoxy-5,6-diphenyl-3,5.-dien-1,2-dione (**37**), an *ortho*-quinone believed to be a natural product isolated from *Phoma* sp.[73a] However, the NMR spectra of synthetic **37** were found to be not identical to those reported for the compound isolated from *Phoma* sp..[73b

]Still in 2013, Fukuyama and co-workers investigated the synthesis of the architectural complex tetraisoquinoline alkaloid ecteinascidin 743 (trabectedin) (**38**),[113] which is an antitumor agent of marine origin with peculiar cytotoxic activity *in vitro* and *in vivo* in a wide range of tumours.[133] The impressive total synthesis of **38**, which was accomplished in 28 steps and 1.1% overall yield starting from *L*-glutamic acid (**129**) as a single homochiral source according to the retrosynthetic analysis shown in Scheme 32,[113] featured the construction of the B ring of compound **124** via a reaction sequence involving a stereoselective Heck reaction between enamide 121 and the diazonium salt prepared from amine **126**, followed by an osmium-mediated dihydroxylation of the resulting compound which gave 1,2-diol **125** in 93% yield based on **121**. Enamide **121** was in turn synthesized from **C32**, the cross-coupling product obtained in 91.6% yield by the S.-M. reaction between **B35** and **A32** (entry 36, Table 2). Compound **C32** was prepared via a 6-step reaction sequence from diketopiperazine **128** available from *L*-glutamic acid (**129**) (Scheme 32).[113]



Scheme 32. Retrosynthesis of ecteinascidin 743 (**38**)

The S.-M. reaction between vinylborane **A33** and (*E*)-vinyl iodide **B36**, illustrated in entry 37 of Table 2, was used by Kobayashi and co-workers for the construction of the (8*E*,10*E*) moiety of (*S*,5*Z*,8*E*,10*E*)-12-hydroxyheptadeca-5,8,10-trienoic acid (12*S*-HTT) (**39**).[114] Iodide (*S*)-**B36** was obtained by kinetic resolution of the corresponding racemic compound according to the literature[134] by using the Sharpless asymmetric epoxidation. Compound **C33** resulting from treatment of the crude cross-coupling product with TBAF was then converted into **39** via the series of reactions illustrated in Scheme 33 in which the 5*Z* double bond of the target compound was constructed by the Wittig reaction of aldehyde **131** with the ylid obtained by treatment of phosphonium iodide **130** with $NaN(TMS)_2$ at -78 °C in THF. This reaction provided compound **132** in 62% yield.[114]



Scheme 33. Synthesis of compound (12*S*-HTT) (**39**) from dienol **C33**

Very recently, Coshi, Hibino and co-workers accomplished the total synthesis of (*S*)(+)-carbazomadurin B (**40**) via a series of 18 reactions in which the preparation of the carbazole ring of the natural product included an allene-mediated electrocyclic reaction of the 6π-electron system involving the indole 2,3-bond.[115] As in the case of the total synthesis of carbazomadurin A (**33**), the alkenyl chain at the 1-position of the carbazole ring of **40** was introduced via the $Pd(PPh_3)_4$-catalyzed S.-M. reaction between the organoboron derivative **A34** and triflate **B37** that gave compound **C34** in 83% yield (entry 38, Table 2).[115]

In 2013, Kato and coworkers accomplished a total synthesis of (+)-gregatin B (**41**) by a synthetic approach in which this phytotoxic fungal metabolite was obtained in 80% yield by the stereoselective $Pd(PPh_3)_4$-catalyzed reaction of alkenyl boronate **A35** with alkenyl iodide **B38** under the condition reported in entry 39 of Table 2.[116] The synthesis of **B38** was achieved in 8 steps and 29.3% overall yield from optically active propargyl acetate **130** (Figure 7),[116] which in turn was prepared I 7 steps according to the literature.[135]

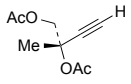
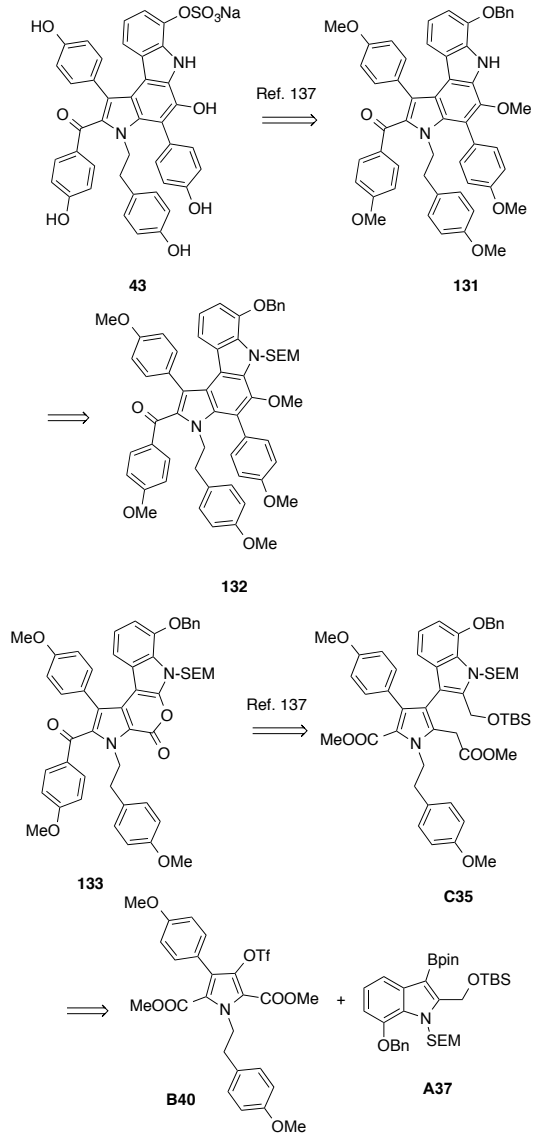


Figure 7. Structure of compound **130**

In 2010, Suh and co-workers described the total synthesis of both enantiomers of rodgersinol (**42**),[117] a 2-arylpropanol natural product. The final step of the synthesis of (*S*)-**42** consisted of the $Pd(PPh_3)_4$-catalyzed reaction of aryl iodide (*S*)-**B39** having 91% ee with (*E*)-propenylboronic acid (**A36**) (entry 40, Table 2). The coupling, which occurred

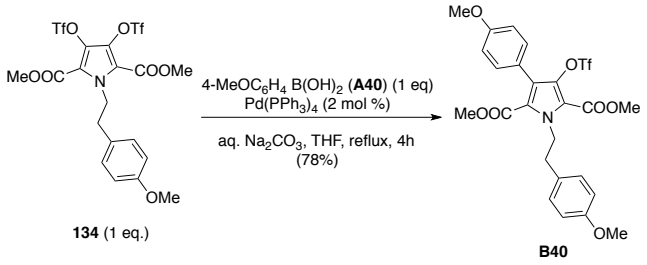
with simultaneous removal of the TBS protecting group, provided **42** as a 6.5 : 1 mixture of *E* and *Z* stereoisomers. However, the $PdCl_2(MeCN)_2$-catalyzed olefin isomerization of the mixture allowed to obtain (*S*)-**42** as an exclusive *E*-stereoisomer.[117] It should be noted that Suh and co-workers had previously reported the first synthesis of (*S*)-rodgersinol in seven linear steps in 31% overall yield[136] and that this synthesis allowed the authors to determine the C-10 absolute configuration of the natural product.

Still in 2010, Ishibashi and co-workers carried out a formal synthesis of the telomerase inhibitory marine pyrrolocarbazole alkaloid dictyodendrin B (**43**).[118] The synthesis of compound **131**, which had previously been employed as a precursor to **43**,[137]was accomplished according to the retrosynthetic analysis shown in Scheme 34.[118]



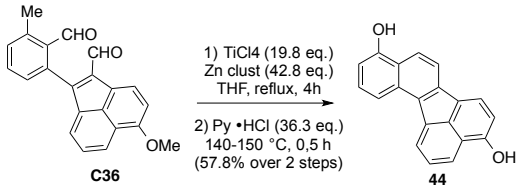
Scheme 34. Retrosynthetic analysis of dictyodendrin B (**43**)

In particular, compound **C35**, which was prepared in 72% yield by $Pd(PPh_3)_4$-catalyzed S.-M. reaction of triflate **B40** with boronate **A37** (entry 41, Table 2), was converted in two steps into lactone **133**, which provided compound **131** via a 6-step reaction sequence involving the SmI_2-promoted pinacol coupling[138] of pyrrole **132.**[118] Triflate **B40** had previously been synthesized in 78% yield by $Pd(PPh_3)_4$-catalyzed monoarylation of bistriflate **134** with 1 equiv of 4-methoxyphenylboronic acid (**A40**) (Scheme 35).[139]



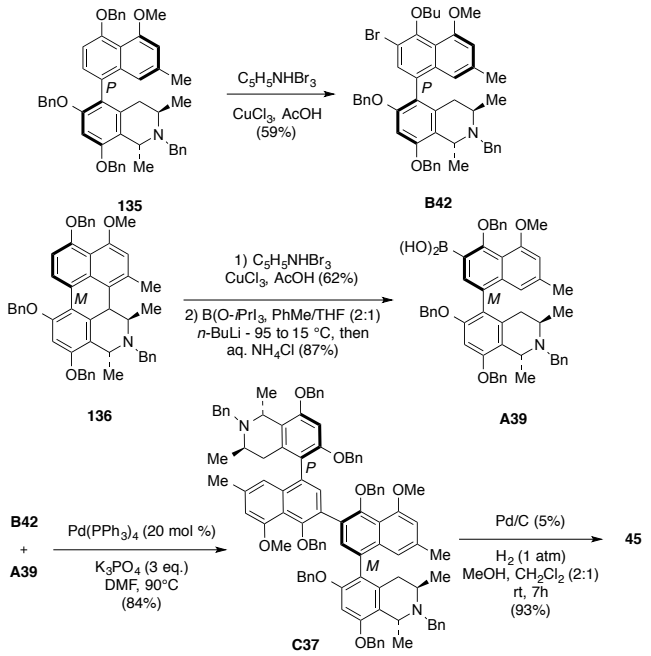
Scheme 35. Synthesis of compound **B40** from bistriflate **134**

In 2013, Dallavalle and co-workers described the first total synthesis of naturally-occurring benzo[*j*]fluoranthene-4,9-diol (**44**).[119] It involved the $Pd(PPh_3)_4$-catalyzed S.-M. reaction between boronate **A38** and 2-bromo-6-methoxyacenaphthylene-1-carbaldehyde (**B41**) (entry 42, Table 2) as a crucial step. Treatment of the resulting cross-coupling product, **C36**, with $Zn/TiCl_4$ in THF[140] under McMurry conditions, followed by deprotection of the hydroxy groups using pyridine hydrochloride at 140–150 °C gave compound **44** in 57.8 yield (Scheme 36).[119]



Scheme 36. Synthesis of compound **44** from **C36**

Still in 2013, Tang and co-workers developed an efficient synthesis of michellamine B (**45**) from the advanced intermediates **135** and **136** (Scheme 37).[120] Compound **135** was converted into bromide **B42** by treatment with $C_5H_5NHBr_3$ in $CHCl_3$ and AcOH and compound **136** gave boronic acid **A39** by bromination with $C_5H_5NHBr_3$ and metal-halogen exchange, followed by treatment with B(O-*i*Pr)$_3$ and hydrolysis of the resulting boronic ester. The S.-M. reaction between **B42** and **A39** in the presence of a catalytic amount of $Pd(PPh_3)_4$ gave compound **C37** in 84% yield (entry 43, Table 2). Finally, removal of all benzyl groups of **139** by Pd/C-catalyzed hydrogenolysis led to compound **45** in 93% yield (Scheme 37).[120]



Scheme 37. Synthesis of michellamine B (**45**) from compounds **135** and **136**

2. TOTAL SYNTHESES VIA S.-M. REACTIONS PROMOTED BY $PdCl_2(PPh_3)_2$ OR A COMBINATION OF PPh_3 WITH $Pd(OAc)_2$ OR $Pd_2(dba)_3$

$PdCl_2(PPh_3)_2$ or systems composed by a combination of $Pd(OAc)_2$ with PPh_3 have frequently been used as catalyst precursors of S.-M. couplings due to their stability and favourable activity.[141,142] They are known to be readily reduced to active Pd(0) species by organoboron reagents or PPh_3. However, reduction of $PdCl_2(PPh_3)_2$ yields not $Pd(PPh_3)_2$ but several anionic species in equilibrium of the types $[PdCl_2(PPh_3)_2]^{2-}$, $[PdCl(PPh_3)_2]^-$ and $[Pd(\mu Cl)(PPh_3)_2]^{2-}$, which are formed in the presence of chloride ions.[143] These species have been thought to undergo oxidative addition more rapidly than does $Pd(PPh_3)_3$. Similarly, the acetate anions introduced through $Pd(OAc)_2$ give the anionic species $Pd(PPh_3)_2(OAc)^-$ in the reduction of $Pd(OAc)_2$ with PPh_3 in DMF.[144]

On the contrary, the catalyst system consisting of a combination of PPh_3 and $Pd_2(dba)_3$, an air stable Pd(0) compound which is considered as a source of Pd(0) complexes formed upon interaction with suitable ligands and substitution of dba,[145] has been relatively little used in S.-M. reactions to date.[146]

Table 3 lists the structures of the natural products **137–152** which have been synthesized via S.-M. reactions involving the use of a catalyst precursor consisting of $PdCl_2(PPh_3)_2$ or a combination of PPh_3 with $Pd(OAc)_2$ or $Pd_2(dba)_3$. Table 3 also reports the literature data on the isolation of these natural products.

TABLE 3 HERE

Fosfotriecin (**137**) is a phosphorylated polyene derivative isolated from *Streptomyces pulveraceous,*[147] which was shown to possess significant activity against tumor cell lines[148a] and antitumor activity against leukemia *in vivo*.[148b] In 2010, Gao and O'Doherty achieved an enantioselective total synthesis of **137** in 24 steps starting from 2-penten-4-yn-1-ol (**153**) (Figure 8).[149]

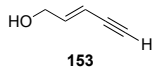
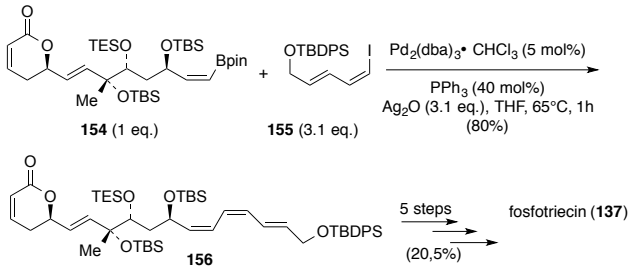


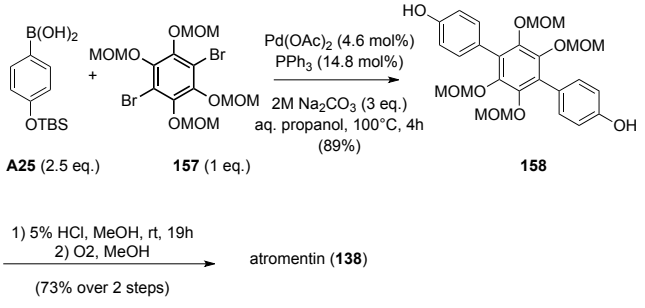
Figure 8. Structure of compound **153**

The conjugated *E,Z,Z*-triene moiety of the natural product was introduced with excellent stereoselectivity (>20 : 1) by the $Pd(PPh_3)_4$-catalyzed reaction of vinyl boronate **154** with dienyl iodide **155** in the presence of 3.1 equiv of Ag_2O, 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ and 40 mol% PPh_3. As shown in Scheme 38, the coupling reaction provided compound **180** in 80% yield. The latter compound was an advanced intermediate in the synthesis of fosfotriecin (**137**).[149]



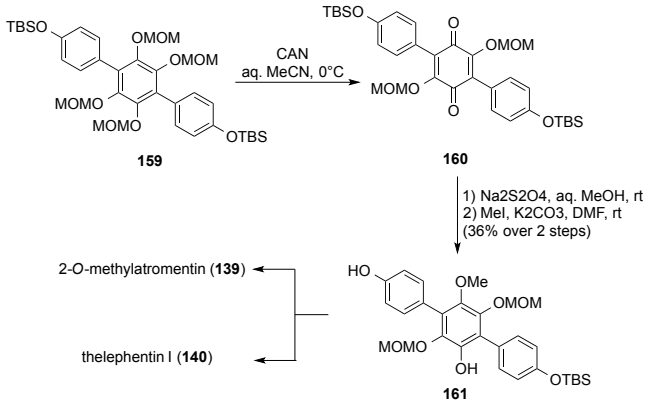
Scheme 38. Synthesis of compound **156**, an advanced intermediate in the synthesis of fosfotriecin (**137**)

Still in 2010, Takahashi and co-workers established the structure of the natural pigment atromentin (**138**) via a total synthesis based on a double S.-M. reaction and X-ray analysis of the synthetic material thereby obtained.[150] Compound **138** had been isolated from the edible mushroom *Thelephora ganbajun*[151a] and from the inedible mushrooms *T. aurantiotincta*[151b,c] and *Hydnellum caeruleum.*[151d] The total synthesis of **138** featured the $Pd(OAc)_2/PPh_3$-catalyzed reaction between 2 equiv of boronic acid **A25** and dibromobenzene **157** in aqueous propanol at 100 °C in the presence of Na_2CO_3 as the key step (Scheme 39).[150] Acidic hydrolysis of the resulting product **158** and subsequent oxidation with dioxygen in methanol provided compound **138** (Scheme 39).[150]



Scheme 39. Synthesis of atromentin (**138**) from compounds **A25** and **157**

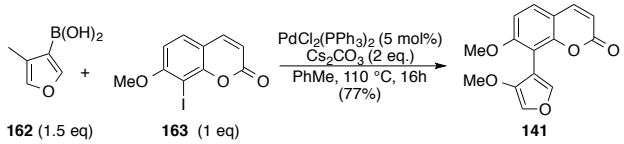
Remarkably, the S.-M. coupling occurred with deprotection of the TBS-protected hydroxyl groups.[150] However, when the $Pd(OAc)_2/PPh_3$-catalyzed reaction of **A25** with **157** was carried out in aqueous THF at 70 °C in the presence of K_3PO_4, TBS ether **159** was obtained in 84% yield. Compound **159** was then selectively oxidized with cerium ammonium nitrate (CAN) providing compound **160** in 86% yield. Reduction of **160** with $Na_2S_2O_4$ in MeOH followed by treatment of the hydroquinone thereby obtained with MeI/K_2CO_3 furnished compound **161** in 36 % yield. Compound **161** was an advanced precursor to 2-*O*-methylatromentin (**139**) and telephantin I (**140**) (Scheme 40).[150]



Scheme 40. Synthesis of naturally-occurring compounds **139** and **140**

2-*O*-Methylatromentin (**139**) and telephantin I (**140**) are two *p*-terphenyl derivatives isolated from the methanolic extract of fruit bodies of the thelephoraceous basidiomycete *T. aurantiotincta.*[151c]

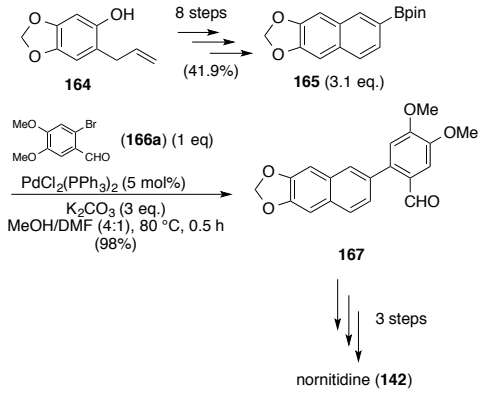
In 2012, the first total synthesis of 7-methyl-8-(4-methylfuryl)-2*H*-chromen-2-one (**141**), a natural product with antileishmanial activity recently isolated from the plant *Galipea panamensis* (Rutaceae),[152] was accomplished by Schmidt and co-workers using the $PdCl_2(PPh_3)_2$-catalyzed reaction of 4-methylfuran-3-ylboronic acid (**162**) with sterically congested 8-iodo-7-methoxy-2*H*-chromen-2-one (**163**) as the key step.[153] As shown in Scheme 41, the cross-coupling reaction gave the natural product in 77% yield.



Scheme 41. Synthesis of naturally-occurring compound **141** by S.-M. reaction

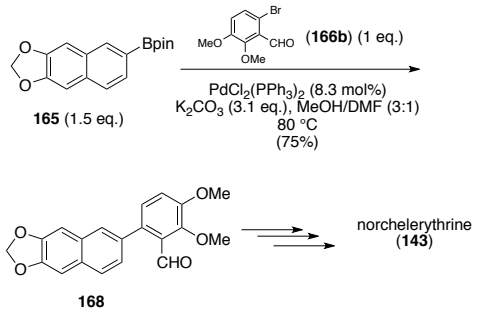
It was also found that $PdCl_2(PPh_3)_2$ was a better catalyst precursor compared to Pd/C and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$.[153]

In 2011, the $PdCl_2(PPh_3)_2$-catalyzed reaction between 3,4-dihydro-6,7-methylenedioxynaphthylboronic acid (**165**) and aryl bromide **166a** was used to prepare compound **167**, [154] a precursor to nornitidine (**142**), a benzo[*c*]phenanthridine alkaloid isolated from the bark of *Zanthoxylum microcarpum* (Rutaceae).[155] As shown in Scheme 42, compound **165** was prepared in 41.9% yield via a 8-step protocol in which 2-allyl-4,5-methylenedioxyphenol (**164**) was the starting material and the cross-coupling reaction between **166a** and **165** gave compound **167** in an excellent yield.[154]



Scheme 42. Synthesis of nornitidine (**142**) via S.-M. reaction of boronate **165** with bromide **166a**

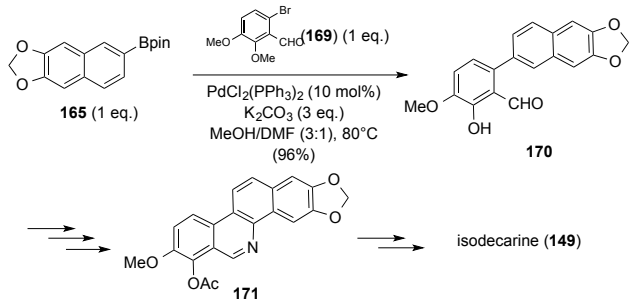
Pinacol boronate **165** was also used in the $PdCl_2(PPh_3)_2$-catalyzed reaction with 6-bromo-2,3-dimethoxybenzaldehyde (**166b**), which gave 6-(3,4-dihydroxy-6,7-methylenedioxy-2-naphthyl)-2,3-dimethoxybenzaldehyde (**168**) in 75% yield (Scheme 43). Compound **168** was then used as a precursor to norchelerythrine (**143**),[154] a cytotoxic alkaloid isolated from *Zanthoxylum integrifolium,*[156a] *Z. capense*[156b]and *Z. scadens.*[156c]



Scheme 43. Synthesis of compound **168**, a precursor to norchelerythrine (**143**)

Moreover, the $PdCl_2(PPh_3)_2$-catalyzed reaction between boronate **165** and 2-acetoxy-6-bromo-3-methoxybenzaldehyde (**169**) was employed by Coshi, Hibino and co-workers as the first step of a total synthesis of isodecarine (**149**),[154] another benzo[*c*]phenanthridine

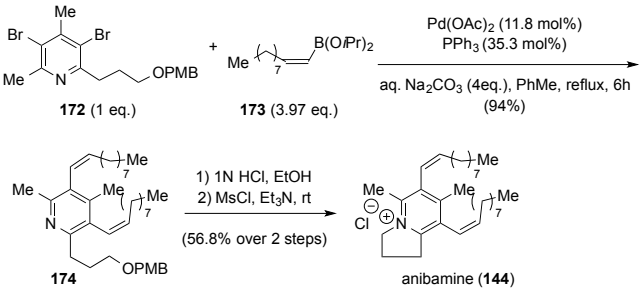
alkaloid isolated from *Z. integrifolium*.[156a] The cross-coupling reaction (Scheme 44) gave compound **170** in 96% yield.



Scheme 44. Synthesis of compound **170**, a precursor to isodecarine (**149**)

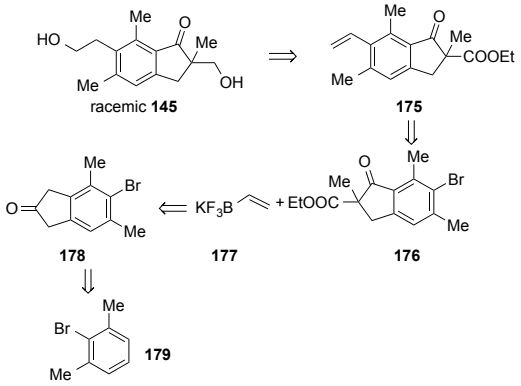
The conversion of **170** to isodecarine was achieved using a microwave-assisted electrocyclic reaction of the 2-acetoxy derivative of the benzaldoxime methyl ether prepared from **170** and subsequent dehydrogenation of the thereby obtained 10,11-dihydrobenzo[*cf*]phenanthridine **171**, followed by saponification.[154] It should be noted that a microwave-assisted electrocyclic reaction of 2-cycloalkenylbenzaldoxime methyl ethers as aza 6 π-electron systems was also employed as the key step in the synthesis of compounds **142** and **143** via aldehydes **166** and **168**.[154]

In 2011, Zhang and co-workers described a regio- and stereoselective synthesis of anibamine (**144**),[157] a pyridine quaternary alkaloid isolated from *Aniba panurensis* (Lauraceae),[158] which was found to effectively inhibit the chemokine receptor CC35 over-expressed in more aggressive forms of prostate cancer.[158a] The synthesis was achieved via a 7-step protocol in which the high yielding $Pd(OAc)_2/PPh_3$-catalyzed cross-coupling reaction between dibromopyridine **172** and diisopropyl (*Z*)-1-decenylboronate (**173**) in toluene and water under reflux in the presence of Na_2CO_3 as the base was a crucial step (Scheme 45). The coupling furnished compound **174** in 94% yield. Removal of the PMB protecting group from **174** under acidic conditions, followed by treatment of the resulting alcohol with MsCl and Et_3N at room temperature allowed ring closure providing **144** in 56.8% yield from **174** (Scheme 45).[157]



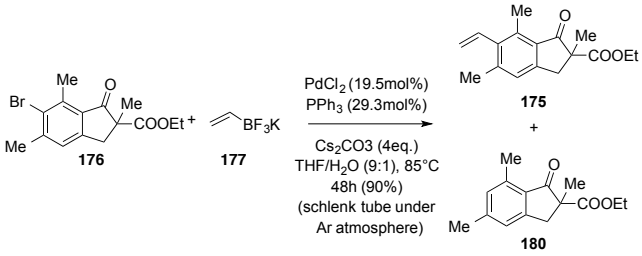
Scheme 45. Synthesis of anibamine (**144**) via S.-M. coupling of **177** with **173**

(2*S*)-Pterosin A (**145**) is a sesquiterpenoid present in *Pteridinium aquilinium* (bracken fern)[159] which revealed to be a potent hypoglycemic agent.[160] In 2013, Uang and co-workers reported a practical synthesis of the racemic form of this compund in 10% yield starting from commercially available 2-bromo-1,3-dimethylbenzene (**171**).[161] The synthesis was based on the retrosynthetic analysis shown in Scheme 46.[161]



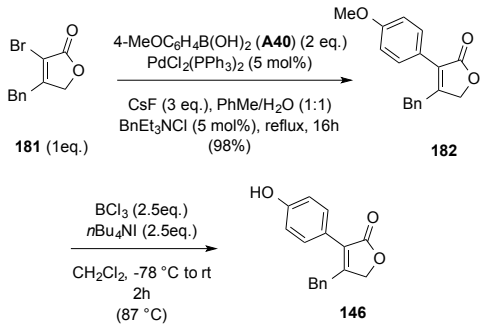
Scheme 46. Retrosynthesis of racemic pterosin A (**145**)

The $PdCl_2/PPh_3$-catalyzed reaction of the C6 bromoindanone **176** with vinyltrifluoroborate (**177**), which under the optimized conditions reported in Scheme 47 gave an inseparable 95:5 mixture of **175** and the reduction product **180** in 90 % yield, was the key step of the reaction. Compound **176** was in turn prepared from aryl bromide **179** via a 4-step reaction sequence in which **178** was an intermediate.



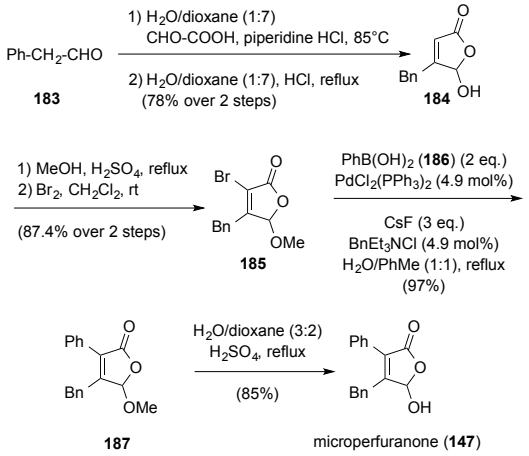
Scheme 47. S.-M. reaction between bromide **176** and potassium vinyltrifluoroborate (**177**)

In 2013, Hutchison and co-workers synthesized eutypoid A (**146**), a 4-benzyl-3-arylbutenoliode isolated from the marine fungus *Eutypa* sp. (#424),[162] using a series of 8 reactions in which compound **182**, the direct precursor to **146**, was obtained in 98% by $PdCl_2(PPh_3)_2$-catalyzed reaction of 4-benzyl-3-bromofuranone (**181**) with 4-methoxyphenylboronic acid (**A40**) in a refluxing mixture of toluene and water in the presence of CsF as base and a catalytic quantity of $BnEt_3NCl$ (Scheme 48).[163]



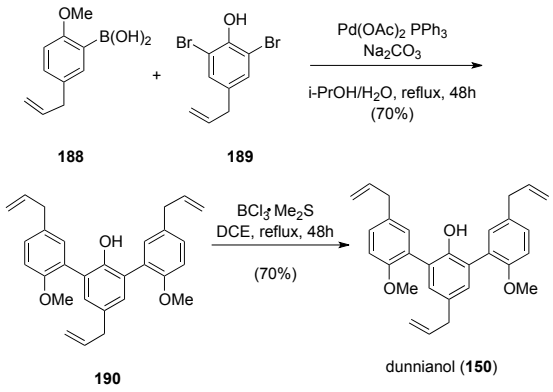
Scheme 48. Synthesis of eutypoid A (**146**) from butenolide **181**

It was also found that the reaction of **181** with phenylboronic acid (**186**) under experimental conditions similar to those illustrated in Scheme 48 gave in 91% yield gymnoascolide A (**148**),[163] a 4-benzyl-3-arylbutenolide isolated from the soil ascomycete *Gymnoascus reessii*[164a] and *Malbranchea filamentosa.*[164b] Moreover, the $PdCl_2(PPh_3)_2$-catalyzed reaction of 3-bromo-2(5*H*)-furanone **185** with phenylboronic acid (**186**) was employed to prepare 3-phenylfuranone **187** in an excellent yield. Acidic hydrolysis of the methoxyacetal moiety of **187** provided racemic microperfuranone (**147**) (Scheme 49), a butenolide isolated from the terrestrial and marine fungi *Anixiella micropertusa,*[165a] *Emericella quadrilineata,*[165b] and *E. nidulans.*[165c] As illustrated in Scheme 49, compound **184**, the direct precursor to **185**, was prepared from 3-phenylpropionaldehyde (**183**) via Mannich-type aminoalkylation and subsequent elimination reaction.[163]



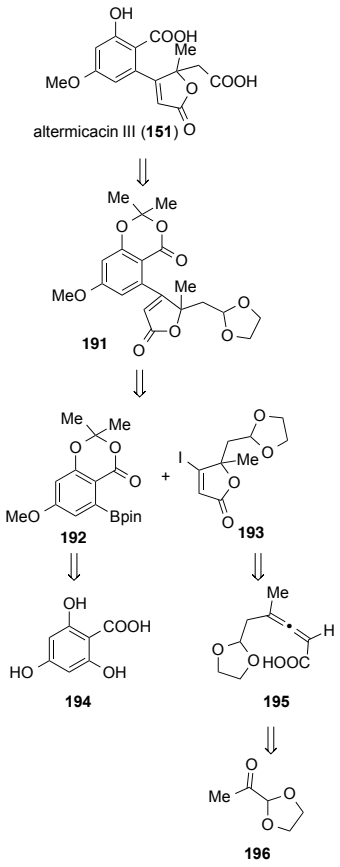
Scheme 49. Synthesis of microperfuranone (**147**) from aldehyde **183**

In 2010, Denton and Scragg described a concise synthesis of the neosesquilignan dunnianol (**150**),[166] a compound isolated from the bark of *Illicium dunnianum.*[167] The synthesis featured a $Pd(OAc)_2/PPh_3$-catalyzed double S.-M. reaction of boronic acid **188** with dibromobenzene **189** (Scheme 50). The reaction, which was carried out in a mixture of *i*-PrOH and water under reflux in the presence of Na_2CO_3 gave compound **190** in 70% yield without isomerization of the allyl groups. Subsequent *O*-demethylation of **190** with $BCl_3 \cdot Me_2S$ in refluxing DCE gave dunnianol (**150**) in 70% yield.[166] Unfortunately, the experimental details of the reactions summarized in Scheme 50 were not reported.



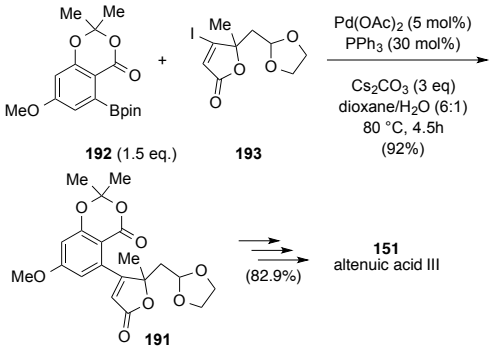
Scheme 50. Synthesis of dunnianol (**150**) from compounds **188** and **189**

In 2014, Podlech and co-workers elucidated the structure of altenuic acid III[168] a micotoxin isolated from the mold *Alternaria tenuis*,[169] and confirmed by total synthesis that the structure of this metabolite was that of compound **151**.[168] The convergent synthesis of **151** was accomplished according to the retrosynthetic analysis given in Scheme 51 where the key intermediate could be accessible by the S.-M. reaction of boronate **192** with alkenyl halide **193**.[168] Thus, boronate **192** was synthesized in 4 steps from phloroglucinic acid (**194**) according to a known procedure[170] and iodide **193** was prepared from the protected ketone **196** in 30.4% yield via a series of 4 reactions involving the halolactonization reaction of allenecarboxylic acid **195** with iodine.[168]



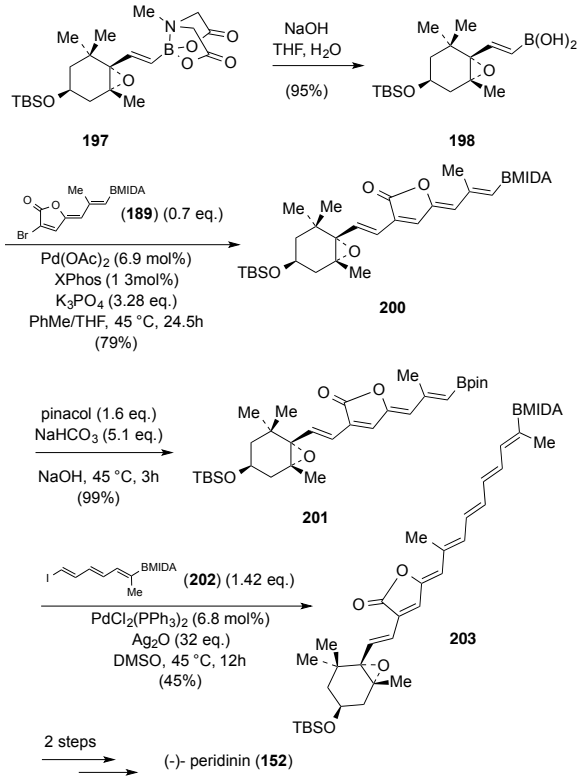
Scheme 51. Retrosynthesis of altenuic acid III (**151**)

The cross-coupling reaction of 1.5 equiv of **192** with 1 equiv of **193** in a mixture of dioxane and water at 80 °C in the presence of 3 equiv of Cs_2CO_3, 5 mol% $Pd(OAc)_2$ and 30 mol" PPh_3 gave compound **191** in 92% yield (Scheme 52). Subsequent deprotection of **191** with TFA at 0 °C and Jones oxidation of the aldehyde thereby obtained, followed by acetal cleavage with a large excess of BCl_3 in CH_2Cl_2 provided altenuic acid III (**151)** in 82.9 % yield based on **181** (Scheme 52).[168]



Scheme 52. Synthesis of altenuic acid III (**151**) via S.-M. cross-coupling of boronate **192** with iodide **193**

In 2010, iterative S.-M. cross-coupling reactions were employed by Burke and co-workers in a stereoselective synthesis of (-)-peridinin (**152**),[171] the major light-harvesting pigment of planktonic dinoflagellates,[172] which is the major biological carotenoid quencher of singlet oxygen in marine algae *Gonyaulax* polyedra173 and is distinguished by its antitumor activity.[174] The $PdCl_2(PPh_3)_2$-catalyzed reaction of pinacol ester **201** with trienyl iodide (**202**) (Scheme 53) was a key step of the synthesis of **152**.[171]

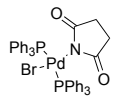


Scheme 53. Synthesis of (-)-peridinin (**152**) from the MIDA boronate **197**

Compound **201** was in turn obtained via a 3-step reaction sequence in which boronic acid **198**, prepared by hydrolysis of the MIDA boronate **197**, was coupled with bromide **199** using a $Pd(OAc)_2$/XPhos catalyst system and the resulting cross-coupling product **200** was converted in the required boronate **201** by treatment with pinacol in the presence of $NaHCO_3$ (Scheme 53).[171]

3. TOTAL SYNTHESES VIA *trans*-PdBr(*N*-Succ)$(PPh_3)_2$-CATALYZED S.-M. REACTIONS

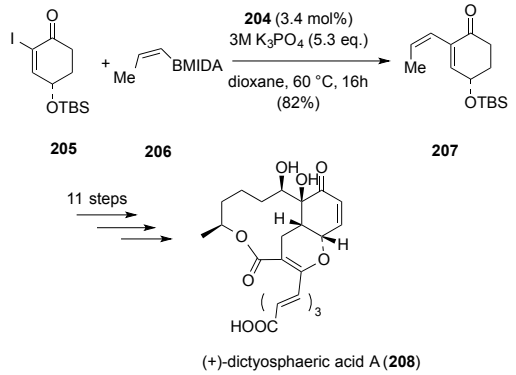
In recent years, *trans*-PdBr(*N*-Succ)$(PPh_3)_2$ (**204**) (Figure 9) has been used as an effective precatalyst for S.-M. cross-couplings of (hetero)arylboronic acids with benzylic halides, substituted aryl halides and halogenated cyclic enones[175] as well as for S.-M. reactions of alkenyl tosylates with alkenyl MIDA boronates.[176] Nevertheless, to our knowledge, complex **204** served as the precatalyst of a single S.-M. reaction invoved in a total symthesis of a natural product.



204

Figure 9. Structure of complex **204**

In fact, in 2010, Taylor and co-workers used the **204**-catalyzed reaction of (*S*)-iodoenone **205** with MIDA boronate **206** in the first step of a 12-step synthesis and structural reassignment of (+)-dictyosphaeric acid A (**208**),[177] a polyketide-derived compound isolated from a fungal isolate (F01V25) obtained from the green macroalgae *Dictyospaeria versluysii*.[178] The cross-coupling reaction (Scheme 54), which was carried out in dioxane at 60 °C in the presence of 3 M aq K_3PO_4, gave compound **207** in 82% yield.



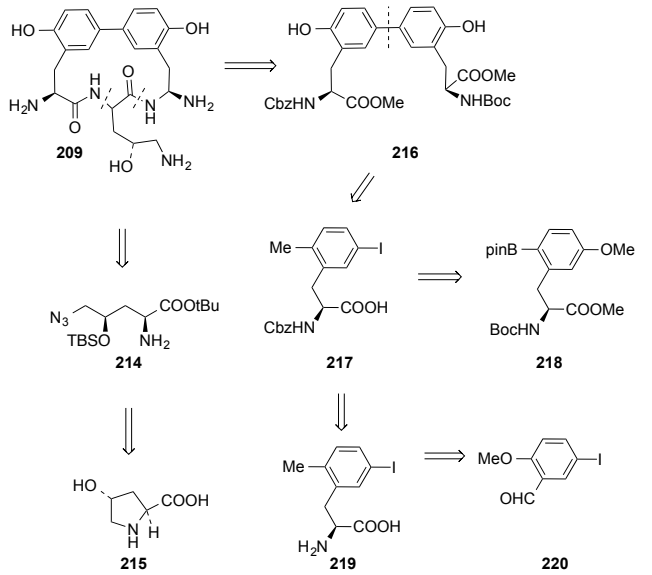
Scheme 54. Synthesis of (+)-dictyosphaeric acid A (**208**) via the **204**-catalyzed S.-M. reaction of iodoenone **205** with MIDA boronate **206**

Interestingly, compound 208 was found to exhibit antibacterial activity against methicillin-resistant *Staphilococcus aureus*, vancomycin-resistant *Enterococcus* faecium, and *Candida albicans*.[178]

4. TOTAL SYNTHESES VIA S.-M. REACTIONS PROMOTED BY A COMBINATION OF Pd(*o*-Tol)$_3$ OR A TRI(CYCLO)ALKYLPHOPSPHANE WITH A Pd(0) OR A Pd(II) DERIVATIVE

Table 4 lists the structures of natural compounds **209–213** that have been synthesized via S.-M. cross-couplings involving the use of a precatalyst composed by a combination of P(*o*-Tol)$_3$ or a tri(cyclo)alkylphosphane with a Pd(0) or a Pd(II) derivative. Literature data on the isolation of these natural substances are also reported in this table.

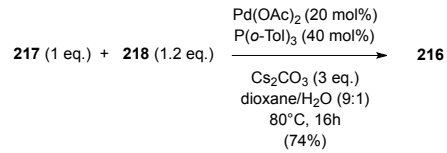
In 2011, Waldmann, Arndt and co-workers accomplished a total synthesis of biphenomycin B (**209**), a peptide antibiotic isolated from cultured broth of *Streptomyces griseorubiginosus* No 43708,[179]. The 14-step synthesis involving the use of aminoacids **215** and **216** was carried out according to the retrosynthetic disconnection shown in Scheme 55 and occurred in 15% overall yield.



Scheme 55. Retrosynthetic disconnection of biphenomycin B (**209**)

Thus, the ornitine derivative **214** was prepared from *trans*- 4-hydroxyproline (**215**) and the biaryl building block **216** was synthesized in 74% yield by Pd(OAc)$_2$/P(*o*-Tol)$_3$ catalyzed reaction of (*S*)-2-(benzyloxycarbonylamino)-3-(5-iodo-2-methoxyphenyl)propionic acid **217** with pinacol boronate **218** (Scheme 56).

TABLE 4 HERE



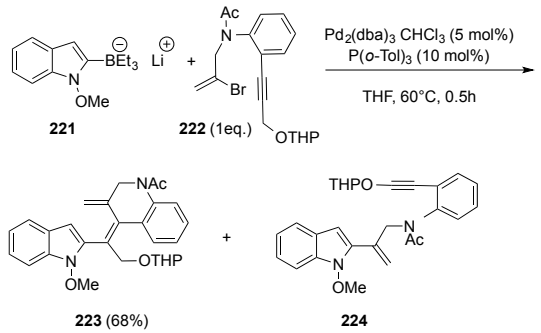
Scheme 56. Cross-coupling reaction of aryl iodide **217** with pinacol boronate **218**

Compound **217** was prepared from aminoacid **219** which in turn was obtained from aldehyde **220** in 79.3% yield via a 4-step reaction sequence. On the other hand, **218** was obtained in an excellent yield from **219** by introduction of a Boc-group, methyl ester formation, and $PdCl_2$(dppf)-catalyzed borylation with $(Bpin)_2$.[180]

In 2011 and 2012, Ishikura and co-workers reported a concise total synthesis of calothrixin B (210),[181] an indolo[3,2-j]phenanthridine alkaloid originally isolated

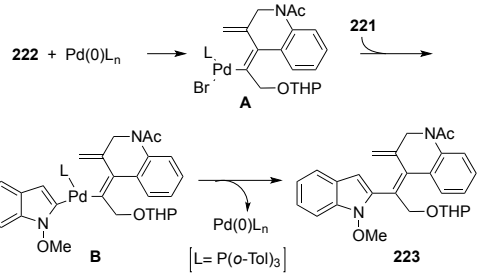
from *Calothrix* cyanobacteria,[182] which was found to inhibit the growth of a chloroquine-resistant strain of the human malaria parasite *Plasmodium falciparum*n and the growth of human HeLa cancer cells.[183] Under optimized conditions, triene **223**, which was the key intermediate of the synthesis, was prepared in 68% yield by the $Pd_2(dba)_3$·$CHCl_3$/P(*o*-Tol)$_3$-catalyzed tandem cyclization/cross-coupling reaction of triethylindolylborate

221 with vinyl bromide **222** (Scheme 57). Compound **223** was produced with a small amount (5%) of 2-vinylindole **224**.[181] It was also found that the cross-coupling reaction using $PdCl_2(PPh_3)_2$ as the precatalyst was slower and produced **223** in 20% yield.[181a]



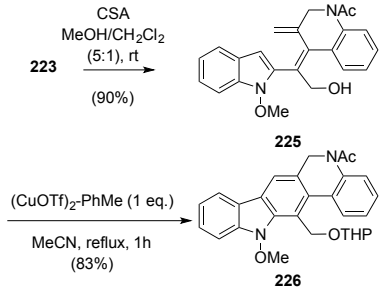
Scheme 57. Pd-catalyzed tandem cyclization/cross-coupling reaction of compound **221** with vinyl bromide **222**

The catalytic cycle of the reaction leading to **223** was proposed to involve the transfer of the indole ring from indolylborate **221** to the tricoordinate complex **A**, leading to **223** via complex **B** (Scheme 58).



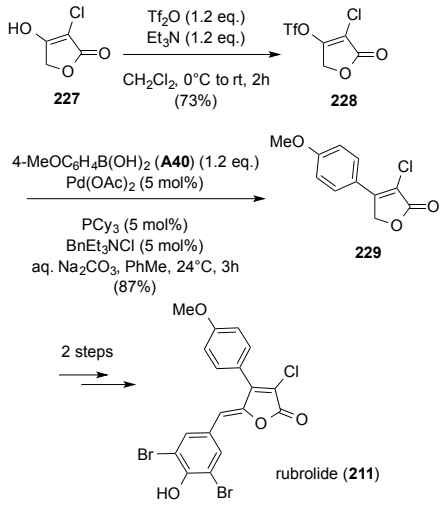
Scheme 58. Catalytic cycle for the Pd-catalyzed reaction between **221** and **222**

Another key step of the total synthesis of calothrixin B (**210**) was the generation of indolo[3,2-j]phenanthridine **226** by the unprecedented use of $(CuOTf)_2$·PhMe for the 6π-electrocyclization of compound **225**, which was obtained by removal of the THP group from **223** (Scheme 59).[181]



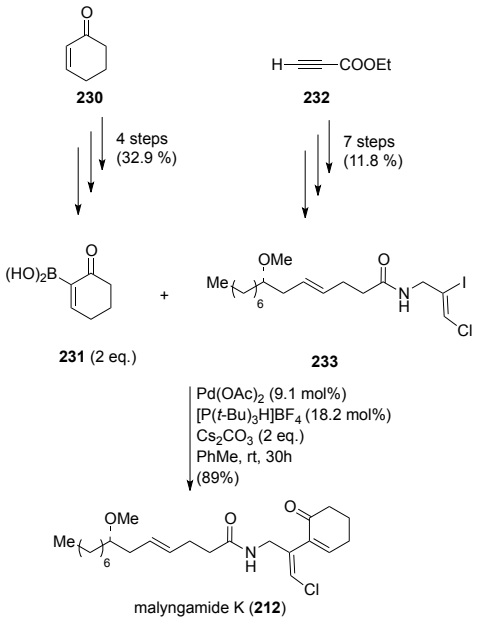
Scheme 59. Synthesis of compound **226** from **223**

In 2010, the first synthesis of rubrolide L (**211**), a butenolide isolated from the ascidian *Synoicum blochmani*[184] which was found to inhibit human aldolase reductase,[185] was achieved by Boukouvalas and McCann by a pathway in which 3-chlorotetronic acid (**227**) was the starting material and the key intermediate **229** was synthesized in 87% yield by the $Pd(OAc)_2/PCy_3$-catalyzed regio- and chemoselective reaction between triflate **328** and 4-methoxyphenylboronic acid (**A40**) (Scheme 60).[186]



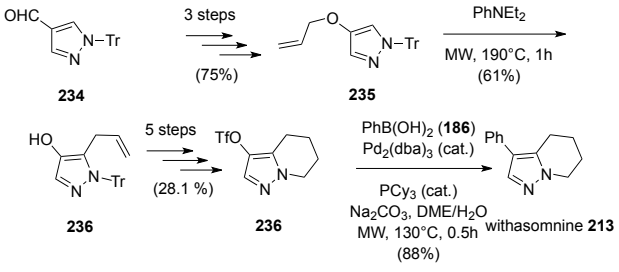
Scheme 60. Synthesis of rubrolide L (**211**) from commercially available 3-chlorotetronic acid (**227**)

In 2011, Cao and co-workers used a catalyst system composed of a combination of $Pd(OAc)_2$ and $[P(t\text{-}Bu_3)H]BF_4$ in the last step of a total synthesis of malyngamide K (**212**),[187] a natural product isolated from the marine cyanophyte *Lygbya majuscola.*[188] In this step, compound **212** was chemoselectively prepared in 89% yield by the S.-M. reaction of boronic acid **231** with (*Z*)-1-chloro-2-iodoalkene **233** (Scheme 61). Compound **231** was in turn obtained in 32.9% yield from enone **230** via a 4-step reaction sequence and compound **233** was synthesized in 11.8% yield from ethyl propiolate (**232**) through a series of seven reactions (Scheme 61).[187]



Scheme 61. Total synthesis of malyngamide K (**212**)

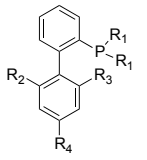
In the same year, Ichikawa, Usami and co-workers described a synthesis of withasomnine (**213**),[189] a pyrazole derivative isolated from the root bark of *Withania somnifera* (Solanaceae)[190] which is known to inhibit TBL_4, COX-1, COX-2 and to exhibit depression of the CNS and cyrculatory systems.[191] In the 9-step reaction sequence used to prepare **213**, 4-formylpyrazole **234** was the starting material and compound **236**, an early precursor to **213**, was obtained by alkaline hydrolysis of the Bayer-Villiger oxidation and *O*-allylation of **234** followed by Claisen rearrangement of the thereby obtained 4-allylpyrazole **231** (Scheme 62).[189] The total synthesis of **213** then featured the $Pd_2(dba)_3/PCy_3$-catalyzed cross-coupling of triflate **237** with phenylboronic acid (**186**), which provided the required natural product in 88% yield(Scheme 62).[189]



Scheme 62. Total synthesis of withasomnine (**213**)

4. TOTAL SYNTHESES VIA S.-M. REACTIONS PROMOTED BY A COMBINATION OF A DICYCLOALKYLBIARYLPHOSPHANE WITH A Pd(II) OR A Pd(0) DERIVATIVE

Since 1998, Buchwald and co-workers have introduced the use of dicycloalkylbiarylphosphane ligands such as S-Phos (**238a**), Ru-Phos (**238b**), X-Phos (**238c**) and JohnPhos (**238d**) (Figure 10) for Pd-catalyzed S.-M. reactions involving a variety of electrophiles.[192]



238a (S-Phos) : R_1= Cy; R_2=R_3= OMe; R_4=H
238b (Ru-Phos) : R_1= Cy; R_2=R_3= O-*i*Pr; R_4=H
238c (X-Phos) : R_1= Cy; R_2=R_3= R_4 = *i*-Pr
238d (JohnPhos) : R_1= *t*-Bu; R_2 R_2=R_3=R_4=H

Figure 10. Structures of ligands **238a–d**

Remarkably, the use of some of these supporting ligands was found to allow S.-M. couplings at low catalyst loadings.

As shown in this section, catalyst precursors consisting of a combination of a dicycloalkylbiarylphosphane with a Pd(II) or a Pd(0) derivative have also been frequently used in S.-M. reactions involved in total syntheses of natural products. Table 5 lists the structures of natural compounds which have been synthesized via Pd(II)/S-Phos-catalyzed S.-M. reactions in the period January 2010–December 2013. Table 5 also includes literature data on the isolation of these natural compounds.

TABLE 5 HERE

These natural compounds include: (+)-korupensamine B (**239**), which was originally isolated from the Cameroonian liana *Ancistrocladus korupensis* and was found to exhibit good antimalarial activity *in vitro* and *in vivo*;[193] graphislactone G (**240**), which was isolated from the endophytic fungus *Cephalosporium acremomium IFB-E007*;[194] (-)-rhazinilam (**241**), a strained nine-membered lactam originally isolated from the poisonous plant *Rhazya stricta* (Apocynaceae),[195] which was found to interfer with tubulin polymerization and dynamycs;[205] malyngamide L (**242**), a metabolite of the marine cyanophyte *Lyngbya majuscola*;[188] altenuisol (**243**), a toxin isolated from the fungus *Alternaria tenuis*;[196] hydroxy-α-sanshool (**244**), which was isolated from the dried fruit of the Japanese pepper *Zanthoxylum piperitum*;[197] altenusin (**245**), a minor toxin produced by *Alternaria* fungi[198] showing a broad antimicrobial activity against several multidrug-resistant bacterial and fungal strains;[206] alterlactone (**246**), a resorcylic lactone produced by *Alternaria* sp., which was found to exhibit moderate cyytotoxicity agains L5178Y cells;[199] lysilactone A (**247**), a 6*H*-dibenzo[*b,d*]pyran-6-one glycoside recently isolated from endophytic *Aspergillus* sp. Yxf3;[201] phenaglydon (**249**), an alkaloid isolated from *Glycosmis cyanocarpa* (Rutaceae);[202] racemic cepharatine A (**250**), an alkaloid which in levorotatory form was isolated from *Stephania cepharantha* (Menispermaceae);[203] and arylomycin A_2 (**251**), a biaryl-bridged lipopeptide antibiotic produced by *Streptomyces* sp. Tu 6075.[204]

In addition, Table 6 shows the structures and the literature data on the isolation of the natural compounds that have been synthesized via $Pd_2(dba)_3$-S-Phos-catalyzed S.-M. reactions.

TABLE 6 HERE

These substances include: honokiol (**252**), a biaryl neolignan originally isolated from *Magnolia officinalis* (Magnoliaceae)[207a] and more recently from *M. obovata;*[207b] (–)-myxalamide A (**253**), a polyene antibiotic first isolated from the gliding bacterium *Myxococcus xanthus*;[208] quebecol (**254**), a polyphenolic compound formed in racemic form during maple syrup production from *Acer saccharum'*s syrup;[209] and riccardin C (**255**), a cyclic bibenzyl derivative originally isolated from the liverwort *Reboulia hemisphaerica*,[210] which was found to function as a liver X receptor α agonist and a liver X receptor β antagonist.[211]

In addition, $Pd(OAc)_2$/RuPhos-catalyzed S.-M. reactions were used in the total synthesis of 4-*O*-methylhonokiol (**256**),[212] trienomycin A (**257**),[223] and virgatolide (**258**)[224] (Figure 11), and a $Pd_2(dba)_3$/JohnPhos-catalyzed S.-M. reaction was used to prepare a key intermediate of the enantioselective total syntheses of (–)-mersicarpine (**259**), (–)-leuconalam (**260**) and (–)-leuconoxine (**261**) (Figure 11),[215] three polycyclic *Aspidosperma* alkaloids.

4-*O*-Methylhonokiol (**256**) was isolated from *Magnolia* species[216a] and was found to exhibit higher anti-inflammatory activity than honokiol (**252**).[216b] (+)-Trienomycin A (**257**) was isolated from the culture broth of *Streptomyces* sp. No 83-16 and was found to exhibit aantineoplastic activity.[217] Spiroketal virgatolide B (**258**) was isolated from the endophytic fungus *Pestalotiopsis virgatula* (L147)[218] and (–)-mersicarpine (**259**), an indole alkaloid having a fused 6/5/6/7 ring system centered around a hemiaminal carbon, was isolated from the bark of *Kopsis fruiticosa* and *K. arborea*.[232] (–)-Leuconalam (**260**), a tetracyclic alkaloid containing a nine-membered lactam and a 1,5-dihydro-2*H*-pyrrol-2-one moiety, was isolated from *Leuconotis* plants,[233] and (–)-leuconoxine (**261**) was isolated from *Leuconotis eugenifolius* (Apocynaceae).[234]

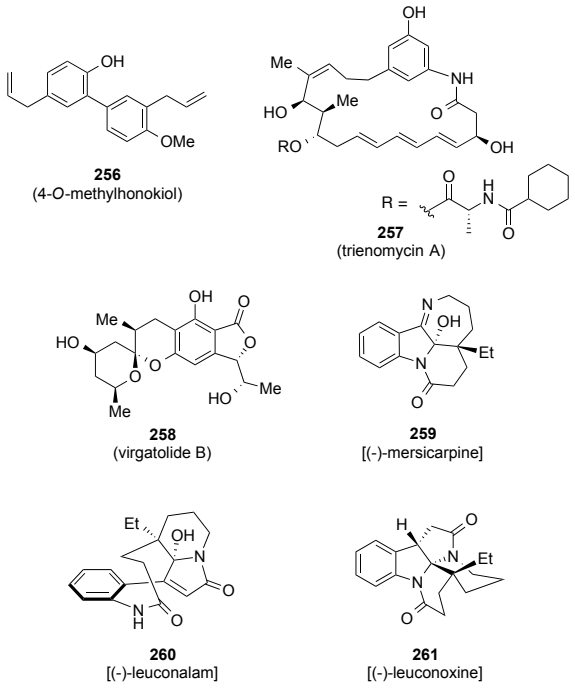
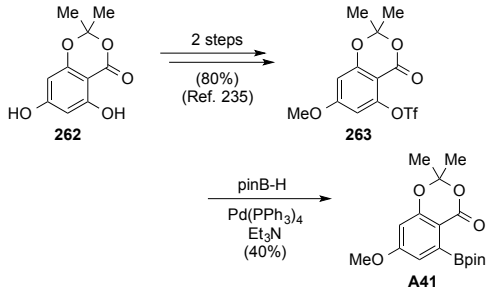


Figure 11. Structures of compounds **256–261**

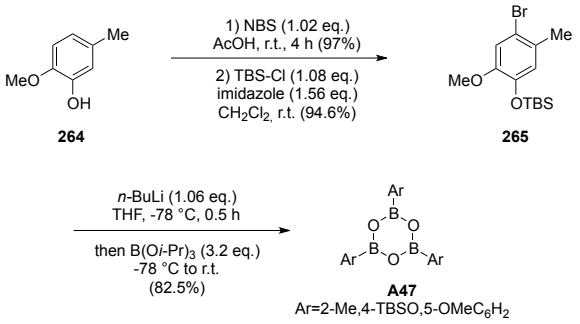
Table 7 shows the S.-M. cross-couplings used in the total syntheses of compounds **239–261**, the experimental conditions and yields of these Pd-catalyzed reactions. Entries 1–16 of this table regard reactions in which S-Phos was used as the ligand, entries 17–19 concern reactions involving the use of Ru-Phos as the ligand, and entry 20 illustrates the S.-M. reaction that provided compound **C52**, a precursor to natural compounds **259–261**. The organoboron reagents that were used in the reactions of Table 7 included boronic acids **A40**, **A43**, **A45**, **A50** and **A54**, pinacol boronates **A41**, **A42, AB1** and **AB2**, MIDA boronates **A44** and **A49**, 9-alkyl-9-BBN **A52**, potassium organotrifluoroborates **A51** and **A53**, and trioxaborinane **A47**. It should be noted that methoxy-substituted pinacol boronate **A41**, which was synthesized in 3 steps starting from commercially available acetal-protected phloroglucinic acid (**262**) via $Pd(PPh_3)_4$-catalyzed borination of aryl triflate **263** (Scheme 63),[223] was employed in the total syntheses of graphislactone (**240**)[219] (entry 2, Table 7), altenuisol (**243**)[231] (entry 5, Table 7), altenusin (**245**), and alterlactone (**246**)[223] (entry 7, Table 7), and lysilactone A (**247**)[200] (entry 8, Table 7).

TABLE 7 HERE



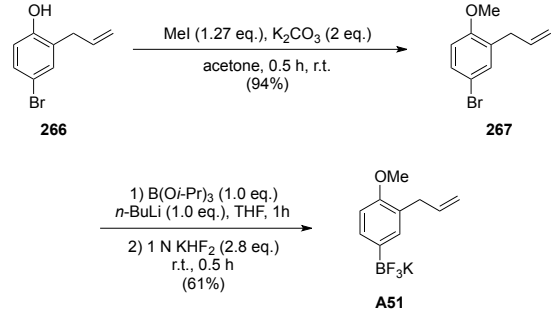
Scheme 63. Synthesis of pinacol boronate **A41**

Trioxaborinane **A47** was synthesized in 3 steps starting from 2-methoxy-5-methylphenol (**244**) via treatment of (4-bromo-2-methoxy-5-methylphenoxy)-*t*-butyldimethylsilane (**265**) with *n*-BuLi at – 78 °C followed by addition of a large molar excess of triisopropylborate (Scheme 64).[226]



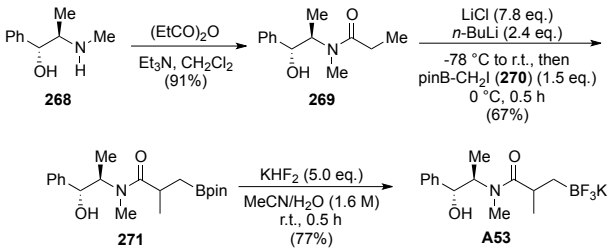
Scheme 64. Synthesis of trioxaborinane **A47**

Potassium aryltrifluoroborate **A51** was obtained as a crystalline solid through methylation of 2-allyl-4-bromophenol (**266**) and treatment of the resulting 2-allyl-4-bromo-1-methoxybenzene (**267**) with *n*-BuLi and triisopropylborate, followed by addition of KHF_2 (Scheme 65).[212]



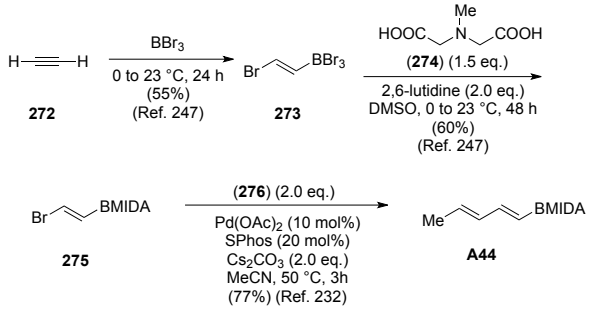
Scheme 65. Synthesis of potassium aryltrifluoroborate **A51**

Potassium (*S*)-3-(trifluoroborato)-*N*-[(1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]-*N*-2-dimethylpropanamide (**A53**), which was used in the synthesis of virgatolide B (**258**),[214] was prepared by the reaction of (*R,R*)-pseudoephedrine (**268**) with propionic anhydride in the presence of Et_3N, metalation of the resulting compound **269** with *n*-BuLi, followed by addition of pinB-CH_2I (**270**) and subsequent conversion of pinacol boronate **271** thereby obtained into trifluoroborate **A53** by the reaction with KHF_2 in MeCN/H_2O according to Molander's procedure[236] (Scheme 66).



Scheme 66. Synthesis of potassium alkyltrifluoroborate **A53**

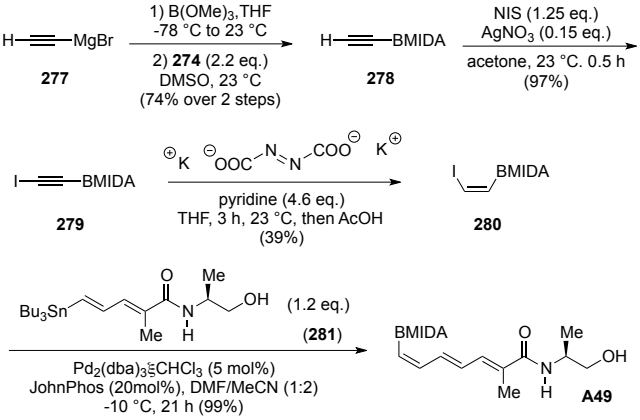
(*E,E*)-*N*-Methyliminodiacetic (MIDA) boronate ester **A44**, which was used in the total synthesis of hydroxy-α-sanshool (**244**) (entry 6, Table 7),[222] was prepared via the reaction sequence illustrated in Scheme 67.[237]



Scheme 67. Synthesis of MIDA boronate **A44**

In particular, (*E*)-(2-bromoethenyl)dibromoborane (**273**), which was prepared in 55% yield from acetylene (**272**) and BBr_3, was reacted with *N*-methyliminodiacetic acid (**274**) in DMSO in the presence of 2,6-lutidine to give (*E*)-MIDA boronate **275**.[237] The subsequent $Pd(OAc)_2$/S-Phos-catalyzed reaction of **275** with (*E*)-1-propenylboronic acid (**276**) gave **A44** in 77% yield.[222]

MIDA boronate **A49**, which was used in the total synthesis of (–)-myxalamide A (**253**) (entry 14, Table 7),[229] was synthesized as depicted in Scheme 68.

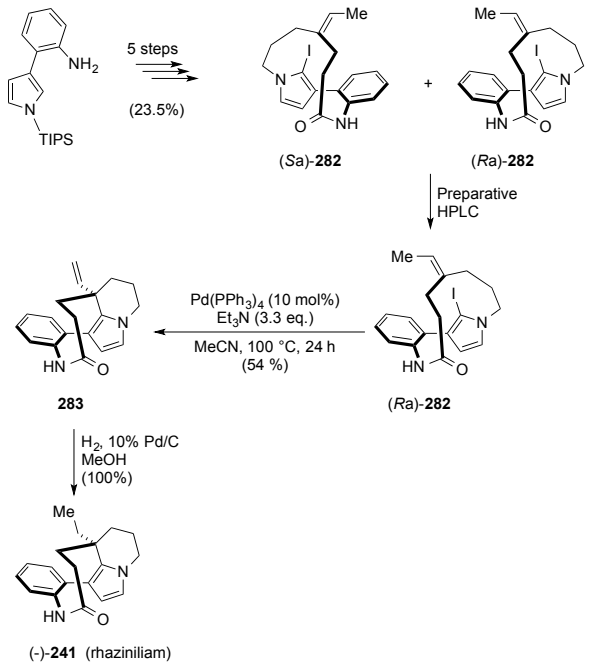


Scheme 68. Synthesis of MIDA boronate **A49**

Specifically, ethynylmagnesium bromide (**277**) was converted to ethynylboronate ester **278**, which by treatment with NIS in the presence of $AgNO_3$, provided 2-(iodoethynyl)boronate ester **279**.[238] (*Z*)-Stereoselective reduction of **279** with diimide generated *in situ* from dipotassium azodicarboxylate and AcOH, gave stereochemically pure (*Z*)-**280** in 39% yield.[238] Finally, the $Pd_2(dba)_3{\cdot}CHCl_3$-catalyzed Stille-type cross-coupling reaction of **280** with dienylstannane **281** gave MIDA boronate **A49** in almost quantitative yield (Scheme 68).[229]

Some reactions reported in Table 7 and/or some total syntheses that have been performed using these cross-couplings deserve comments. Thus, the optimized conditions developed for the S.-M. reaction between boronic acid **A40** and aryl iodide **B43** (entry 1, Table 7), which was used in the total synthesis of (+)-korupensamine B (**239**), led to compound **C38** with an unprecedented atropodiastereoselectivity (*M:P* = 11:1).[218]

The $Pd(OAc)_2$/S-Phos-catalyzed reaction between pinacol boronate A42 and 2-iodoaniline (**B45**) (entry 3, Table 7) provided compound **C39** in 91% yield.[220] As shown in Scheme 69, **C39** was used in a 7-step synthesis of (–)-rhazinilam (**241**) that involved as key features the separation of the enantiomers of lactam **282** by preparative chiral HPLC and the highly enantiospecific $Pd(PPh_3)_4$-catalyzed transannular Heck-type cyclization of (*Ra*)-**282**, which provided 1-alkene **283**, the direct precursor to (–)-rhazinilam (**241**).[220]



Scheme 69. Synthesis of (–)-rhazinilam (**241**) from compound **C39**

The chemoselective $Pd(OAc)_2$/S-Phos-catalyzed reaction of boronic acid **A43** with unsaturated carboxyamide **B46** possessing a chlorovinyl moiety (entry 4, Table 7), which gave compound **C40** in 38% yield, was the key step of an enantioselective total synthesis of malyngamide L (**242**).[187] The determination of the absolute configuration of C(3") and C(4") in the amine portion of the natural compound was accomplished by the synthesis of 3",4"-*epi*-malyngamide L (**284**) and **242** (Figure 12).[187]

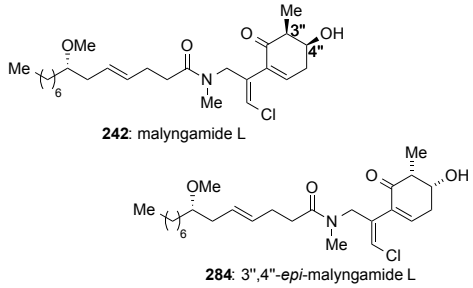
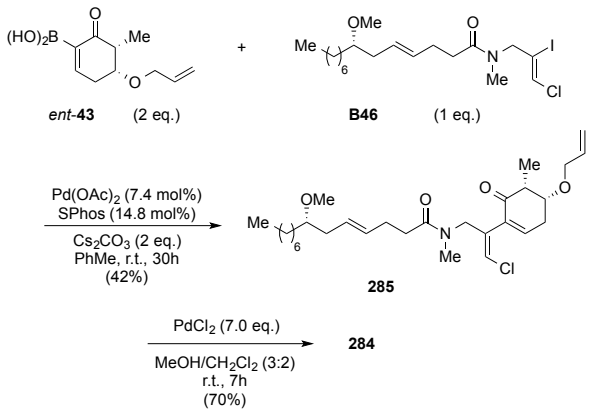


Figure 12. Structures of compounds **242** and **284**

A key step in the synthesis of **284** was the $Pd(OAc)_2$/SPhos-catalyzed S.-M. reaction of boronic acid *ent*-**43** with **B46** that provided compound **285** in 42% yield (Scheme 70).[187]



Scheme 70. Synthesis of 3",4"-*epi*-malyngamide L (**284**) from compounds *ent*-**43** and **B46**

It is worth noting that when *t*-$Bu_3P{\cdot}HBF_4$ was used as the ligand of the Pd-catalyzed S.-M. reaction between *ent*-**43** and **B46** no desired product resulted. The synthesis of 3",4"-*epi*-malyngamide L was then completed by removal of the allyl group of **285** with $PdCl_2$ in a mixture of MeOH and CH_2Cl_2.[187]

The $Pd(OAc)_2$/SPhos-catalyzed reaction between pinacol boronate **A41** and aryl bromide **B47** (entry 5, Table 7) was the key step of a total synthesis of altenuisol (**243**), which was achieved in 10 steps and 23% yield starting from phloroglucinic acid (**286**) and aldehyde **287** (Figure 12).[221] The S.-M. coupling led to benzyl-protected resorcylic lactone **C41** in a single step. The subsequent hydrogenolysis of the benzyl group of **C41** with H_2 (5 bar) in the presence of Pd/C led to altenuisol in quantitative yield. This total synthesis allowed Podlech and co-workers to establish that the originally proposed structure **243** of the natural product was nor correct. Consequently, two isomers

of **243**, i.e. compounds **288** and **289** (Figure 12) were synthesized.

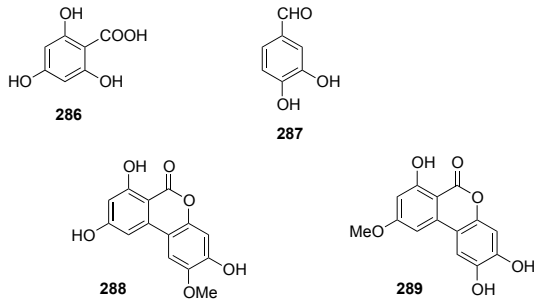
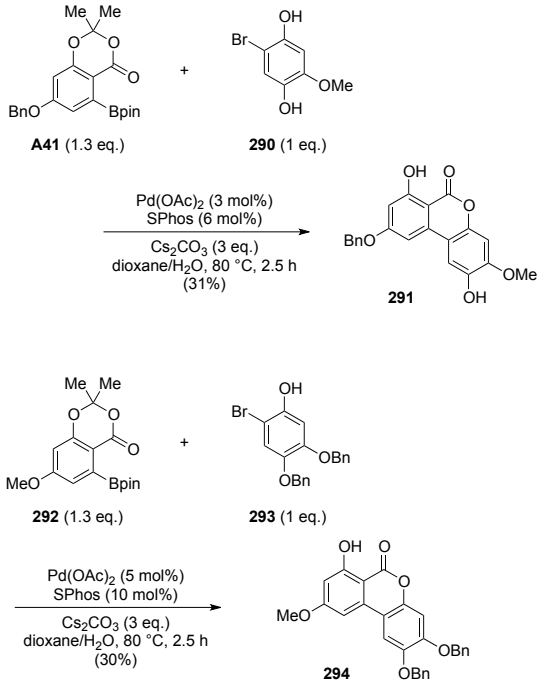


Figure 12. Structures of compounds **286–289**

The key step of the synthesis of **288** was the S.-M. reaction illustrated in Scheme 7, which involved boronate **A41** and aryl bromide **290** producing compound **291** in 77% yield. On the other hand, the key step of the synthesis of **289** was the S.-M. reaction between boronate **292** and aryl bromide **293**, which gave compound **294** in 39% yield (Scheme 71).



Scheme 71. Synthesis of compounds **291** and **294**

The comparison of the NMR spectra of compounds **243**, **288** and **289** and their peracetylated derivatives with those of naturally-occurring altenuisol and its triacetate showed that the spectra of **289** matched perfectly with those of the natural product.[221]

In 2012, Igarashi and co-workers described the first total synthesis of hydroxy-α-sanshool (**244**).[232] It involved the $Pd(OAc)_2$/SPhos-catalyzed S.-M. coupling of bromoalkyne **B48** with boronate **A44** (entry 6, Table 7).[232] (*Z*)-Stereoselective reduction of the triple bond of the cross-coupling product **C42** by treatment with Zn dust in water and MeOH, $Cu(OAc)_2$ and $AgNO_3$ at room temperature gave **244** in 84% yield.[222]

In the same year, the $Pd(OAc)_2$/SPhos-catalyzed cross-coupling reaction of pinacol boronate **A41** with aryl bromide **B49** (entry 7, Table 7) was achieved with concomitant translactonization in a similar manner to the reaction of entry 5, Table 7 and to those illustrated in Scheme 71.[223] The reaction of entry 7 gave in 81% yield compound **C42**, which is the common precursor to naturally-occurring alterlactone (**246**) and altenusin (**245**).[223] In fact, hydrogenolysis of **C42** in a 1:10 mixture of AcOEt and EtOH in the presence of Pd/C quantitatively led to **246**, while use of AcOEt as the sole sovent led to **245** (Scheme 72).[223

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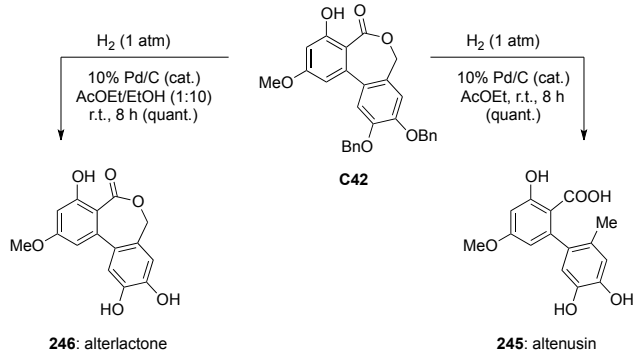
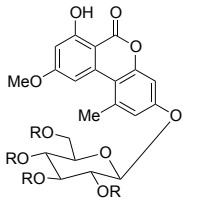


Scheme 72. Synthesis of altenusin (**245**) and alterlactone (**246**) from **C42**

More recently, concomitant cross-coupling and translactonization reactions were also found to occur when **A41** was reacted with aryl bromide **B50** in the presence of catalytic amounts of $Pd(OAc)_2$ and SPhos (entry 8, Table 7).[200] Phase-transfer glycosylation of the resulting alternariol 9-methyl ether (**C43**) with commercially available acetobromoglucose produced glycoside **295** (Figure 13), which was converted to lysilactone A (**247**) (Figure 13) by treatment with sodium methoxide in MeOH.[200]

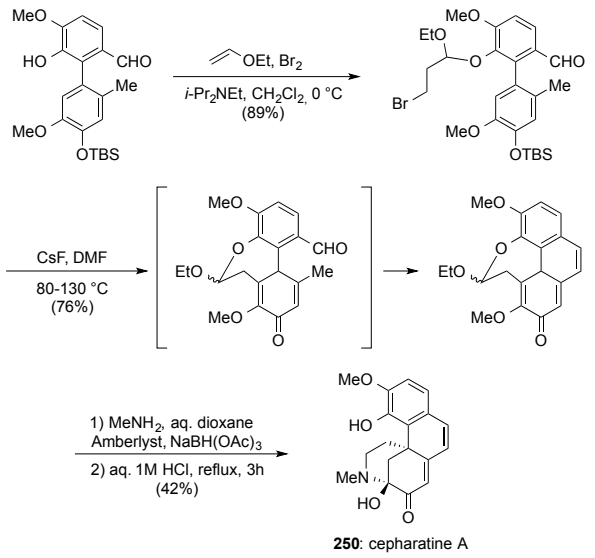


295: R=Ac
247: R=H (lysilactone A)

Figure 13. Structures of compounds **247** and **295**

In 2013, compound **C45**, which was prepared in 70% yield by $Pd(OAc)_2$/SPhos-catalyzed reaction of **A47** with aryl bromide **B53** (entry 11, Table 7), was used as a key intermediate in a concise synthesis of the hasubanan alkaloid cepharatine A (**250**).[226] In particular, compound **C45** was converted to *O*-alkylated biaryl **296** by treatment with the dibromide *in situ* generated by addition of bromine to ethyl

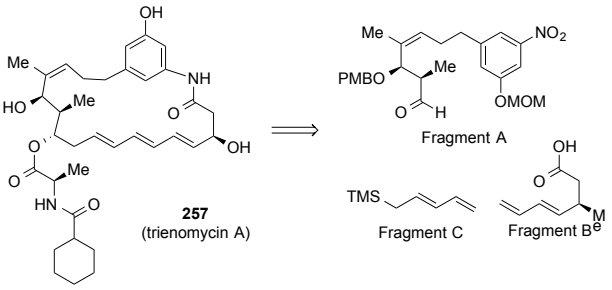
vinyl ether. The subsequent key step was the reaction of **296** with CsF in DMF at 80 °C, which gave compound **296** (Scheme 73). Finally, reductive amination of **298** followed by treatment of the resulting crude product with aqueous 1M HCl gave cepharatine A (**250**) in 42% yield (Scheme 73).[226]



Scheme 73. Synthesis of cepharatine A (**250**) from compound **C45**

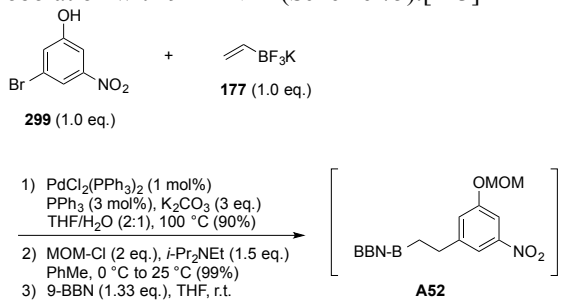
In 2011, naturally-occurring 4-*O*-methylhonokiol (**256**) was synthesized in 72% yield by the microwave-promoted $Pd(OAc)_2$/RuPhos-catalyzed reaction illustrated in entry 17 of Table 7.[212]Remarkably, when the microwave-mediated cross-coupling reaction was conducted using $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst precursor and K_2CO_3 as the base in a mixture of toluene and water the desired natural product was not obtained.[212]

In 2013, Del Valle and Krische accomplished the total synthesis of (+)-trienomycin A (**257**) on the basis of the retrosynthetic analysis shown in Scheme 74, which invoked a convergent assembly of fragments **A**, **B** and dienylsilane **C**.[213]



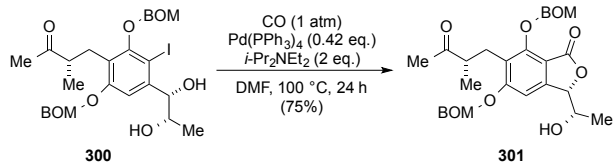
Scheme 74. Retrosynthesis of (+)-trienomycin A (**257**)

Fragment A was prepared through a reaction sequence in which intermediate **C50** was obtained in 90% yield by $Pd(OAc)_2$/RuPhos-catalyzed reaction of crude organoborane **A52** with vinyl iodide **B58** (entry 18, Table 7).[213] Compound **A52** was in turn prepared by S.-M. coupling of 3-bromo-5-nitrophenol (**299**) with potassium ethenyltrifluoroborate (**177**) and MOM protection of the resulting cross-coupling product, followed by regioselective hydroboration with 9-BBN-H (Scheme 75).[213]



Scheme 75. Synthesis of alkylborane **A52**

Again in 2013, the sp^3-sp^3 S.-M. cross-coupling reaction of enantiomerically enriched (*S*)-3-(trifluoroborato)-*N*-2-dimethylpropanamide **A53** with electron rich aryl bromide **B59** in a mixture of toluene and water in the presence of K_2CO_3 as the base and a catalysts system consisting of a mixture of $Pd(OAc)_2$ and RuPhos (entry 19, Table 7) was a key feature of the first total synthesis of the benzannulated spiroketal virgatolide B (**258**).[214c] The cross-coupling reaction proceeded cleanly producing compound **C51** in 52% yield. A 6-step reaction sequence in which intermediate aryl iodide **300** was converted into phthalide **301** by carbonylation with concomitant intramolecular alkoxylation (Scheme 76) allowed then to obtain **258** in 13.6% yield based on **C51**.[214c]



Scheme 76. Synthesis of phthalide **301** from compound **300**

Very recently, compound **C52**, the key intermediate in an enantioselective total synthesis of (–)-mersicarpine (**259**), (–)-leuconalam (**260**) and (–)-leoconoxine (**261**) was synthesized in 75% yield by the $Pd_2(dba)_3$/John-Phos-catalyzed S.-M. coupling of alkenyl iodide **B60** with 2-nitrophenylboronic acid (**A54**) (entry 20, Table 7).[215] Compound **C52** was subsequently diversified into the three natural products by controlled oxidation/reduction/polycyclization sequences.[215]

6. TOTAL SYNTHESES VIA $PdCl_2(dppf)$ OR $PdCl_2(dppf)\cdot CH_2Cl_2$-CATALYZED S.-M. REACTIONS

Dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium [$PdCl_2(dppf)$] is a complex that in 1984 Hayashi

and Higuchi found to be an effective catalyst for cross-couplings of primary and secondary alkyl Grignard and alkylzinc reagents with organic halides.[239] In 1986, it was employed by Suzuki and co-workers for very efficient cross-coupling reactions of 9-alkyl-9-BBN derivatives or trialkylboranes with aryl and 1-alkenyl halides.[240] $PdCl_2$(dppf) or its complex with CH_2Cl_2 was subsequently used as catalyst precursor for borylation of aryl halides,[241a,b] triflates,[241c] or diazonium salts with a dialkoxyborane[241b] or a tetraalkoxydiborane[241a,c] and for a wide range of reactions such as *B*-alkyl S.-M. cross-couplings of trialkylboranes with diversely functionalized aryl bromides,[242] S.-M. vinylation of hindered aryl bromides with potassium vinyltrifluoroborate,[243] intramolecular double or triple S.-M. coupling reactions of substituted di- or tribromobenzenes,[244] the arylation reaction of 4(5)-bromo-1*H*-imidazole with arylboronic acids under phase-transfer conditions,[245] cross-couplings of alkenyl bromides with potassium alkyltrifluoroborates,[246] cross-couplings of diverse potassium β-aminotrifluoroborates with aryl halides,[247] cross-couplings of aryl-and electron-rich heteroaryltrifluoroborates with aryl and activated heteroaryl bromides,[248] cross-couplings of benzyl halides with potassium aryltrifluoroborates,[249] reaction of (organo-1,2,3-triazol-4-yl)trifluoroborates with aryl and alkenyl bromides;[,50] and cyanomethylation of aryl halides through domino S.-M. coupling-isoxazole fragmentation.[251] In addition, $PdCl_2$(dppf) and its complex with CH_2Cl_2 have been used in several S.-M. reactions and one-pot borylation/S.-M. couplings involved in total syntheses of naturally-occurring substances.

Table 8 lists the structures of naturally-occurring compounds **43**, **255** amd **302–335** that, during the period January 2010–December 2013 were synthesized through $PdCl_2$(dppf) or $PdCl_2$(dppf)·CH_2Cl_2-catalyzed S.-M. reactions. Table 8 also reports the literature data on the isolation of these natural substances.

Edaxadiene (**302**) is a halimane-type diterpenoid produced by the pathogen *Mycobacterium tuberculosis*.[252] Hirtellanine A (**303**) is a cumarochromone derivative isolated from the roots of *Campylotropis hirtella* (Fabaceae), which was found to exhibit *in vivo* very strong lymphocyte suppression activity.[253] Canthin-6-one (**304**) is a β-carboline alkaloid first isolated from *Pentaceras australis* (Rutaceae),[254] and 9-methoxycanthin-6-one (**305**) is a cytotoxic compound isolated from the roots of *Eurycoma longifolia* (Simaroubaceae).[255] (+)-Ottelione A (**306**) is a potently cytotoxic 4-methylene-2-cyclohexenone which was isolated from the fresh water plant *Ottelia alismoides* (Hydrocharitaceae) collected in the Nile Delta.[256] Riccardin C (**255**), as previously mentioned, is a macrocyclic bis(bibenzyl) compound, which was isolated from the liverwort *Reboulia hemisphaerica* (Aytoniaceae).[210] (–)-Brevisin (**307**) is a polycyclic ether, which was isolated from the red tide dinoflagellate *Karenia brevis*.[257] Brevenal (**308***)* is another member of the family of marine polycyclic ethers, which was isolated from *K. brevis*.[258] (–)-Brevisamide (**309**) is a monocyclic ether amide, which was isolated from *K. brevis*.[259] SCH351448 (**310)** is a dimeric polyketide, which was isolated from an unspecified *Micromonospora* sp.[260] and was found to be a selective activator of low-sensity lipoprotein receptor promotor. (*R*)-(–)-Tylophorine (**311**) is an alkaloid, which was isolated from the Indian plant *Tylophora indica* (Asclepiadaceae).[261] Mycocyclosin (**312**) is a diketopiperazine produced by *M. tuberculosis*.[262] Ajudazol B (**313**) is a polyketide produced by a myxobacterium *Chondramyces crocatus* strain,[263a] which proved to be an highly effective inhibitor of the mitochondrial respiratory chain.[263b] Lycoramines A (**314**) and B (**315**) are two alkaloids isolated from the bulbs of *Lycoris radiata* (Amaryllidaceae), a Chinese plant the crude extract of which have been used as folk remedies for laringal problems as well as for the treatment of carbuncles and boils.[264] 2-Methoxypratosin (**316**) is an alkaloid isolated from whole plants of *Narcissus serotinus* (Amaryllidaceae).[265] Acerogenin E (**317**) is a macrocyclic diarylheptanoid, which was isolated from the stem bark of *Acer nikoense* (Aceraceae), a plant traditionally used in Japan as a folk medicine for the treatment of eye-related diseases and hepatic disorders.[266] Ginkgolic acid (13:0) (**318**) is a salicylic acid derivative found in several plant materials including cashew nuts.[267] Didemnaketal B (**319**) is a spiroacetal derivative isolated from the magenta ascidian *Didemnum* sp., which was found to exhibit potent inhibitory activity against HIV-1 protease.[268] Lodopyridone (**320**) is a cytotoxic alkaloid isolated from the marine bacterial strain *Narcissus serotinus* collected near the mouth of la Jolla Canyon.[269] Primin (**321)** is an allergenic 1,4-benzoquinone first isolated from the plant *Primula obconica* (Primulaceae) [270a] and subsequently from the endophytic fungus *Botryosphaeria mamane* PSU-M76.[270b] (+)-Cacospongionolide B (**322**) is a secondary metabolite of the marine sponge *Fasciospongia cavernosa*, which was shown to possess aantimicrobial and cytotoxic activitites.[271] Norchelerythrine (**323**) is a benzo[*c*]phenanthridine alkaloid isolated from *Zanthoxylum simulans*,[282a] *Z. integrifolium*,[272b] and *Z. capense*.[272c] Norsanguinarine (**324**) is another benzo[*c*]phenanthridine alkaloid isolated from callus tissue of *Papaver somniferum* (Papaveraceae),[273a] from Fumaria indica (Papaveraceae)[273b] and *Corydalis tashiroi* (Papaveraceae).[273c] Narseronine (**325**) is an Amaryllidaceae alkaloid, which was isolated from the flowering plant *Narcissus serotinus*.[274] (+)-Spiculoic acid (**326**) is a secondary metabolite produced from the Caribbean marine sponge *Plakortis angulospicatus*.[275] (+)-Zyggomphic acid (**327**) is a bioactive marine polyketide, which was isolated from *P. angulospicatus*[276a] and *P. zyggompha*.[276b] Dictyobiphenyls A (**328**) and B (**329**) and dictyoterphenyls A (**330**) and B (**331**) are four aromatic compounds, which were isolated from the fruiting bodies of the cellular slime mold *Dictyostelium discoideum*.[277] Cedrelin A (**332**) is a dihydrophenthrapyran isolated from the flowering plant *Cedrelinga catenaeformis* (Fabaceae).[278] Paracaseolide A (**333**) is a natural product featuring oxa-bowl architecture, which was isolated from the

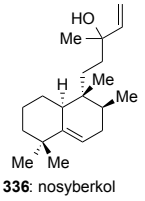
stem bark of *Sonneratia paracaseolaris* (Lythraceae), an endemic mangrovia found in China, and was shown to exhibit significant bioactivity against dual specificity phosphatase CDC25B, a key enzyme for cell progression.[279] Synechoxanthin (**334**) is an aromatic C40 xanthophyll that is a major carotenoid in the cyanobacterium *Synechoccus sp.* PCC 7002.[280] Dyctyodendrins A (**335**) and B (**43**) are two marine alkaloids isolated from the marine sponge *Dictyodendrilla verongiformis* that posseses inhibitory activity against telomerase.[79]

TABLE 8 HERE

The $PdCl_2$(dppf)- or $PdCl_2$(dppf)·CH_2Cl_2-catalyzed S.-M. cross-coupling reactions used in the total syntheses of naturally compounds **43**, **255**, and **302–335** are illustrated in Table 9, which also contains the detailed experimental conditions and yields of the reactions. Applications of these couplings are outlined after this table.

TABLE 9 HERE

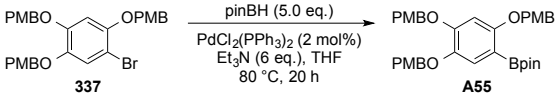
The sp^3-sp^2 coupling of alkylborane **A54** with alkenyl bromide **B60** (entry 1, Table 9) was used in a protocol developed for the synthesis of the *M. tuberculosis*-produced diterpene edaxadiene.[281] However, discrepancies between the spectroscopic data of the natural product and those of the synthetic construct raised questions regarding the proposed structure **302** of edaxadiene. Re-evaluation of the spectral data led to propose that edaxadiene is nosyberkol (**336**) (Figure 14), a diterpene previously isolated from a marine sponge *Raspailia* sp.[282] The structural reassignment was then validated by a synthesis of the correct structure of the natural product.[281]



336: nosyberkol

Figure 14. Structure of compound **336**

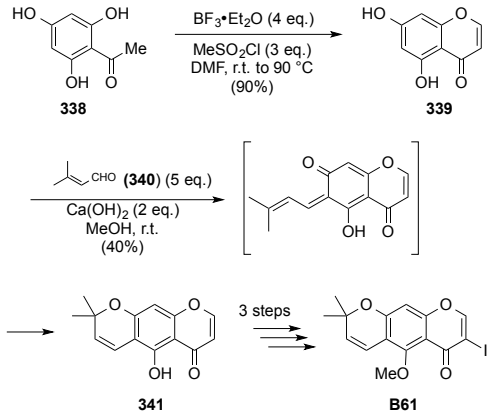
The key step of a regioselective total synthesis of hirtellanine A (**303**) was the high yielding $PdCl_2$(dppf)-catalyzed reaction between crude pinacol boronate **A55** and iodide **B61** (entry 2, Table 9).[283] Compound **A55** was prepared by $PdCl_2(PPh_3)_2$-catalyzed boronation of aryl bromide **337** with pinacol borane (Scheme 77).



337 **A55**

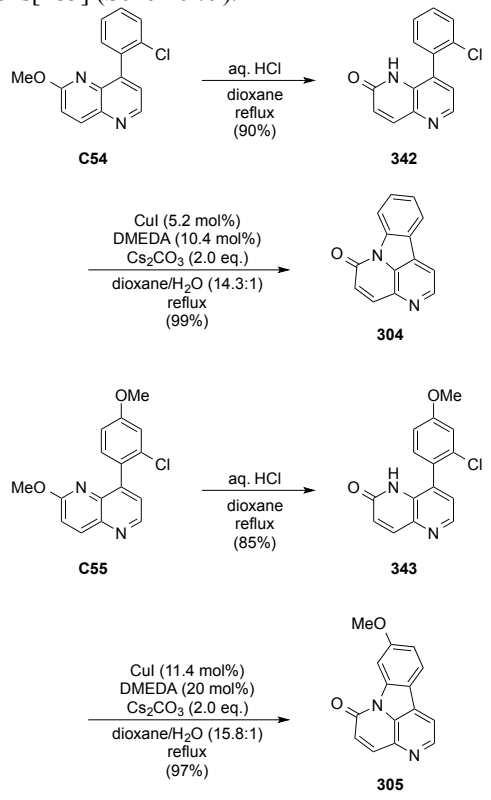
Scheme 77. Synthesis of compound **A55**

Iodide **B61** was in turn synthesized in 30.7% overall yield starting from acetylphloroglucinol (**338**) through a reaction sequence (Scheme 78) involving formation of compound **342** by a $Ca(OH)_2$-induced tandem regioselective Knoevenagel electrocyclic reaction of 5,7-dihydroxychromen-4-one (**339**) with 5 equiv of 3-methyl-2-butenal (**340**) in MeOH at room temperature that provided the chromone derivative **341** in 40% yield.[283]



Scheme 78. Synthesis of iodide **B61**

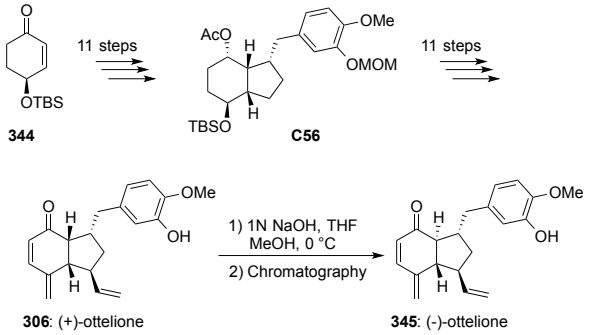
Compounds **C54** and **C55**, which were synthesized in high yields by the reactions illustrated in entries 3 and 4 of Table 9, were used as advanced intermediate in the synthesis of canthin-6-one (**304**) and 9-methoxycanthin-6-one (**305**), respectively.[284] In particular, compounds **342** and **343**, which were obtained by demethylation of **C54** and **C55**, were converted into **305** and **306** respectively,[284] via Cu-catalyzed intramolecular amidation using Buchwald's conditions[285] (Scheme 79).



Scheme 79. Synthesis of compounds **304** and **305** starting from **C54** and **C55**, respectively

It is also worth mentioning that canthin-6-one and 9-methoxycanthin-6-one were also synthesized in 95 and 92% yield, respectively, using a simple one-pot protocol involving a sequential $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. cross-coupling reaction, followed by a CuI/DMEDA-catalyzed C–N coupling.[284a]

In 2010, compound **C56**, which was synthesized in 65% yield by the S.-M. reaction of entry 5 of Table 9, followed by treatment of the cross-coupling product thereby obtained with TBAF in THF at 60 °C, was used by Sha and co-workers as a key intermediate in an enantioselective total synthesis of (+)-ottelione A (**306**) involving the use of chiral enone **344**[286] as the starting material (Scheme 80).[287] It was also reported that treatment of **306** with NaOH at 0 °C gave (–)-ottelione B (**345**) and (+)-ottelione A (**306**) in a 10:1 ratio, respectively. Silica gel chromatography allowed to isolate pure **345** (Scheme 80),[287] a natural compound isolated from *Ottelia alismoides* (Hydrocharitaceae).[256]



Scheme 80. Synthesis of (+)-ottelione A (**306**) and (–)-ottelione B (**345**) from enone **344**

In 2011, an efficient total synthesis of riccardin C (**255**) was accomplished by Kagechika and co-workers in 16 steps and 7.4% overall yield by using the $PdCl_2(dppf)$-catalyzed S.-M. reaction of pinacol boronate **A59** with aryl bromide **B64** (entry 6, Table 9) to link the B and C rings of the natural product.[288] The cross-coupling reaction, which was carried out in a 50:1 mixture of DMF and water in the presence of K_3PO_4 as base, provided compound **C57** in 76% yield.[288]

In the same year, the first total synthesis of the hexacyclic polyether (–)-brevisin (**307**) was achieved connecting the side chain fragments **X** and **Y** of the natural product (Figure 16) by means of the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. cross-coupling reaction of *B*-methoxyboronate **A60** with vinyl bromide **B64** (entry 7, Table 9).[289]

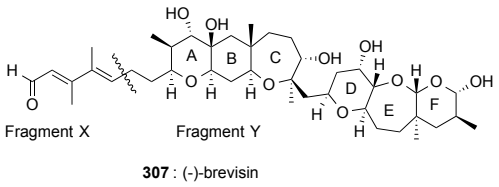
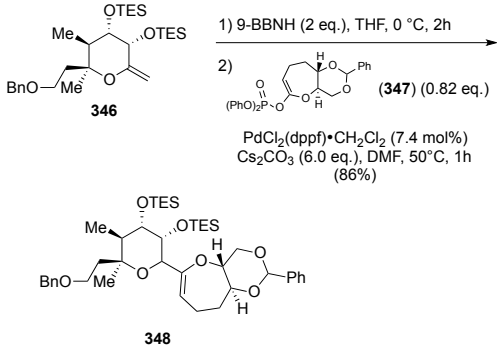


Figure 15. Structure of (–)-brevisin (**307**)

On the other hand, the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. reaction between ketene acetal phosphate **347** and the organoboron reagent obtained by the reaction of alkene **346** with 9-BBN-H was a key step in the synthesis of the **ABC** fragment of **307**.[289] As shown in Scheme 81, the cross-coupling reaction provided compound **348** in 86% yield.[289]



Scheme 81. Pd-catalyzed synthesis of compound **348**

The $PdCl_2(dppf)$-catalyzed S.-M. reaction of alkylmethoxyboronate **A61** with ketene acetal phosphate **B65** (entry 8, Table 9) had previously been employed in a convergent total synthesis of brevenal (**308**).[290] Compound **A61** was prepared from the known iodide **349**[291] (Figure 16) and compound **B65** was synthesized in 11 steps starting from the known alcohol **350**[292] (Figure 16). Compound **C58** resulting from the S.-M. coupling was then used in the synthesis of the ABC ring segment **351** (Figure 16) of the natural product.[290]

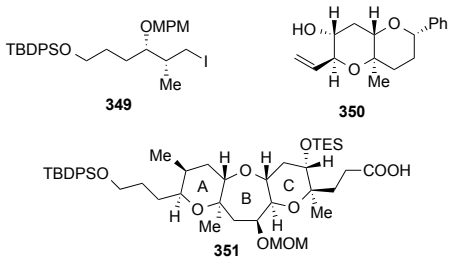
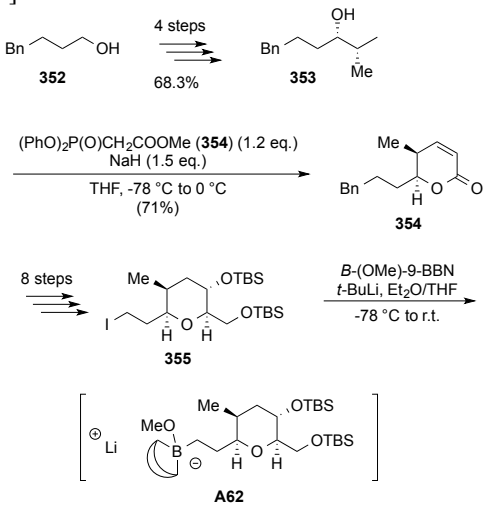


Figure 16. Structures of compounds **349–351**

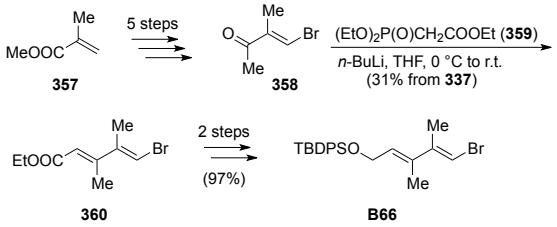
In 2010, Satake, Tachibana and co-workers accomplished a total synthesis of (–)-brevisamide (**309**) that featured the preparation of compound **C59** by **the** $PdCl_2(dppf)$-catalyzed S.-M. reaction of alkylmethoxyboronate **A62** with alkenyl bromide **B66** (entry 9, Table 9) as key step.[293] Alkyl

iodide **356**, the direct precursor to **A62**, was synthesized from 3-benzyloxy-1-propanol (**352**) via a 13 step reaction sequence involving formation of α,β-unsaturated lactone **355** by treatment of β-hydroxyaldehyde **353** with methyl diphenylphosphono-acetate (**354**) and NaH in THF (Scheme 82).[293]



Scheme 82. Synthesis of compound **A62**

Alkenyl bromide **B66** was prepared starting from methyl methacrylate (**357**) through a stereoselective Horner-Wadsworth-Emmons reaction of the intermediate bromoenone **358** with ethyl diethylphosphonoacetate (**359**) that provided compound **360** in 31% yield from **357** (Scheme 83).[293]



Scheme 83. Synthesis of dienyl bromide **B66**

In 2011, Hong and co-workers accomplished an elegant enantioselective formal synthesis of SCH 351448 (**310**) using the S.-M. reaction illustrated in entry 10 of Table 9 that provided compound **C60** in 73% yield.[294] Compound **C60** was then converted via a 5-step reaction sequence into compound **361** (Figure 17), which had previously been reported to be a precursor to SCH 351448.[295]

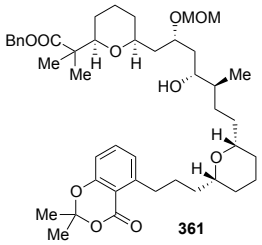
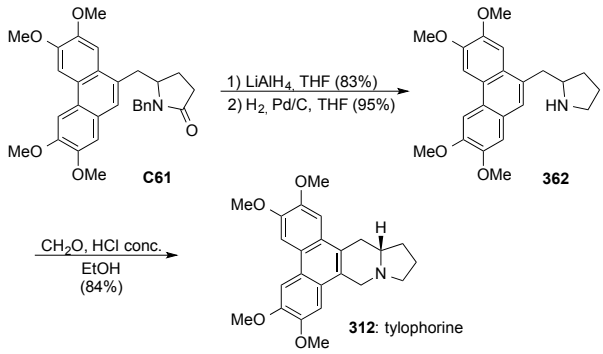


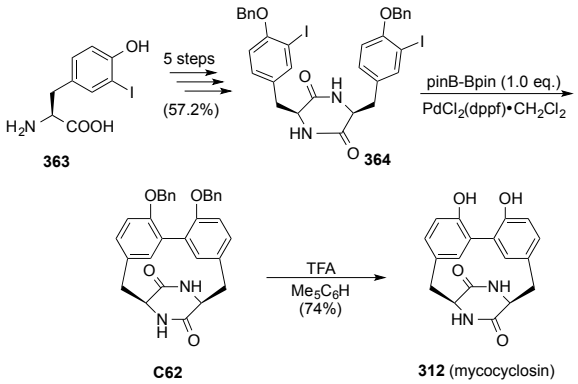
Figure 17. Structure of compound **361**

In 2013, Lin and Ho synthesized the phenanthrolidine alkaloid tylophorine (**312**) in racemic form via a route involving the $PdCl_2$(dppf)-catalyzed reaction between (*Z*)-1-benzyl-5-[2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]-2-pyrrolidinone (**A64**) and 2,2'-dibromo-4,5,4',5'-tetramethoxybiphenyl (**B68**) (entry 11, Table 9).[296] The reaction provided in 61% yield compound **C61** which was then deoxygenated on reaction with $LiAlH_4$ and further *N*-debenzylated by treatment with H_2 in the presence of Pd/C to give compound **362**. Finally, the Pictet-Spengler reaction of **362** with a formalin solution in concentrated HCl gave **312** in 84% yield (Scheme 84).[296]



Scheme 84. Synthesis of racemic tylophorine from compound **C61**

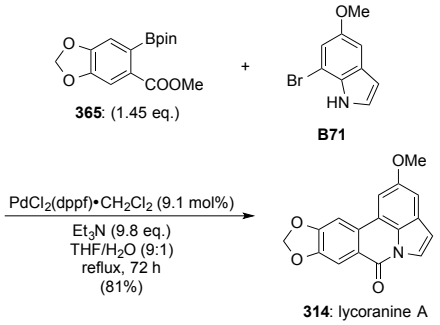
In 2012, Hutton and co-workers accomplished the first total synthesis of mycocyclosin (**312**) starting from *L*-iodotyrosine (**363**) via a series of reactions involving a one-pot Pd-catalyzed borylation/S.-M. cross-coupling reaction to generate the biaryl linkage of the natural product (Scheme 85).[297] In particular, cyclodi(3-iodo-4-*O*-benzyl-*L*-tyrosine) (**364**) was reacted with bispinacolatodiboron in the presence of $PdCl_2$(dppf)·CH_2Cl_2 and K_2CO_3 in DMSO at 90 °C to give bis(*O*-benzyl)mycocyclosin (**C62**) in 42% yield (entry 12, Table 9). Compound **C62** was the treated with trifluoroacetic acid (TFA) in pentamethylbenzene for 1 h to give **312** in 74% yield (Scheme 85).[297]



Scheme 85. Synthesis of mycocyclosin (**3120**) from compound **363**

In the same year, Menche and co-workers assigned the full stereochemistry of ajudazol (**313**) by an innovative bioinformatic approach and validated this assignment by a total synthesis in which the key step was the late-stage stereocontrolled $PdCl_2$(dppf)-catalyzed S.-M. reaction of (*Z*)-boronate ester **A65** with (*Z*)-vinyl iodide **B69** (entry 13, Table 9).[298]

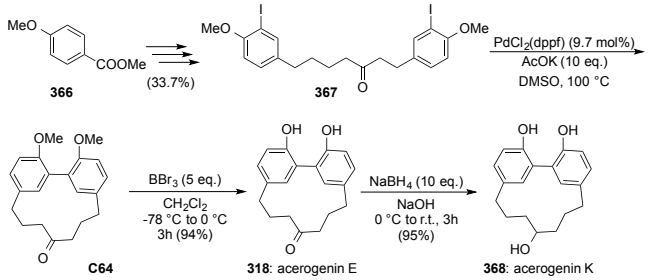
In 2013, Banwell and co-workers synthesized the amaryllidaceae alkaloids lycoranines A (**314**) and B (**315**) in 88 and 65% yield, respectively, by the $PdCl_2$(dppf)·CH_2Cl_2–catalyzed reactions of aryl bromide **B70** with borylindoles **A66** and **A67**, respectively, in a mixture of THF and water in the presence of Et_3N as base (entries 14 and 15, respectively, Table 9).[299] They also reported that the $PdCl_2$(dppf)·CH_2Cl_2–catalyzed reactions of pinacol boronate **A68** with 2-bromobenzoate **B71** in a mixture of THF and water in the presence of Et_3N (entry 16, Table 9) gave 2-methoxypratosine (**316**) in 83% yield.[299] Remarkably, Banwell and coworkers also synthesized employed the reversal of the polarity of the cross-coupling process used in the synthesis of **316** for the efficient preparation of compounds **314** and **315**. For instance, compound **314** was obtained in 81% yield by the $PdCl_2$(dppf)·CH_2Cl_2–catalyzed reaction between the bromoindole derivative **A71** and pinacol boronate **365** (Scheme 86).[299]



Scheme 86. Synthesis of lycoranine A (**314**) from pinacol boronate **365** and bromide **B71**

It is also worth pointing out that efficient intermolecular C–C bond formation and intramolecular amidation occurred in the $PdCl_2$(dppf)·CH_2Cl_2–catalyzed S.-M. reactions used to prepare compounds **314–316**.[299]

In the same year, Ogura and Usuki achieved the first total synthesis of acerogenin E (**317**) using a domino process involving a Miyaura borylation-intermolecular S.-M. cross-coupling.[300] In particular, the diiodo derivative **367**, which was prepared in 37.6% overall yield starting from methyl 4-methoxybenzoate (**366**), was reacted with 1.2 equiv of bis(pinacolato)diboron, 9.7 mol% $PdCl_2$(dppf) and 10 equiv of AcOK in DMSO at 100 °C to give compound **C64** (entry 17, Table 9). Deprotection of this dimethylether with BBr_3 provided acerogenin E (**317**) in 94% yield. Moreover, reduction of **317** with $NaBH_4$ gave acerogenin K (**368**) (Scheme 87),[300] another diarylheptanoid isolated from *Acer nikoense*.[266]



Scheme 87. Synthesis of acerogenins E (**317**) and K (**368**) from compound **366**

More recently, ginkgolic acid (13:0) (**318**) was synthesized using the $PdCl_2$(dppf)-catalysed reaction of aryl triflate **B72** with organoborane **A68**, which was prepared by hydroboration of 1-tridecene with 9-BBN-H (entry 18, Table 9).[301] The cross-coupling product **C65** was hydrolyzed with KOH in DMSO at 80 °C for 2 h and then acidified with HCl to give **318** in an unspecified low yield.[301] In order to explain this disappointing results, the cross-coupling reaction was examined and it was found that compound **369** (Figure 18) a byproduct of the reaction was which presumably was generated directly from the $PdCl_2$(dppf)-catalysed coupling of 1-tridecene with triflate **B72** without the assistance of BBN-H.[301]

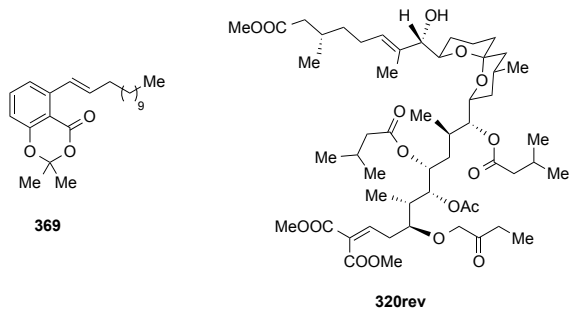
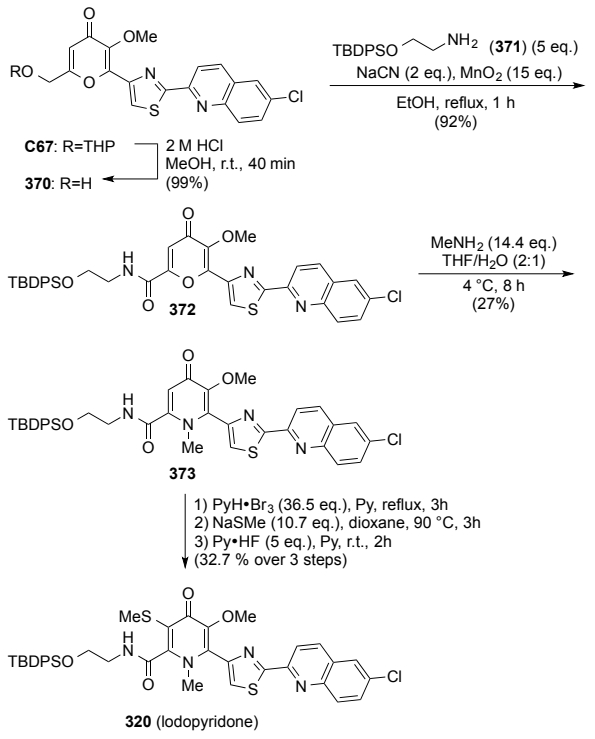


Figure 18. Structures of compounds **369** and **320rev**

In 2013, Fuwa and co-workers accomplished the first total synthesis of the proposed structure of didemnakel B (**319**)

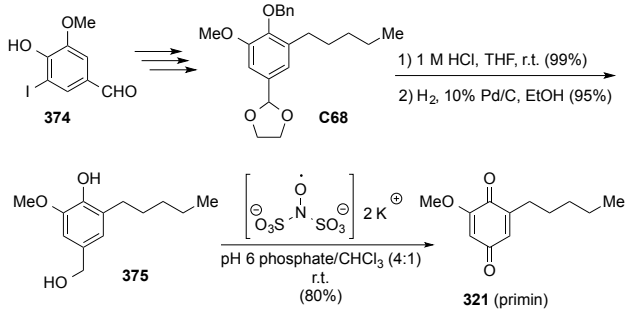
according to a synthetic plan in which compound **C65**, a key intermediate was synthesized in 84% yield by means of the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed reaction of *B*-methoxyboronate **A70** with ketene acetal phosphate **B73** (entry 19, Table 9).[302a] However, comparison of the NMR data of the synthetic material with those of an authentic sample of the natural product revealed that the proposed structure **320** of natural didemnaketal B required stereochemical reassignment.[302a] Interestingly, the NMR data of compound **320rev** (Figure 18), which was synthesized in 2014, were in good agreement with those of naturally occurring didemnakel B .[302b]

Still in 2013, Moody and co-workers performed the total synthesis of the 4-pyridone marine metabolite lodopyridone (**320**) using the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. coupling of pinacol boronate **A71** with bromopyrone **B74** (entry 20, Table 11) to form the key pyrone-thiazole bond of this unusual metabolite.[303] The total synthesis also involved the installation of the ethanolamide side-chain of **320** by a modified Corey-Ganem-Gilman reaction[304] of the primary alcohol **370**, obtained by deprotection of the cross-coupling product **C67**, with silylethanamine **371** (Scheme 88).[333] The reaction, which achieved both oxidation and carboxyamide formation, provided pyrone **372** in an excellent yield. A disappointing 27% yield was then obtained in the conversion of **372** into pyridone **373**. The synthesis of **320** was then completed in 3 steps and 32.7% yield based on **373** (Scheme 88).[303]



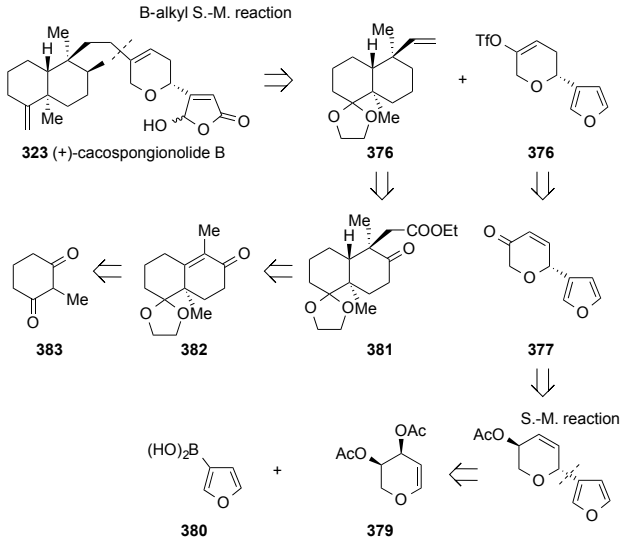
Scheme 88. Synthesis of lodopyridone (**320**) from the cross-coupling derivative **C67**

A year earlier, Katoh and co-workers synthesized the contact allergen primin (**321**) in 6 steps and 57% overall yield starting from commercially available 5-iodovanillin (**374**) (Scheme 89).[305] A crucial step of the synthesis was the $PdCl_2(dppf)$-catalyzed reaction of alkylborane **A72** with aryl iodide **B75** (entry 21, Table 9) that installed the alkyl side chain on the aromatic ring providing compound **C68** in 92% yield. The synthetic method also involved elaboration of the quinone functionality by degradative oxidation of compound **375** using Frémy's salt (Scheme 89).[305]



Scheme 89. Synthesis of primin (**321**) starting from iodide **374**

The $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed coupling reaction of crude alkylborane **A73**, generated by hydroboration of vinyl *trans*-decalin **376**, with alkenyl triflate **B76** (entry 22, Table 9) had previously been employed as a key step of a convergent synthesis of the Mediterranean sponge metabolite (+)-cacospongionolide B (**322**).[306] Scheme 90 illustrates the retrosynthesis of this natural compound. The pivotal transformations included the highly stereoselective *C*-glycosylation of glycal **379**, derived from *D*-arabinose,[307] with 3-furylboronic acid (**380**). in NMP at room temperature for 12 h under 1 atm of dioxygen by using 2 equiv of **380** and 9.7 mol% $Pd(OAc)_2$ and the conversion of the resulting cross-coupling product **378** into **B76** via enone **377**. The synthesis of **322** also involved the preparation of **376** via a series of 6 reactions in which ester **381** was synthesized from 2-methylcyclohexan-1,3-dione (**383**) through enone **382** (Scheme 90).[306]



Scheme 90. Retrosynthesis of (+)-cacospongionolide B (**322**)

In 2011, the first step of a total synthesis of norchelerythrine (**323**) was carried out by using the $PdCl_2$(dppf)-catalyzed cross-coupling reaction between pinacol boronate **165** and aryl bromide **167** in MeOH at 80 °C in the presence of K_2CO_3 as base, which provided compound **C70** in 75% yield (entry 23, Table 9).[154] In addition, compound **C71**, which was used as a precursor to norsanguinarine (**324**), was synthesized in 97% yield by the $PdCl_2$(dppf)-catalyzed S.-M. reaction of **165** with aryl bromide **B77** in a mixture of DMF and MeOH at 80 °C in the presence of K_2CO_3 as base (entry 24, Table 9).[154] Microwave-assisted electrocyclic reactions of the aza 6π-electron systems of the 2-cycloalkenylbenzaldoxime methyl ethers **384** and **385** (Figure 20) derived from **C70** and **C71**, respectively, were then used as key steps of the syntheses of compounds **323** and **324**.[154]

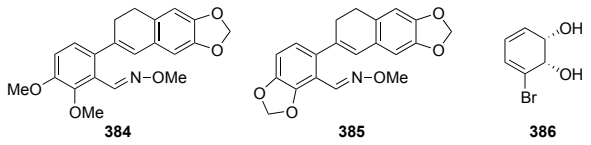
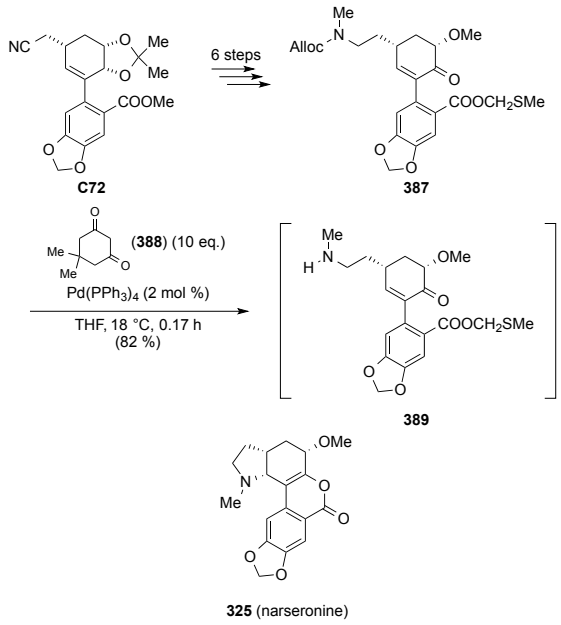


Figure 20. Structures of compounds **384–386**

In the same year, compound **C72**, which was prepared in 75% yield by S.-M. reaction of pinacol boronate **A74** with cycloalkenyl bromide **B78** (entry 25, Table 9),[308a] was used as a precursor to the Amaryllidaceae alkaloid narsorenine (**325**) in a 15-step and fully stereocontrolled total synthesis in which enantiomerically pure and enzymatically-derived *cis*-1,2-dihydroxycatechol **386**[308b] (Figure 20) was the starting material. In the final step of the total synthesis, carbamate **387**, which was obtained in 6 steps from **C72**, was treated with a molar excess of dimedone (**388**) and 2 mol% $Pd(PPh_3)_4$ to give narsorenine (**325**) in 82% yield, presumably through amine **389** (Scheme 91).[308a]



Scheme 91. Synthesis of narsorenine (**325**) from compound **C72**

It should be noted that compound **C72** had previously been employed in the first synthesis of compound **391** (Figure 21), a degradation product of the alkaloid (–)-lycorine (**390**) (Figure 21).[308b]

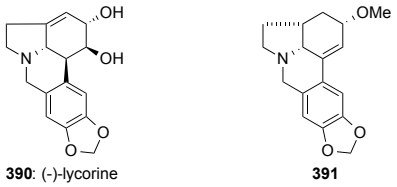
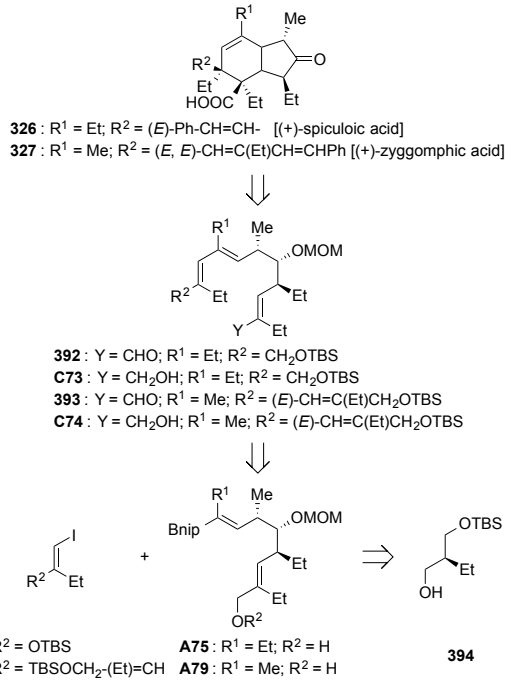


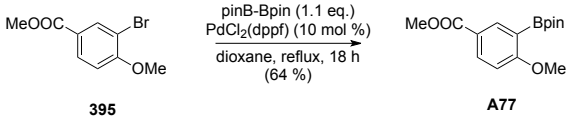
Figure 21. Structures of compounds **390** and **391**

Again in 2011, the first total syntheses of the cytotoxic marine natural products (+)-spiculoic acid (**326**) and (+)-zyggomphic acid (**327**) were accomplished on the basis of the retrosynthetic analysis depicted in Scheme 92 in which the central feature was the highly stereoselective and high yielding intramolecular Diels-Alder reaction of the (*E,E,E*)-dodecatrienal derivatives **392** and **393**, respectively.[309] These compounds were obtained by Dess-Martin oxidation of the cross-coupling products **C73** and **C74**, respectively, which were synthesized by the stereoselctive S.-M. reactions reported in entries 26 and 27 of Table 9, respectively.[309] (*E*)-Vinylboronates **A75** and **A76**, which were employed in these cross-couplings, were in turn synthesized from known enantiomerically pure (*S*)-2-[(*t*-butyldimethylsilyloxy)methyl]butan-1-ol (**394**) (Scheme 92).[310]



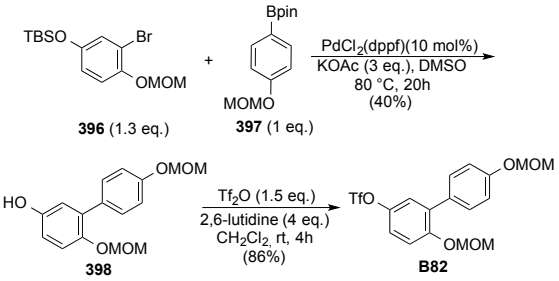
Scheme 92. Retrosynthesis of (+)-spiculoic acid (**326**) and (+)-zyggomphic acid (**327**)

In 2012, Kikuchi and co-workers reported the divergent syntheses of dictyobiphenyls A (**328**) and B (**329**) from the intermediate compound **C75**.[311] The latter compound was obtained in 93% yield by the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. reaction of pinacol boronate **A77** with aryl bromide **B81** in dioxane in the presence of K_3PO_4 (entry 28, Table 9). Compound **A77** was prepared in 64% yield by the $PdCl_2(dppf)$-catalyzed boronation of methyl 3-bromo-4-methoxybenzoate (**395**) with bis(pinacolato)diboron (Scheme 93).[311]



Scheme 93. Synthesis of compound **A77**

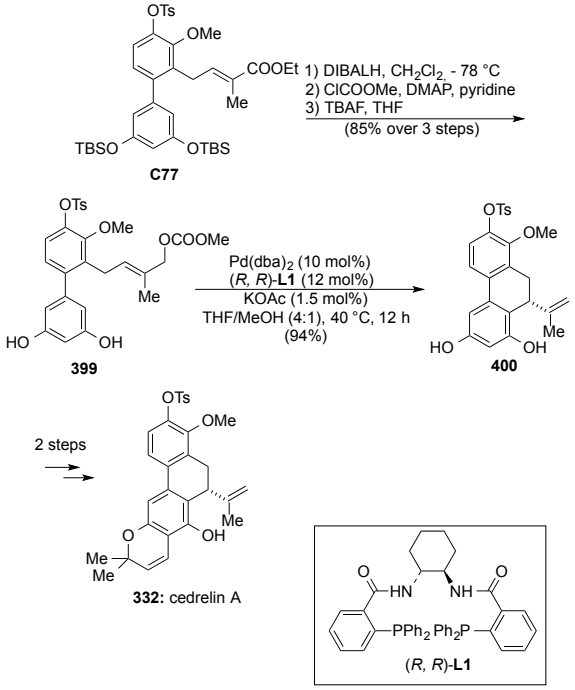
Kikuchi and co-workers aloso found that, unfortunately, the synthesis of compound **C76**, which they used as an advanced common precursor to dictyoterphenyls A (**330**) and B (**331**), occurred in a modest yield. In fact, the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. reaction of pinacol boronate **A77** with biaryl triflate **B82** in refluxing dioxane in the presence of K_3PO_4 yielded **C77** in 43% yield (entry 29, Table 9).[311] Compound **B82** was in turn synthesized through a reaction sequence involving the preparation of compound **398** by the $PdCl_2(dppf)$-catalyzed reaction of aryl bromide **396** with pinacol boronate **397** (Scheme 94).[311]



Scheme 94. Synthesis of compound **B82**

Interstingly, dictyoterphenyl A (**330**) was shown to inhibit the proliferation of several human cancer cell lines in a concentration dependent manner.[311]

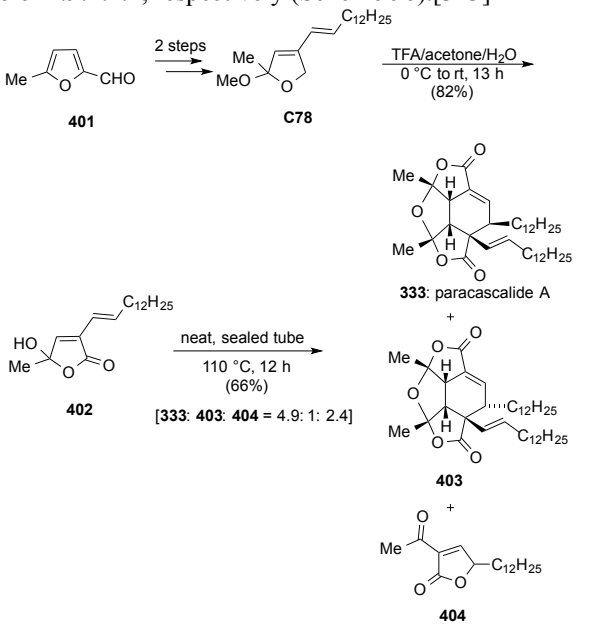
More recently, Hamada and co-workers described the first enantioselective synthesis of cedrelin A (**332**), wherein α,β-unsaturated ester **C77** was an intermediate.[312] This highly functionalized biphenyl derivative was synthesized in an excellent yield by the S.-M. cross-coupling reaction illustrated in entry 30 of Table 9. The key step of the total synthesis was the preparation of compound **400** by $Pd(dba)_2$/(*R,R*)-**L1**-catalyzed asymmetric intramolecular Friedel-Crafts allylic alkylation of compound **399** which was obtained in 3 steps from **C77** (Scheme 95).[312]



Scheme 95. Synthesis of cedrelin A (**332**) from compound **C77**

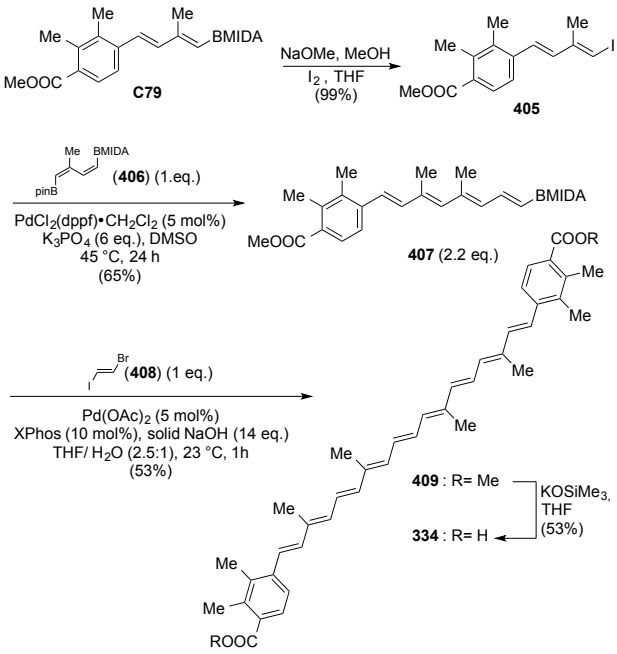
In 2013, Vasamsetty, Khan and Mehta accomplished a concise total synthesis of the novel oxa-bowl natural product paracaseolide A (**333**) via a series of reactions in which compound **402**, a key intermediate, was obtained by methoxy deprotection of butenolide **C78**, which was prepared in 60% yield by the $PdCl_2(dppf)$-catalyzed reaction of pinacol boronate **A79** with iodobutenolide **B84** in a

mixture of THF and water in the presence of *n*-Bu_4NBr and CsF (entry 31, Table 9).[313] The key step of the total synthesis, in which 5-methyl-2-furfural (**401**) was used as the starting material, was the thermal [4+2]-dimerization of **402** (Scheme 96). Unfortunately, this reaction was not clean and led to the formation of **333** together with its stereoisomer and the ring-opened compound **404** in 66% yield and in a ratio of 4.9:1:2.4, respectively (Scheme 96).[313]



Scheme 96. Synthesis of paracaseolide A (**333**) starting from compound **401**

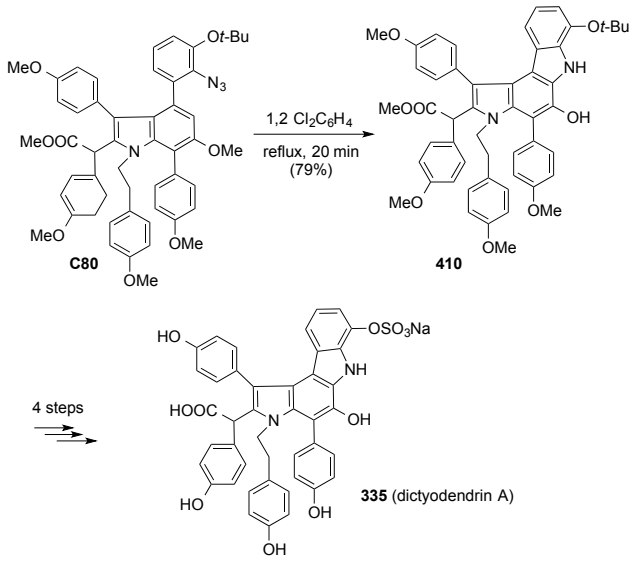
Two years earlier, Burke and co-workers used an iterative cross-coupling strategy for the total synthesis of the aromatic C_{40} dicarboxylate xanthophyll synechoxanthin (**334**).[314] The $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed S.-M. reaction of bisborylated compound **A80** with the activated aryl iodide **B85** in DMSO in the presence of K_3PO_4 gave MIDA boronate **C79** in 79% yield (entry 32, Table 9).[324] Iododeborylation of **C79** gave dienyl iodide **405** in 99% yield, which was then reacted with the bifunctional building block **406** in DMSO in the presence of K_3PO_4 and a catalytic amount of $PdCl_2(dppf)\cdot CH_2Cl_2$ providing stereoisomerically pure tetraenyl MIDA boronate **407** in 65% yield (Scheme 97). The total synthesis of **334** was then completed via a concise and efficient route in which an *in situ* MIDA boronate hydrolysis/two-directional double $Pd(OAc)_2$/XPhos-catalyzed cross-coupling reaction between 2.2 equiv of **407** and (*E*)-1-bromo-2-iodoethene (**408**) yielded diester **409** in 53% yield. Finally, hydrolysis of the methyl esters of **409** provided **335** in 53% yield (Scheme 97).[314]



Scheme 97. Synthesis of synechoxanthin (**334**) from compound **C79**

Tokuyama and co-workers had previously accomplished the total synthesis of dictyodendrin A (**335**) using the $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed reaction of pinacol boronate **A81** with iodide **B86** (entry 33, Table 9) for the construction of the pyrrole [2,3-*c*] carbazole skeleton of the natural product.[315]Interestingly, the azido group of **B86** remained untouched in this reaction which provided compound **C80** in 79% yield. Thermolysis of **C80** at 180 °C and subsequent insertion of the thereby obtained nitrene into the adjacent Csp^2–H bond gave compound **410**, which was converted into **335** via a 4-step-reaction sequence (Scheme 98).[315]

Tokuyama and co-workers also used an analogous reaction sequence in a highly efficient total synthesis of dictyodendrin B (**43**), which involved the preparation of compound **C81** as a key intermediate by the S.-M. reaction of pinacol boronate **A82** with aryl iodide **B86** (entry 34, Table 9).[315]



Scheme 98. Synthesis of dictyodendrin A (**335**) from compound **C80**

7. TOTAL SYNTHESES VIA S.-M. REACTIONS PROMOTED BY $PdCl_2$(dppf) WITH As(Ph)$_3$

Several papers testify that an excellent catalyst system for *B*-alkyl S.-M. reactions consists of a combination of $PdCl_2$(dppf) with $AsPh_3$.[316] As early as 1983, Johnson and Braun noticed that when the $PdCl_2$(dppf)-catalyzed cross-coupling reaction of an α-iodoenone with a *B*-alkyl-9-BBN derivative was carried out in the presence of $AsPh_3$ as a coligand a higher turnover rate and a cleaner reaction was observed.[317] In fact, a Pd species with a large bite angle when associated to an electron-rich and weakly coordinating ligand such as $AsPh_3$ improves the reaction rate of sp^2–sp^3 C–C bond forming reactions by making reductive elimination more facile than the competing β-hydride elimination.

Thus, despite that $AsPh_3$ is a compound very toxic to aquatic life with long lasting effects, the catalyst system consisting of a combination of $AsPh_3$ with $PdCl_2$(dppf) has been extensively used in S.-M. reactions involved in total syntheses of natural products. Table 10 lists the natural substances synthesized from January 2010 to December 2013 via $PdCl_2$(dppf)/$AsPh_3$-catalyzed S.-M. cross-couplings. These natural products include: anguinomycins C (**411**) and D (**412**), two antitumor antibiotics isolated from a strain belonging to *Streptomyces*, which were reported as selective agents targeting immortalized cells;[318] the cyclic peptide antillatoxin (**413**), a potent toxin which was isolated from the marine cyanobacterium *Lyngbya majuscola*;[319] aspergillides A (**414**) and B (**415**), which were isolated from the marine fungus *Aspergillus ostianus* strain 01F313, cultured in a bromine-modified medium;[320] indolizine (+)-195B (**416**), an alkaloid isolated from a population of the Colombian poison-frog *Dendrobates histrionicus*;[321] the toxic pyrrolizidine alkaloid (+)-xenovenine (**417**), which was isolated from the skin of the frog *Solenopsis xenoveneum*;[322]the resorcylic acid lactone (*R*)-(+)-lasiodiplodin (**418**), which was isolated form the fungus *Botrysdiplodia theobromae* and from the wood of *Euphorbia splendens* and *E. fidjiana*;[323] the potent cytotoxic 20-membered macrolide iriomoteolide-1a, which was isolated from a benthic dinoflagellate *Amphidinium* sp. (strain HYA024) and possessed the proposed structure **419**;[324] the marine lethal toxin (–)-polycarvenoside A (**420**), which was isolated from the edible red alga *Gracilaria edulis* (*Polycavernosa tsudai*);[325] the polyketide apiosporic acid (**421**), a secondary metabolite isolated from the marine endophytic fungus *Apiospora montagnei*;[326] the potent antifungal polycyclic ether metabolite gambieric acid A (**422**), which was isolated from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*;[327] the effective HIV-1 protease inhibitor didemnaketal A, which was isolated from the Ascidian *Didemnum* sp. and for which the structure **423** was proposed;[328] the antimitotic macrocyclic polyketide spirastrellolide A (**424**), which was isolated from the Caribbean marine sponge *Spirastrella coccinea*;[329] the jatrophane diterpenes (–)-15-*O*-acetyl-3-*O*-propionylcharaciol (**425**) and 15-*O*-acetyl-3-*O*-benzoylcharaciol-(5*R*,6*R*)-oxide (**426**), which were isolated from *Euphorbia characias* (Euphorbiaceae);[330] (+)-lycoposerramine Q (**427**), an alkaloid which was isolated from the club moss *Lycopodium serratum* (*Huperzia serrata*);[331] (+)-fawcettidine (**428**), a compound which was first isolated from the Jamaican *Lycopodium* plant *L. fawcettii*;[332] and the oxylipin (–)-ecklonialactone B (**429**), which was isolated from the brown alga *Ecklonia stolonifera*[333] and the Oregon phaephyte *Egregia menziesii*.[334]

TABLE 10 HERE

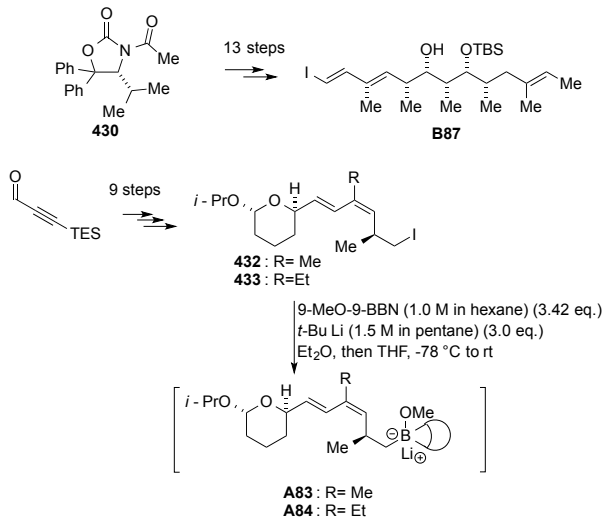
Entries 1–19 of Table 11 illustrate the detailed experimental conditions and yields of $PdCl_2$(dppf)/$AsPh_3$-catalyzed S.-M. reactions which were used in the syntheses of compounds **411–429**. Some comments on these couplings and the application of these reactions in the total syntheses of compounds **411–429** are reported below.

TABLE 11 HERE

The Csp^3–Csp^2 bond forming reactions of entries 1, 2, 8–10, 13 and 19 of Table 11 were carried out using *B*-alkyl S.-M. reactions via the 9-methoxy-9-BBN variant in which the necessary organolithium reagent was generated in the presence 9-MeO-9-BBN and immediately intercepted by this additive to give the corresponding boronate complex. On the other hand, the Csp^3–Csp^2 bond forming reactions of entries 4–7, 11, 12 and 14–18 of Table 11 were performed using crude 9-alkyl-9-BBN derivatives which were prepared by treatment of the corresponding 1-alkene with 9-BBN-H dimer in THF. Finally, the Csp^2–Csp^2 bond forming reaction of entry 3 of Table 11 was carried out using alkenyl iodide **B88** and alkenyl pinacol boronate **A85**, which was prepared

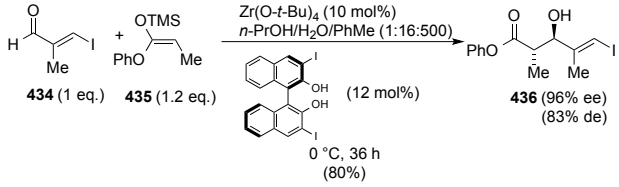
by hydroboration of the corresponding 1-alkyne with pinacolborane.[351]

Compounds **C82** and **C83**, which were synthesized in entries 1 and 2, respectively, of Table 11, were used as advanced intermediates in the first total syntheses of anguinomycins C (**411**) and D (**412**), respectively, which were achieved in total 29 steps with a longest linear sequence of 18 steps from (*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**430**)[352] and in an overall yield of 6.7 and 6.0%, respectively.[335] Vinyl iodide **B87**, which was the electrophile of the sp^3–sp^2 9-MeO-9-BBN-mediated cross-coupling reactions of entries 1 and 2 of Table 11, was synthesized from **430** via a 13 step reaction sequence (Scheme 99).[335]In addition, the known aldehyde **431**[363] was used as the starting material in the synthesis of alkyl iodides **432** and **433**, the direct precursors to boronates **A53** and **A54**, respectively (Scheme 99).[335]



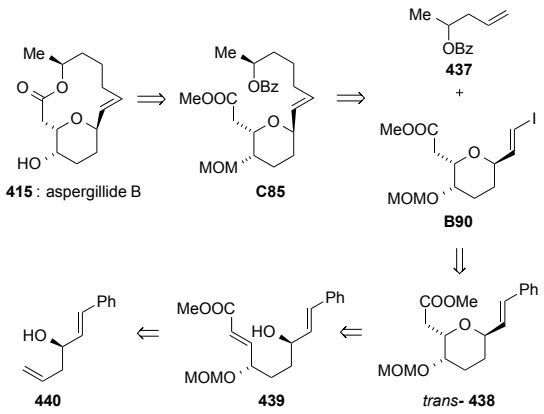
Scheme 99. Synthesis of compounds **B87**, **A83** and **A84**

The high yielding S.-M. reaction between pinacol boronate **A85** vinyl iodide **B88** (entry 3, Table 11) was the last stage of a 13 step total synthesis of the potent toxin antillatoxin (**413**),[336] which began with an *anti*-selective asymmetric aldol reaction between aldehyde **434**[354] and silyl ether **435** to set the two stereocenters at C-4 and C-5 and produced compound **436** in 80% yield with 96% ee (Scheme 100).[336]



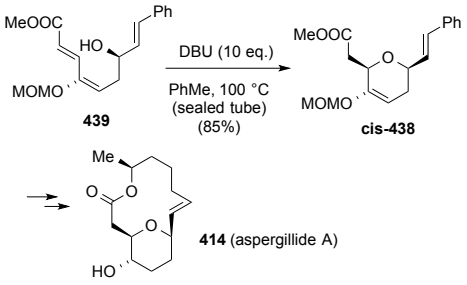
Scheme 100. Asymmetric synthesis of compound **436**

In 2010, Fuwa and co-workers accomplished an enantioselective synthesis of (–)-aspergillide B (**415**), a 14-membered macrolide embedded with a tetrahydropyrane ring, on the basis of the retrosynthetic analysis shown in Scheme 101.[337] A key step of this synthesis was the $PdCl_2$(dppf)/$AsPh_3$-catalyzed S.-M. reaction of vinyl iodide **B90** with alkylborane **A86** (entry 5, Table 11) derived from 1-alkyne **437**, which delivered *trans*-olefin **C85b** in 73% yield. Iodide **B90** was in turn obtained from the known homoallylic alcohol **440**[355] through a 11-step reaction sequence in which compound *trans*-**438**, which was obtained by intramolecular oxa-conjugate cyclization of alcohol **439** in THF at -78 °C in the presence of 0.05 equiv of KO*t*-Bu, was converted to iodide **B90** by ozonolysis followed by Takai olefination[356] ($CrCl_2$, CHI_3, THF/dioxane, rt) (Scheme 101).[337]



Scheme 101. Retrosynthesis of (–)-aspergillide B (**415**)

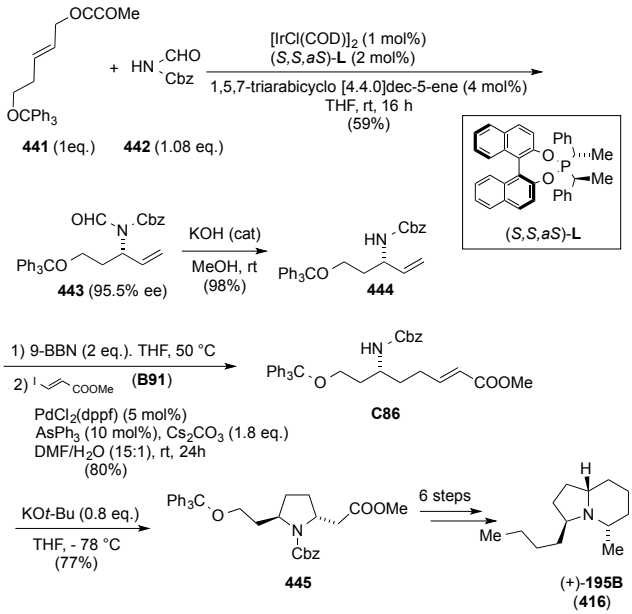
Fuwa and co-workers also carried out the total synthesis of aspergillide A (**414**) by using compound *cis*-**438** as an intermediate, which was obtained in 85% yield with 7:1 diastereoselectivity by exposure of alcohol **439** to 10 equiv of DBU in toluene at 100 °C (Scheme 102).[337]



Scheme 102. Synthesis of aspergillide A (**414**) starting from compound **439**

In 2011, Helmchen and co-workers developed a high quality enantioselective total synthesis of the indolizidine alkaloid (+)-195B (**416**) in which compound **C86**, a key intermediate, was prepared using a reaction sequence, which involved the asymmetric iridium-catalyzed allylic amination of allylic carbonate **441** with the pronucleophile **442**, the *N*-formyl deprotection of the resulting compound **443** and hydroboration with 9-BBN-H of the thereby obtained amine

444, followed by $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction with methyl (*E*)-3-iodoacrylate (**B91**) (Scheme 103).[338] As shown in entry 6 of Table 11, this cross-coupling reaction gave compound **C86** in 80% yield. The subsequent intramolecular aza-Michael addition reaction of **C86** yielded the *trans*-2,5-disubstituted pyrrolidine **445**, which was then converted to **416** via a 6-step reaction sequence (Scheme 103).[338]Unfortunately, compound **416** proved to be contaminated by 5% of an epimer.[338]



Scheme 103. Synthesis of (+)-195B (**416**) from allylic carbonate **441**

A combination of an asymmetric Ir-catalyzed allylic amination, a $PdCl_2$(dppf)/$AsPh_3$-catalyzed S.-M. reaction and an intramolecular Michael addition was also employed for a total synthesis of the alkaloid (+)-xenovenine (**417**) in 95.5% ee.[338] Key intermediates of this process were compounds **C87** and the *trans*-2,5-disubstituted pyrrolidine (**446**) (Figure 22). Compound **C87** was obtained in 80% yield by the S.-M. reaction between alkylborane **A88** and methyl (*E*)-3-iodoacrylate (**B91**) illustrated in entry 7 of Table 11. Compound **446** was in turn obtained by aza-Michael cyclization of compound **447** (Figure 22).[338]

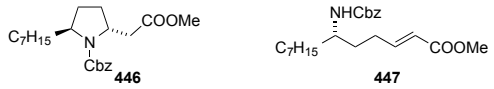
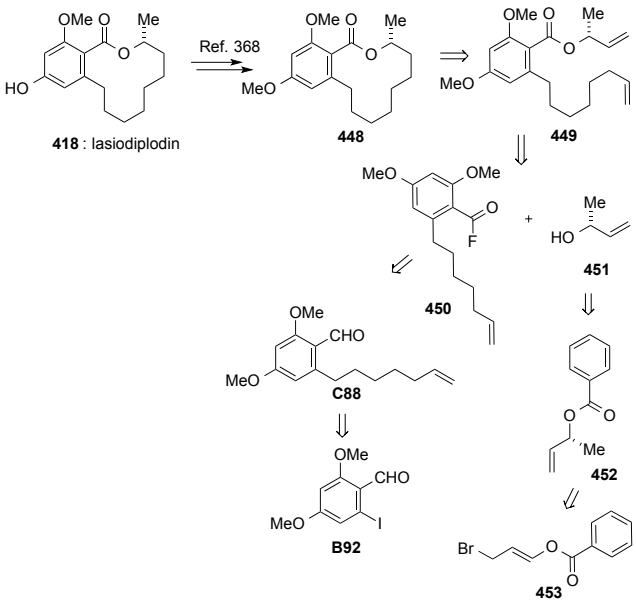


Figure 22. Structures of compounds **446** and **447**

In the same year, Feringa and co-workers used the sp^3-sp^2 9-MeO-9-BBN-mediated coupling reaction illustrated in entry 8 of Table 11 as a key step of a formal synthesis of (*R*)-(+)-lasiodiplodin (**418**), which they accomplished on the basis of the retrosynthetic analysis shown in Scheme 104.[339]

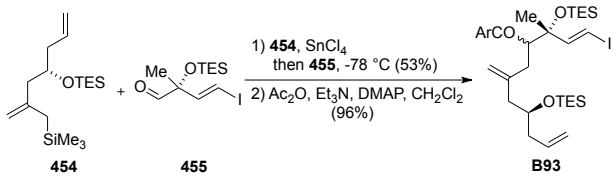


Scheme 104. Retrosynthesis of (*R*)-(+)-lasiodiplodin (**418**)

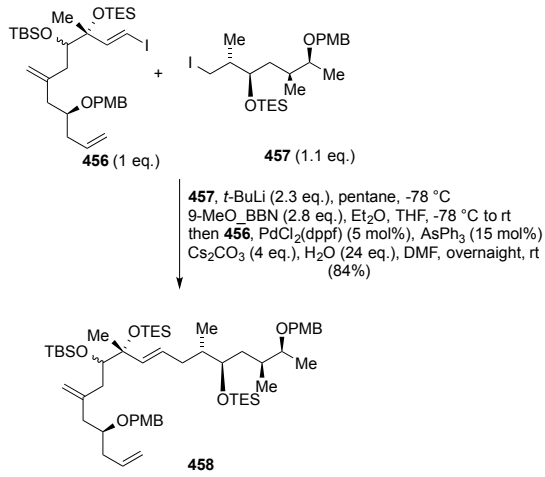
In particular, compound **448** containing the macrolactone ring of **418** was planned to be formed by ring-closing metathesis of diene **449** followed by catalytic hydrogenation. Compound **449** could be available from the tetrasubstituted benzene derivative **450** and allylic alcohol **451**, which could be accessible in high yield and enantioselectivity by CuBr/TaniaPhos-catalyzed asymmetric allylic alkylation of allyl bromide **453**[357] followed by hydrolysis of the resulting ester **452**.[339] Thus, compound **450** was synthesized from **C88**, which in turn was obtained in 52% yield by the $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction of aryl iodide **B92** with boronate **A89** (entry 8, Table 11). Interestingly, the presence of $AsPh_3$ as a coligand was essential for the successful outcome of this cross-coupling reaction. In fact, isomerization of the terminal C–C double bond of **C88** was observed when the reaction was carried out in the absence of $AsPh_3$.[339] Finally, (*R*)-(+)-lasiodiplodin methyl ether **448**, which was obtained in the last step of the formal synthesis of (*R*)-(+)-lasiodiplodin (**418**), was converted into the natural compound according to literature procedures,[358] although in a low yield.[339]

Still in 2011, Horne and co-workers performed the total synthesis of the proposed structure of iriomoteolide-1a (**419**) via an approach in which the C7-C23 fragment of this compound was assembled by the $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction of boronate **A90** with vinyl iodide **B93** (entry 9, Table 11).[340] The latter compound was synthesized in a 4:1 dr by the Sakurai reaction of allylsilane **454** with aldehyde **455** followed by acetylation (Scheme 105).

In a second generation synthesis of the C7-C23 fragment of **419**, the $PdCl_2$(dppf)/$AsPh_3$-catalyzed *B*-alkyl S.-M. reaction between vinyl iodide **456** and alkyl iodide **457** produced fragment **458** in 84% yield (Scheme 106).[340]

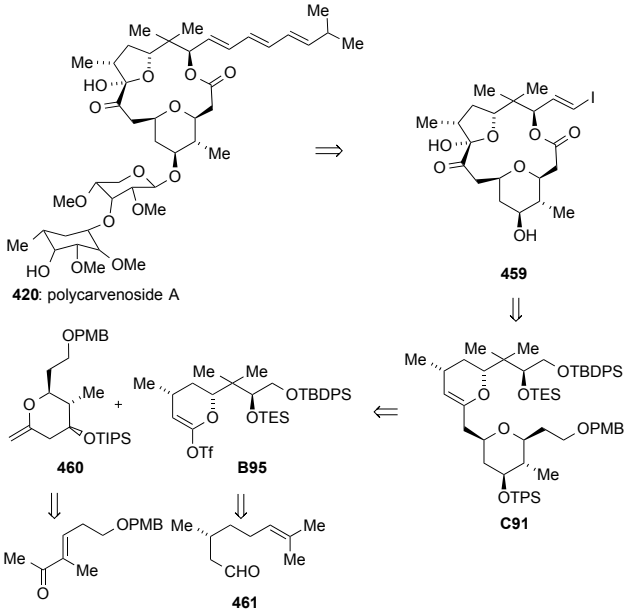


Scheme 105. Synthesis of vinyl iodide **B93**



Scheme 106. Synthesis of compound **458**

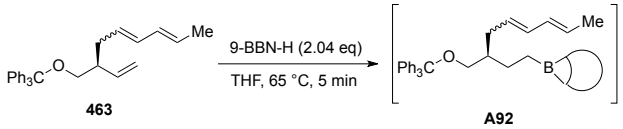
In 2012, Sasaki and co-workers accomplished a total synthesis of the marine lethal toxin (–)-polycarvenoside A (**420**) in 29 steps and 2.4% overall yield via a convergent approach (Scheme 107) in which intermediate **459** was prepared from bis-pyran **C91** and the latter compound was obtained by the $PdCl_2(dppf)\cdot CH_2Cl_2/AsPh_3$-catalyzed reaction of enol triflate **B95** with alkylborane **A91** (entry 11, Table 11) generated by hydroboration of *exo*-olefin **460** with 9-BBN-H in THF.[341]



Scheme 107. Retrosynthesis of (–)-polycarvenoside A (**420**)

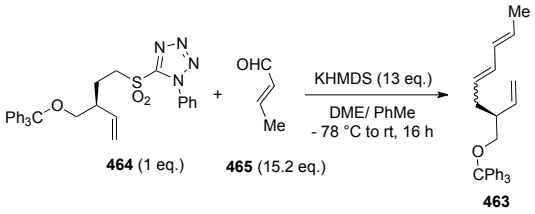
Enol triflate **B95** was asymmetrically generated in 15 steps starting from (*R*)-citronellol (**461**) and *exo*-olefin **460** was prepared through a catalytic asymmetric synthesis starting from the known enone **462**, which was available from 1,3-propanediol.[360] On the other hand, the macrolactone core of the natural product was formed by using the Keck macrolactonization protocol[361] in which DCC, pyridine and PPTS under reflux were used.[362]

In the same year, the $PdCl_2(dppf)/AsPh_3$-catalyzed coupling of methyl (*E*)-3-iodoacrylate (**B91**) with alkylborane **A92** (entry 12, Table 11) was used by Helmchen and co-workers as a key step of the first enantioselective total synthesis of apiosporic acid (**421**).[342] Crucial for the success of the reaction was a short reaction time of the hydroboration reaction of trityl (2*S*,4*E*,6*E*)-2-vinylocta-4,6-dien-1-yl ether (**463**) with 9-BBN-H, which provided crude alkylborane **A92** (Scheme 108).[342]



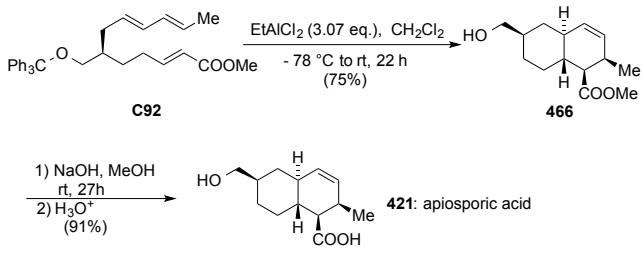
Scheme 108. Synthesis of crude alkylborane **A92**

Compound **463** was in turn synthesized in 69% yield by the reaction of 1-phenyl-5-{(3*S*)-3-[(trityloxy)methyl]pent-4-en-1-yl}sulfonyl-1*H*-tetrazole (**464**) with crotonaldehyde (**465**) in the presence of KHMDS as base (Scheme 109).[342]



Scheme 109. Synthesis of compound **463** from tetrazole **464**

Another key step of the total snthesis of **421** was the $EtAlCl_2$-mediated intramolecular Diels-Alder reaction of the cross-coupling product **C92** of the S.-M. reaction between **A92** and **B91**. (Scheme 110). Hydrolysis of the resulting compound **466** provided apiosporic acid (**421**) (Scheme 110).[342]



Scheme 110. Synthesis of apiosporic acid (**421**) from compound **C92**

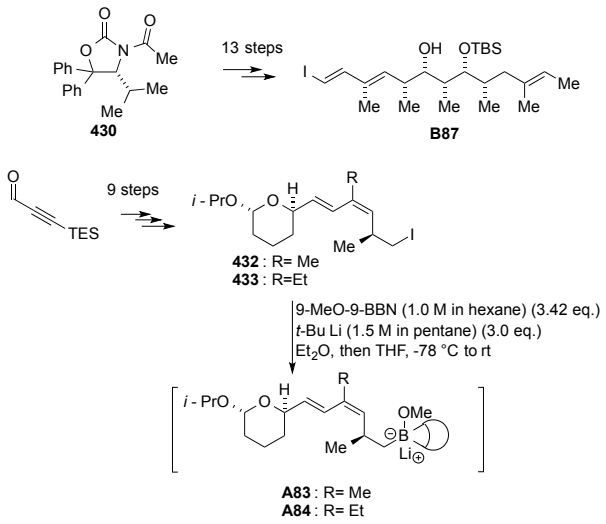
In the same year, Fuwa, Sasaki and co-workers synthesized in quantitative yield compound **C93**, an early precursor to gambieric acid A (**422**), by the $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction of (*Z*)-vinyl iodide **B96** with boronate **A93** which was generated *in situ* from the corresponding alkyl iodide (entry 13, Table 11).[343]Furthermore, compound **469**, a more advanced intermediate in the first total synthesis of **422**, was synthesized in 95% yield by the $PdCl_2$(dppf)·CH_2Cl_2-catalyzed reaction of crude enol phosphate **468** with the alkylborane prepared *in situ* by hydroboration of alkene **467** with 9-BBN-H (Scheme 111).[343]

Interestingly, synthetic gambieric acid A (**422**) was found to display antifungal activity against *Aspergillus niger*, resulting equipotent to that of the natural product.[353]

Still in 2012, a notable total synthesis of the proposed structure of didemnaketal A (**423**) was described by Tu and co-workers.[344] This compound featuring a spiroketal moiety and a main chain containing 23 carbons and 12 stereocenters was synthesized in 31 steps for the longest linear sequence.

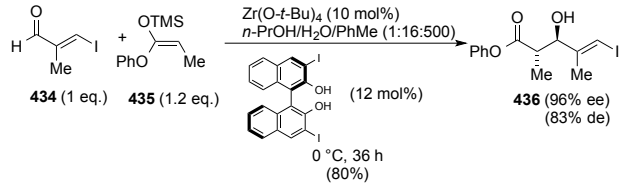
The Csp^3–Csp^2 bond forming reactions of entries 1, 2, 8–10, 13 and 19 of Table 11 were carried out using *B*-alkyl S.-M. reactions via the 9-methoxy-9-BBN variant in which the necessary organolithium reagent was generated in the presence 9-MeO-9-BBN and immediately intercepted by this additive to give the corresponding boronate complex. On the other hand, the Csp^3–Csp^2 bond forming reactions of entries 4–7, 11, 12 and 14–18 of Table 11 were performed using crude 9-alkyl-9-BBN derivatives which were prepared by treatment of the corresponding 1-alkene with 9-BBN-H dimer in THF. Finally, the Csp^2–Csp^2 bond forming reaction of entry 3 of Table 11 was carried out using alkenyl iodide **B88** and alkenyl pinacol boronate **A85**, which was prepared by hydroboration of the corresponding 1-alkyne with pinacolborane.[351]

Compounds **C82** and **C83**, which were synthesized in entries 1 and 2, respectively, of Table 11, were used as advanced intermediates in the first total syntheses of anguinomycins C (**411**) and D (**412**), respectively, which were achieved in total 29 steps with a longest linear sequence of 18 steps from (*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**430**)[352] and in an overall yield of 6.7 and 6.0%, respectively.[335] Vinyl iodide **B87**, which was the electrophile of the sp^3–sp^2 9-MeO-9-BBN-mediated cross-coupling reactions of entries 1 and 2 of Table 11, was synthesized from **430** via a 13 step reaction sequence (Scheme 99).[335]In addition, the known aldehyde **431**[363] was used as the starting material in the synthesis of alkyl iodides **432** and **433**, the direct precursors to boronates **A53** and **A54**, respectively (Scheme 99).[335]



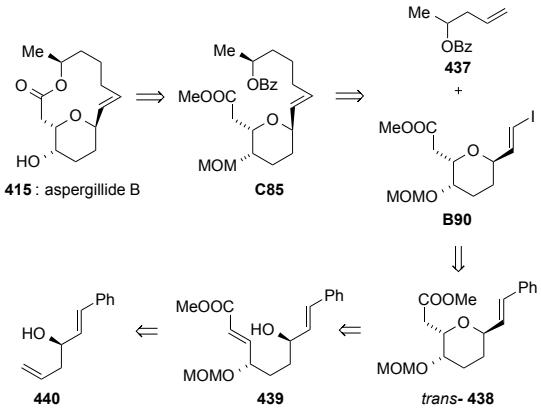
Scheme 99. Synthesis of compounds **B87**, **A83** and **A84**

The high yielding S.-M. reaction between pinacol boronate **A85** vinyl iodide **B88** (entry 3, Table 11) was the last stage of a 13 step total synthesis of the potent toxin antillatoxin (**413**),[336] which began with an *anti*-selective asymmetric aldol reaction between aldehyde **434**[354] and silyl ether **435** to set the two stereocenters at C-4 and C-5 and produced compound **436** in 80% yield with 96% ee (Scheme 100).[336]



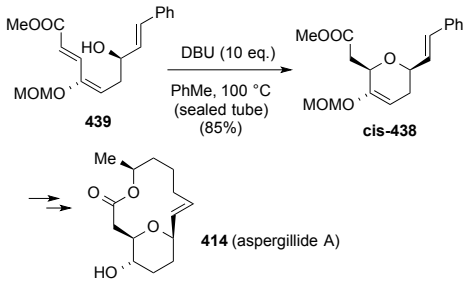
Scheme 100. Asymmetric synthesis of compound **436**

In 2010, Fuwa and co-workers accomplished an enantioselective synthesis of (–)-aspergillide B (**415**), a 14-membered macrolide embedded with a tetrahydropyrane ring, on the basis of the retrosynthetic analysis shown in Scheme 101.[337] A key step of this synthesis was the $PdCl_2$(dppf)/$AsPh_3$-catalyzed S.-M. reaction of vinyl iodide **B90** with alkylborane **A86** (entry 5, Table 11) derived from 1-alkyne **437**, which delivered *trans*-olefin **C85b** in 73% yield. Iodide **B90** was in turn obtained from the known homoallylic alcohol **440**[355] through a 11-step reaction sequence in which compound *trans*-**438**, which was obtained by intramolecular oxa-conjugate cyclization of alcohol **439** in THF at -78 °C in the presence of 0.05 equiv of KO*t*-Bu, was converted to iodide **B90** by ozonolysis followed by Takai olefination[356] ($CrCl_2$, CHI_3, THF/dioxane, rt) (Scheme 101).[337]



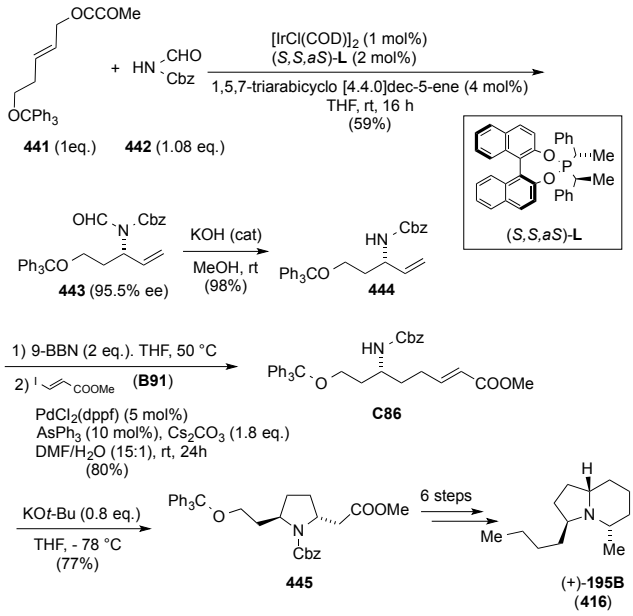
Scheme 101. Retrosynthesis of (–)-aspergillide B (**415**)

Fuwa and co-workers also carried out the total synthesis of aspergillide A (**414**) by using compound *cis*-**438** as an intermediate, which was obtained in 85% yield with 7:1 diastereoselectivity by exposure of alcohol **439** to 10 equiv of DBU in toluene at 100 °C (Scheme 102).[337]



Scheme 102. Synthesis of aspergillide A (**414)** starting from compound **439**

In 2011, Helmchen and co-workers developed a high quality enantioselective total synthesis of the indolizidine alkaloid (+)-195B (**416**) in which compound **C86**, a key intermediate, was prepared using a reaction sequence, which involved the asymmetric iridium-catalyzed allylic amination of allylic carbonate **441** with the pronucleophile **442**, the *N*-formyl deprotection of the resulting compound **443** and hydroboration with 9-BBN-H of the thereby obtained amine **444**, followed by $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction with methyl (*E*)-3-iodoacrylate (**B91**) (Scheme 103).[338] As shown in entry 6 of Table 11, this cross-coupling reaction gave compound **C86** in 80% yield. The subsequent intramolecular aza-Michael addition reaction of **C86** yielded the *trans*-2,5-disubstituted pyrrolidine **445**, which was then converted to **416** via a 6-step reaction sequence (Scheme 103).[338]Unfortunately, compound **416** proved to be contaminated by 5% of an epimer.[338]



Scheme 103. Synthesis of (+)-195B (**416**) from allylic carbonate **441**

A combination of an asymmetric Ir-catalyzed allylic amination, a $PdCl_2$(dppf)/$AsPh_3$-catalyzed S.-M. reaction and an intramolecular Michael addition was also employed for a total synthesis of the alkaloid (+)-xenovenine (**417**) in 95.5% ee.[338] Key intermediates of this process were compounds **C87** and the *trans*-2,5-disubstituted pyrrolidine (**446**) (Figure 22). Compound **C87** was obtained in 80% yield by the S.-M. reaction between alkylborane **A88** and methyl (*E*)-3-iodoacrylate (**B91)** illustrated in entry 7 of Table 11. Compound **446** was in turn obtained by aza-Michael cyclization of compound **447** (Figure 22).[338]

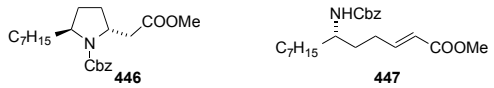
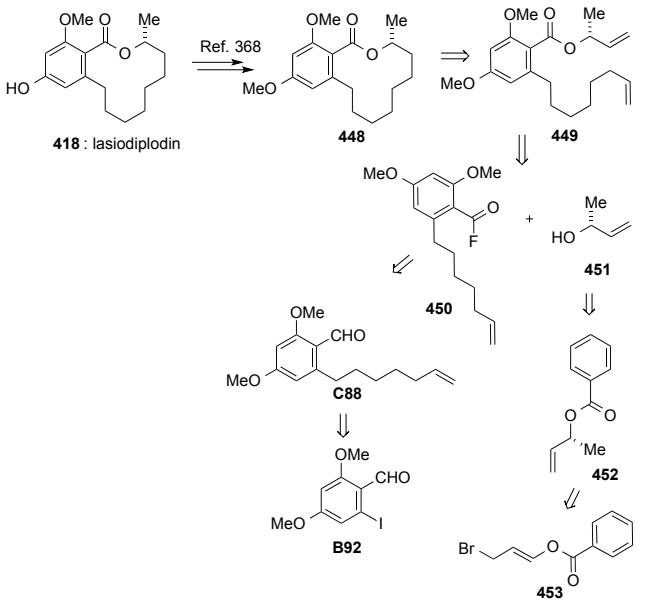


Figure 22. Structures of compounds **446** and **447**

In the same year, Feringa and co-workers used the sp^3-sp^2 9-MeO-9-BBN-mediated coupling reaction illustrated in entry 8 of Table 11 as a key step of a formal synthesis of (*R*)-(+)-lasiodiplodin (**418**), which they accomplished on the basis of the retrosynthetic analysis shown in Scheme 104.[339]

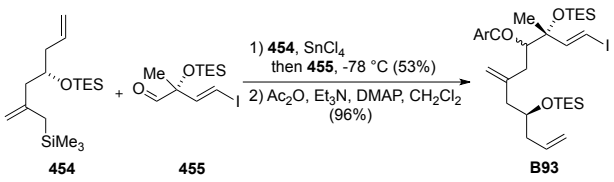


Scheme 104. Retrosynthesis of (*R*)-(+)-lasiodiplodin (**418**)

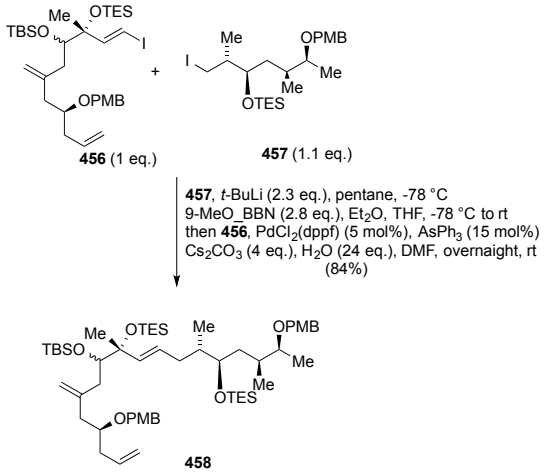
In particular, compound **448** containing the macrolactone ring of **418** was planned to be formed by ring-closing metathesis of diene **449** followed by catalytic hydrogenation. Compound **449** could be available from the tetrasubstituted benzene derivative **450** and allylic alcohol **451**, which could be accessible in high yield and enantioselectivity by CuBr/TaniaPhos-catalyzed asymmetric allylic alkylation of allyl bromide **453**[357] followed by hydrolysis of the resulting ester **452**.[339] Thus, compound **450** was synthesized from **C88**, which in turn was obtained in 52% yield by the $PdCl_2(dppf)/AsPh_3$-catalyzed reaction of aryl iodide **B92** with boronate **A89** (entry 8, Table 11). Interestingly, the presence of $AsPh_3$ as a coligand was essential for the successful outcome of this cross-coupling reaction. In fact, isomerization of the terminal C–C double bond of **C88** was observed when the reaction was carried out in the absence of $AsPh_3$.[339] Finally, (*R*)-(+)-lasiodiplodin methyl ether **448**, which was obtained in the last step of the formal synthesis of (*R*)-(+)-lasiodiplodin (**418**), was converted into the natural compound according to literature procedures,[358] although in a low yield.[339]

Still in 2011, Horne and co-workers performed the total synthesis of the proposed structure of iriomoteolide-1a (**419**) via an approach in which the C7-C23 fragment of this compound was assembled by the $PdCl_2(dppf)/AsPh_3$-catalyzed reaction of boronate **A90** with vinyl iodide **B93** (entry 9, Table 11).[340] The latter compound was synthesized in a 4:1 dr by the Sakurai reaction of allylsilane **454** with aldehyde **455** followed by acetylation (Scheme 105).

In a second generation synthesis of the C7-C23 fragment of **419**, the $PdCl_2(dppf)/AsPh_3$-catalyzed *B*-alkyl S.-M. reaction between vinyl iodide **456** and alkyl iodide **457** produced fragment **458** in 84% yield (Scheme 106).[340]

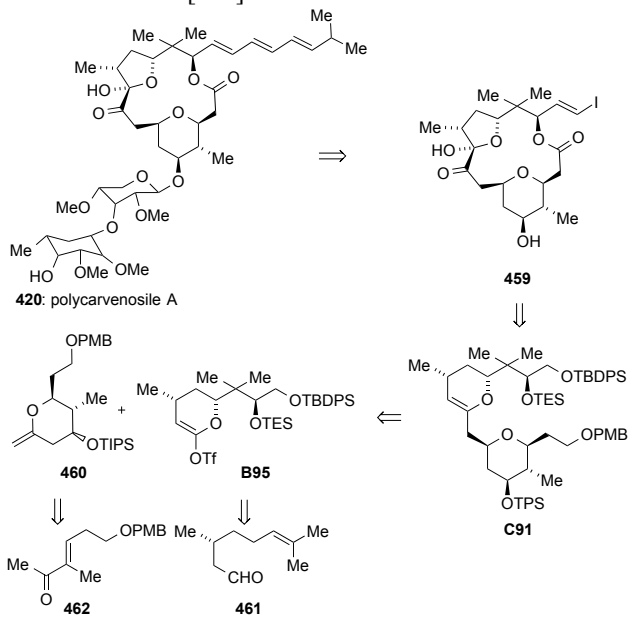


Scheme 105. Synthesis of vinyl iodide **B93**



Scheme 106. Synthesis of compound **458**

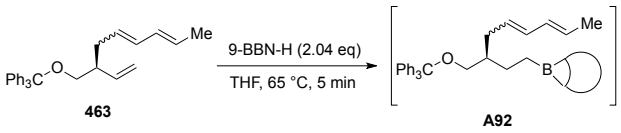
In 2012, Sasaki and co-workers accomplished a total synthesis of the marine lethal toxin (–)-polycarvenoside A (**420**) in 29 steps and 2.4% overall yield via a convergent approach (Scheme 107) in which intermediate **459** was prepared from bis-pyran **C91** and the latter compound was obtained by the $PdCl_2(dppf)\cdot CH_2Cl_2/AsPh_3$-catalyzed reaction of enol triflate **B95** with alkylborane **A91** (entry 11, Table 11) generated by hydroboration of *exo*-olefin **460** with 9-BBN-H in THF.[341]



Scheme 107. Retrosynthesis of (–)-polycarvenoside A (**420**)

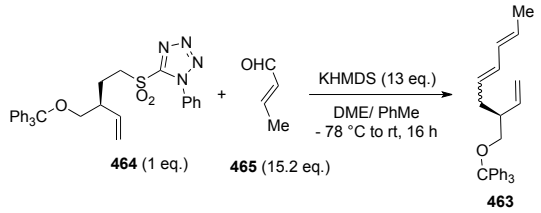
Enol triflate **B95** was asymmetrically generated in 15 steps starting from (*R*)-citronellol (**461**) and *exo*-olefin **460** was prepared through a catalytic asymmetric synthesis starting from the known enone **462**, which was available from 1,3-propanediol.[360] On the other hand, the macrolactone core of the natural product was formed by using the Keck macrolactonization protocol[361] in which DCC, pyridine and PPTS under reflux were used.[362]

In the same year, the $PdCl_2$(dppf)/$AsPh_3$-catalyzed coupling of methyl (*E*)-3-iodoacrylate (**B91**) with alkylborane **A92** (entry 12, Table 11) was used by Helmchen and co-workers as a key step of the first enantioselective total synthesis of apiosporic acid (**421**).[342] Crucial for the success of the reaction was a short reaction time of the hydroboration reaction of trityl (2*S*,4*E*,6*E*)-2-vinylocta-4,6-dien-1-yl ether (**463**) with 9-BBN-H, which provided crude alkylborane **A92** (Scheme 108).[342]



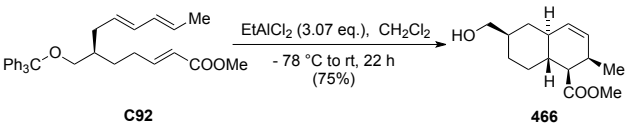
Scheme 108. Synthesis of crude alkylborane **A92**

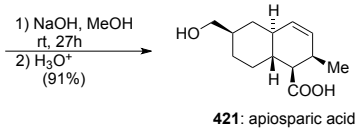
Compound **463** was in turn synthesized in 69% yield by the reaction of 1-phenyl-5-{(3*S*)-3-[(trityloxy)methyl]pent-4-en-1-yl}sulfonyl-1*H*-tetrazole (**464**) with crotonaldehyde (**465**) in the presence of KHMDS as base (Scheme 109).[342]



Scheme 109. Synthesis of compound **463** from tetrazole **464**

Another key step of the total snthesis of **421** was the $EtAlCl_2$-mediated intramolecular Diels-Alder reaction of the cross-coupling product **C92** of the S.-M. reaction between **A92** and **B91**. (Scheme 110). Hydrolysis of the resulting compound **466** provided apiosporic acid (**421**) (Scheme 110).[342]



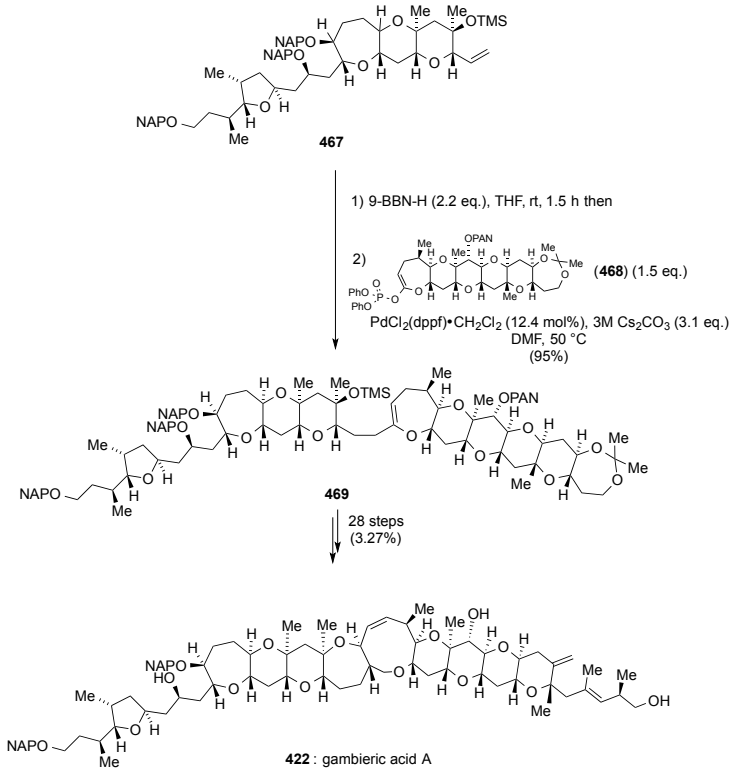


Scheme 110. Synthesis of apiosporic acid (**421**) from compound **C92**

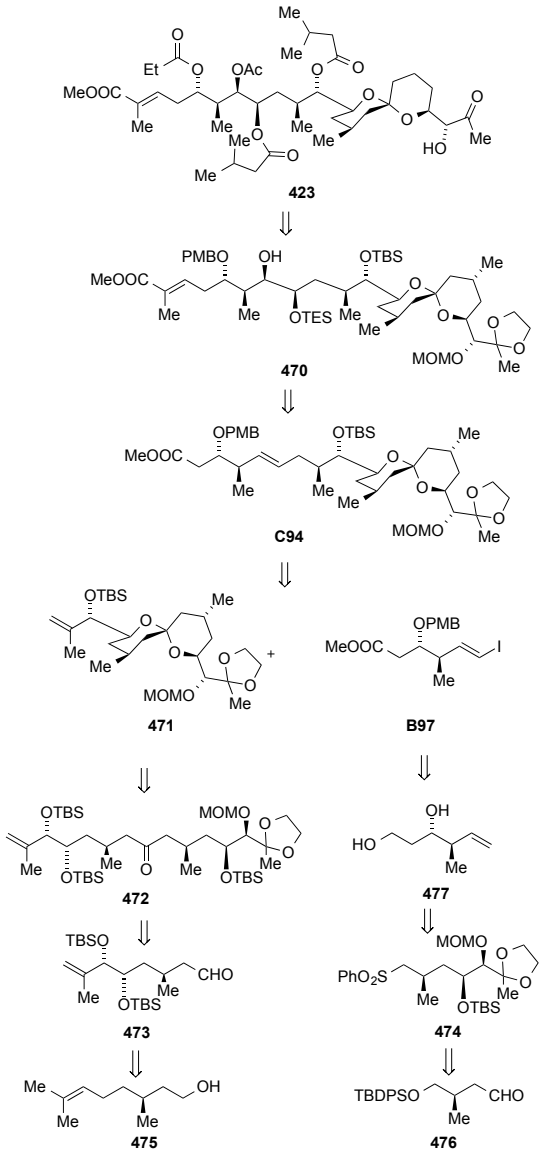
In the same year, Fuwa, Sasaki and co-workers synthesized in quantitative yield compound **C93**, an early precursor to gambieric acid A (**422**), by the $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction of (*Z*)-vinyl iodide **B96** with boronate **A93** which was generated *in situ* from the corresponding alkyl iodide (entry 13, Table 11).[343]Furthermore, compound **469**, a more advanced intermediate in the first total synthesis of **422**, was synthesized in 95% yield by the $PdCl_2$(dppf)·CH_2Cl_2-catalyzed reaction of crude enol phosphate **468** with the alkylborane prepared *in situ* by hydroboration of alkene **467** with 9-BBN-H (Scheme 111).[343]

Interestingly, synthetic gambieric acid A (**422**) was found to display antifungal activity against *Aspergillus niger*, which was equipotent to that of the natural product.[353]

Still in 2012, a notable total synthesis of the proposed structure of didemnaketal A (**423**) was described by Tu and co-workers.[344] This compound featuring a spiroketal moiety and a main chain containing 23 carbons and 12 stereocenters was synthesized in 31 steps for the longest linear sequence.



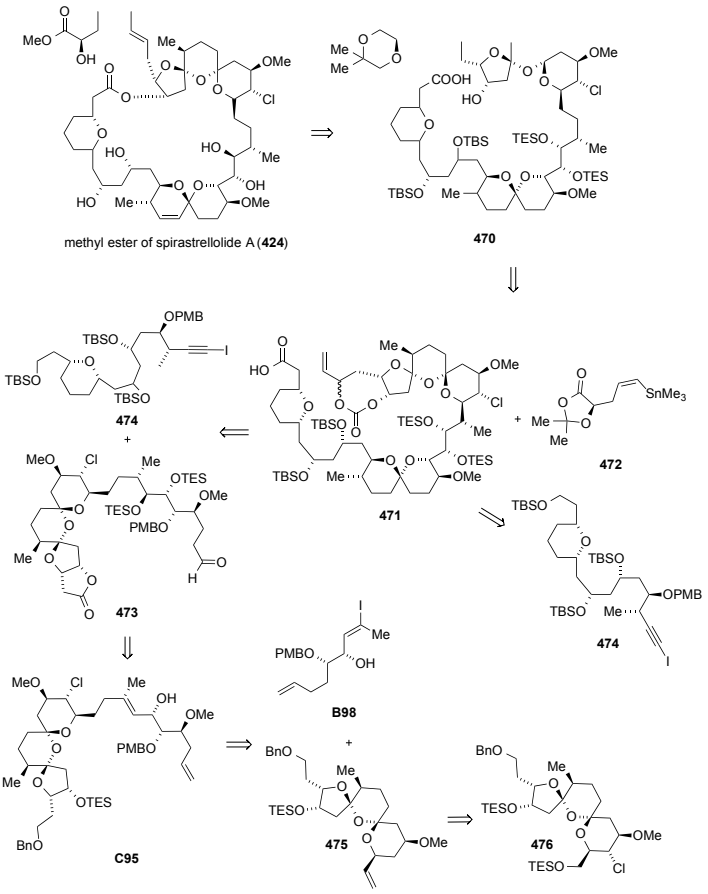
Scheme 111. Synthesis of gambieric acid A (**422**) from compound **467**



Scheme 112. Retrosynthesis of the nominal didemnaketal A

As shown in the retrosynthesis illustrated in Scheme 112, the advanced intermediate **470** containing all stereocenters and the entire C1–C23 chain was available from compound **C94** containing the C3–C23 chain. It was synthesized in 77% yield from vinyl iodide **B97** and alkylborane **A94** (entry 14, Table 11), which was prepared by hydroboration of alkene **471** with 9-BBN-H. Iodide **B97** was obtained from the known diol **477**[363] in 42.5% overall yield via a 6-step reaction sequence. Alkene **471** was in turn obtained via $NH_4F{\cdot}HF$-promoted spirocyclization of compound **472**, which was available in 82% yield from aldehyde **473** and sulfone **474**. In turn, **473** was synthesized in 22.4% yield starting from (*S*)-citronellol (**475**) via a series of five reactions and sulfone **474** was prepared from aldehyde **476**[364] in 30.4% overall yield through a series of five reactions.[344]

A few month before the publication of this synthesis of didemnaketal A, Paterson and co-workers successfully developed a total synthesis of the methyl ester of the antimitotic marine macrolide spirastrellolide A (**424**).[345] The synthesis that proceeded in 6% overall yield over 23 steps was carried out starting from the known bis(spiroacetal) intermediate **476** according to the retrosynthesis shown in Scheme 113.[365]

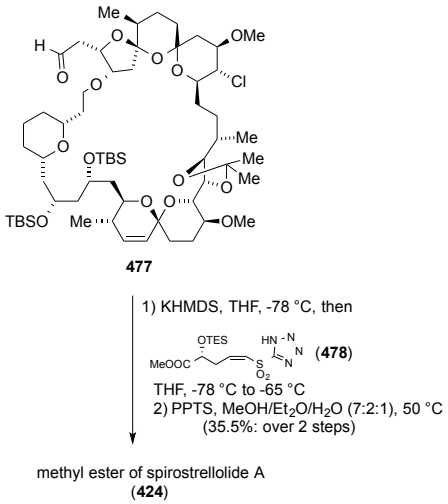


Scheme 113. Retrosynthesis of the methyl ester of spirastrellolide A (**424**)

The synthesis commenced with the selective desilylation of **476** and oxidation of the resulting alcohol, followed by a methylenation reaction ($MePPh_3Br$, *n*-BuLi), which provided alkene **475** in 70% overall yield. Hydroboration of **475** with 9-BBN-H gave alkylborane **A95**, which was subjected to $PdCl_2(dppf)/AsPh_3$-catalyzed reaction with vinyl iodide **B98** in a mixture of THF and DMF at room temperature in the presence of Cs_2CO_3 as base delivering diene **C95** in quantitative yield (entry 15, Table 11). A subsequent 5-step reaction sequence allowed to convert **C95** into the building block **473**, which was coupled with iodoalkyne **474** under Nozaki-Hiyama-Kishi conditions ($NiCl_2$, $CrCl_2$).[366] The resulting propargylic alcohol was converted into the C1–C42 carboxylic acid **471** in 30% overall yield by using a 9-step reactions sequence. The full spirastrellolide A side chain was then assembled by the $PdCl_2(MeCN)_2$-catalyzed smooth coupling of **471** with the C43-C47 stannane **472**, which gave

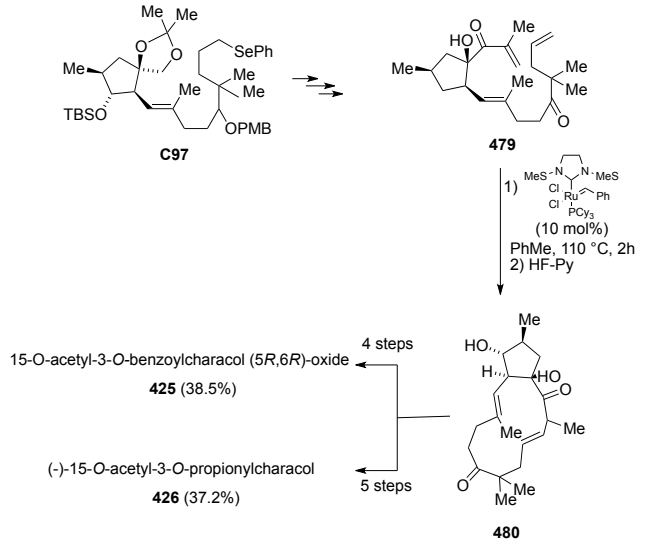
the C1-C47 diene **470** as a single stereoisomer in 86% yield. Finally, a series of reactions involving removal of the silyl groups, Yamaguchi macrolactonization[367] and cleavage of the dioxolane protecting group provided the methyl ester of spirastrellolide A (Scheme 113).[345]

More recently, a second total synthesis of spirastrellolide A methyl ester was accomplished by Fürstner and co-workers.[356] A crucial step of this concise synthesis was the $PdCl_2(dppf)\cdot CH_2Cl_2/AsPh_3$-catalyzed reaction between alkenyl triflate **B99** and alkylborane **A96** in THF at room temperature in the presence of 1M aq NaOH (entry 16, Table 11). The coupling, which gave compound **C96** in 65% yield, allowed to join the northern and eastern sectors of the target compound. Another crucial step was the Yamaguchi lactonization of **C96**, which forged the macrocyclic ring of the methyl ester of **424**. Finally, the lateral side-chain of this compound, comprising the remote C46 stereocenter, was attached to the core structure via a Julia-Kocienski olefination reaction[368] of aldehyde **477** with the known sulfone **478**[369] (Scheme 114).



Scheme 114. Synthesis of the methyl ester of spirastrellolide A from compound **477**

In 2011, Wiese, Hiersemann and co-workers reported the details of the total syntheses of (–)-15-*O*-acetyl-3-*O*-propionylcharaciol (**425**), a compound which was found to be cytotoxic against human cancer cell lines and to possess multidrug resistance-modulating properties,[370] and of 15-*O*-acetyl-3-*O*-benzoylcharaciol (5*R*,6*R*)-oxide (**426**).[347] The tactic used for the assembly of the *trans*-bicyclo[10.3.0]pentadecane scaffold of **425** involved the formation of the C5–C6 double bond of this natural compound via the $PdCl_2(dppf)/AsPh_3$-catalyzed reaction between alkylborane **A97** and alkenyl iodide **B100** in a mixture of DMF, THF and water at 80 °C in the presence of Cs_2CO_3 as base (entry 17, Table 11).[347]Furthermore, a Ru-catalyzed ring-closing metathesis of compound **479**, which was obtained in 6 steps from the S.-M. cross-coupling product **C97**, was used to establish the fully substituted *trans*-bicyclo[10.3.0]pentadecane framework of **425** (Scheme 115). Diene **480** resulting from the ring-closing metathesis reaction was then used as the common precursor to compounds **425** and **426** (Scheme 115).[347]



Scheme 115. Synthesis of compounds **425** and **426** from the cross-coupling product **C97**

In 2013, G. Zhao and co-workers performed the total syntheses of (+)-lycoposerramine Q (**427**) and (+)-fawcettidine (**428**) from the common intermediate **C98**, which was obtained in 92% yield by the $PdCl_2(dppf)/AsPh_3$-catalyzed reaction of alkylborane **A98** with cycloalkenyl triflate **B101** in a mixture of THF, water and DMF at 60 °C in the presence of C_2CO_3 as base (entry 18, Table 11).[348] The Hajos-Parrish-like diketone **481** (Figure 23), which was used as the starting material of the total syntheses, was easily prepared from 1,3-cyclopentanedione through a 3-step procedure.[371]

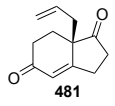
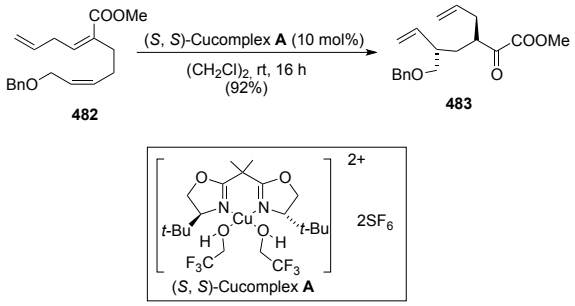


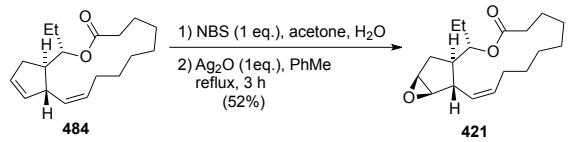
Figure 23. Structure of diketone **481**

Still in 2013, Hiersemann and co-workers described a notable synthesis of (–)-ecklonialactone B (**429**) in 2% overall yield starting from allyl vinyl ether **482**.[349] The building block **483** was prepared on a gram scale in 91% yield, dr ≤95:5 and >99% ee by catalytic asymmetric Gosteli-Claisen rearrangement[372] of **482** (Scheme 116).[349]



Scheme 116. Synthesis of compound **483**

The total synthesis also included the efficient preparation of intermediate **C99** by $PdCl_2$(dppf)/$AsPh_3$-catalyzed reaction of *B*-alkyl borate complex **A99** with vinyl iodide **B102** in a mixture of THF and DMF at room temperature in the presence of Cs_2CO_3 as base (entry 19, Table 11). However, compound **C99** proved to be contaminated by ca. 10% of the corresponding *E*-stereoisomer.[349] Finally, the last step of the total synthesis of **429** was the regio- and diastereoselective epoxidation of diene **484**, which was accomplished by a two-step procedure involving the reaction of **484** with 1 equiv of NBS in aqueous acetone and subsequent treatment of the resulting isolated and purified bromohydrin with Ag_2O in refluxing toluene (Scheme 117).[349]



Scheme 117. Epoxidation of diene **484**

8. CONCLUSION

Although in the last years a wide variety of new palladium-based catalyst systems have been developed for the S.-M. cross-coupling reaction, a large number of recent total syntheses of natural products have continued to benefit from efficient and chemoselective S.-M. couplings involving the use of "classical" phosphane-based Pd-catalysts. In such total syntheses, the construction of Csp^3–Csp^2 bonds and iterative cross-coupling reactions have often been performed by using organoboron reagents such as 9-alkyl-9-BBN derivatives, 9-MeO-9-BBN boronates and MIDA boronates.

Nevertheless, despite the good results achieved so far and illustrated in this review through the use of phosphane-based Pd-catalyst systems, which are also testified by those reported in some papers published in the early months of 2014,[373] we can expect that, given the remarkable progress recently gained on the catalyst systems and the experimental conditions of the S.-M. reaction, future studies on the synthesis, especially on a large scale, of natural products that are particularly important for their bioactivity are aimed at developing the use of Pd-catalysts of S.-M. reactions that operate with high turnover numbers and in the absence of ligands as well as at identifying experimental conditions in which such cross-couplings are carried out in the absence of organic solvents, at mild temperatures and without the use of a large molar excess of bases.

LIST OF ABBREVIATIONS

Ac, acetyl; acac, acetylacetonate; Ar, aryl; AIBN, 2,2'-azobisisobutyronitrile; 9-BBN-H, 9-borabicyclo[3.3.1]nonane; 9-BBN, 9-borabicyclo[3.3.1]nonyl; BMIDA, *N*-methyliminodiacetic acid-protected boronate; Bn, benzyl; Boc, *t*-butoxycarbonyl; *n*-Bu, *n*-butyl; *t*-Bu, *t*-butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, carbobenzyloxy; Cy, cyclohexyl; dba, dibenzylideneacetone; DBU, 1,5-diazabicyclo[5.4.0]undec-5-ene; DCC, dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIAD, diisopropyl azodicarboxylate; DIBAL-H, diisobutylaluminum hydride; DMAP, 4-(*N,N'*-dimethylamino)pyridine; DMEDA, *N,N'*-dimethyl-1,2-ethanediamine; DMF, *N,N*-dimethylformamide; dppf, 1,1'-bis(diphenylphosphino)ferrocene; d.r., diastereomeric ratio; ee, enantiomeric excess, EE, ethoxyethyl; Et, ethyl; Ipc, isopinocampheyl; JohnPhos, (2-biphenyl)di-*t*-butylphosphine; KHMDS, potassium hexamethyldisilazane; Me, methyl; MPM, 4-methoxybenzyl; MOM, methoxymethyl; MW, microwave; NaHMDS, sodium hexamethyldisilazane; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide; n.r., not reported; *N*-Succ, *N*-succinimidyl; Ph, phenyl; pin, pinacol; Piv, pivaloyl; PMB, *p*-methoxybenzyl; PPTS, pyridinium *p*-toluenesulfonate; *i*-Pr, *i*-propyl; *n*-Pr, *n*-propyl; Py, pyridine; rt, room temperature; RuPhos, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; SEM, 2-(trimethylsilyl)ethoxymethyl; SPhos, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; TBAB, tetrabutylammonium bromide; TBAF, tetrabutylammonium fluoride; TBDPS, *t*-butyldiphenylsilyl; TBS, *t*-butyldimethylsilyl; TES, triethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofurane; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl; *o*-Tol, *o*-tolyl; Tr, trityl; *p*-Ts, *p*-toluenesulfonyl; XPhos, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

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