Chapter 3
Natural Product Synthesis

Yasuhiro Okuda and Yasushi Nishihara

Abstract The synthetic routes to the natural products are designed with consideration of the structures of the reagents, functional group tolerance, total yields, and the environmental benignness of wastes. In natural product syntheses, the cross-couplings as carbon–carbon bond-forming reactions have been widely utilized for the construction of fragments as the key steps in the total syntheses.

Keywords Natural product · Total synthesis · Selectivity · Convergent synthesis · Hybridization

3.1 Introduction

Natural organic compounds with specific chemical structures and bioactivities have intimate relationships with pharmaceuticals, dyes, spices, etc., and are thus extremely important industrially. Frequently, only a small amount of a natural product can be harvested from its naturally occurring source; in these cases, organic synthesis is necessary if a large amount of the natural product is required. Furthermore, the synthetic route is often simply more cost-effective or practical. Some naturally occurring products with unique physical and chemical properties are preferable for the production of fine chemicals. In fact, the proportion of these products supplied from nature is only about 5 %. This extensive demand implies that partial or total synthesis is necessary and indispensable [1].

Although a variety of organic reactions (e.g., aldol reactions and Grignard reactions) have been conventionally used for carbon–carbon bond formation in natural product syntheses, these reactions are not able to satisfy some demands due

Y. Okuda (✉) · Y. Nishihara
Division of Earth, Life, and Molecular Sciences Graduate School of Natural, Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku 700-8530 Okayama, Japan
e-mail: ynishiha@okayama-u.ac.jp

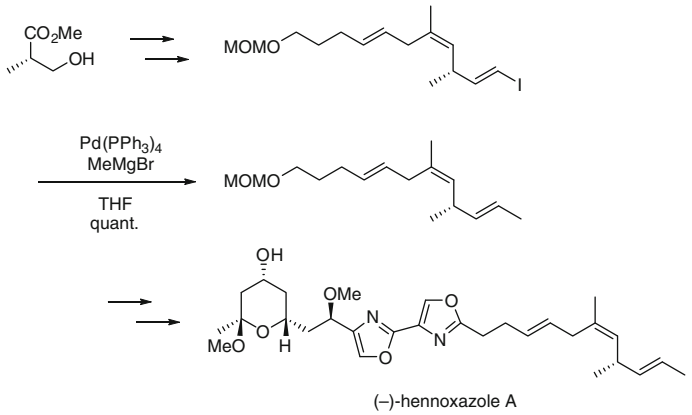
Y. Nishihara (ed.), *Applied Cross-Coupling Reactions*, Lecture Notes in Chemistry 80,
DOI: 10.1007/978-3-642-32368-3_3,

to a low selectivity and due to substrate limitations. However, the cross-coupling reactions are widely accepted as carbon–carbon bond-forming methodologies that can achieve high selectivity and functional group tolerance in the synthesis of natural products with complicated chemical structures [2].

Considering the establishment of convergent synthesis and the easy availability of starting materials in natural product syntheses, the cross-coupling methods introduced in this publication are very powerful strategic tools for carbon–carbon bond formation. However, when the target molecules are synthesized with these cross-coupling reactions, appropriate selection of substrates and reagents is essential. This chapter will review recent examples of how the cross-coupling reactions have been used in practical natural product syntheses.

3.2 Kumada–Tamao–Corriu Coupling (sp^3–sp^2)

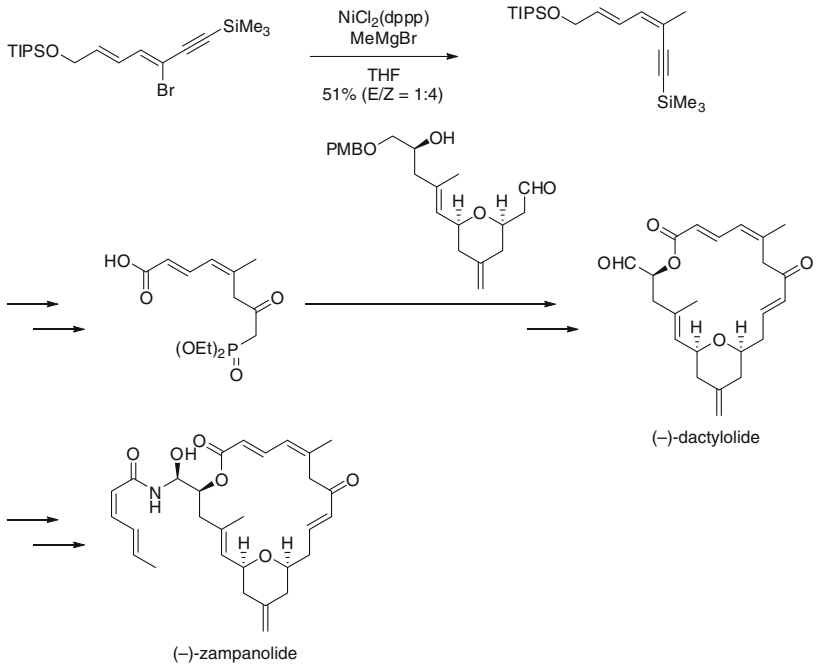
Because the highly reactive Grignard reagents can be employed in Kumada–Tamao–Corriu coupling, these reactions have been applied to natural product syntheses in recent years. Kumada–Tamao–Corriu coupling is advantageous due to the utility of commercially available Grignard reagents. For example, a precursor of (−)-hennoxazole A was synthesized selectively and quantitatively by methylation of the substrate bearing a protected hydroxy group with methylmagnesium bromide under palladium catalysis (Scheme 3.1) [3].



Scheme 3.1 Total synthesis of (–)-hennoxazole A

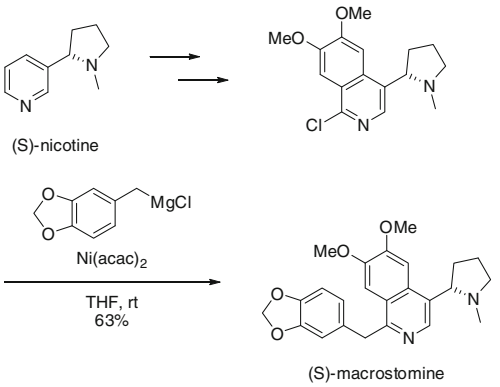
Since Kumada–Tamao–Corriu coupling lacks functional group tolerance, its utilization in the final stages of synthesis of the natural products is rare. However, there is a natural abundance of magnesium with the eighth Clark's number (1.93 wt %), and the preparation of Grignard reagents is relatively easy. Thus, Kumada–Tamao–Corriu coupling can play an important part in synthesis if the substrates are stable enough toward Grignard reagents. Hereafter, more examples of Kumada–Tamao–Corriu coupling as the key step in an overall synthesis will be introduced.

E/Z stereoisomerization is known to be one of the side reactions in the nickel-catalyzed Kumada–Tamao–Corriu coupling of alkenyl halides with Grignard reagents. However, this isomerization has been utilized for the selective synthesis of (−)-zampanolide by manipulating the steric effect of the substituent (Scheme 3.2) [4]. In this method, a selective synthesis of the trisubstituted dienyne as a target product was attained by the introduction of an alkynyl group stereoselectively through Sonogashira–Hagihara coupling and the subsequent isomerization of an olefinic moiety during the Ni-catalyzed Kumada–Tamao–Corriu coupling. Thus, this example shows the advantageous features of the Ni-catalyzed Kumada–Tamao–Corriu coupling—appropriate selection of the substituents and ligands enable control of the stereoselectivity of the products. In this reaction, the undesired side reaction does not take place at all, even under basic conditions, and the cross-coupling of aryl halides with achiral Grignard reagents can be achieved without isomerization.



Scheme 3.2 Total synthesis of (–)-zampanolide using (–)-dactylolide as a precursor with an inversion of the olefin geometry

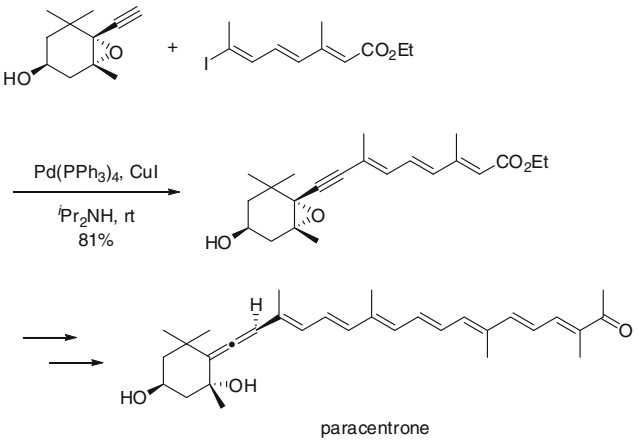
Furthermore, in the next synthetic pathway, the catalyst was carefully selected. $Ni(acac)_2$, which does not contain the phosphine ligands, was used for the enantioselective synthesis of (S)-macrostomine (Scheme 3.3) [5]. This result suggests that Kumada–Tamao–Corriu coupling has the drawbacks of poor selectivity and of substrate limitations. However, this reaction is an economical and preparative approach to natural product syntheses when substrates that are highly reactive toward Grignard reagents are not involved.



Scheme 3.3 Total synthesis of (S)-macrostomine from (S)-nicotine

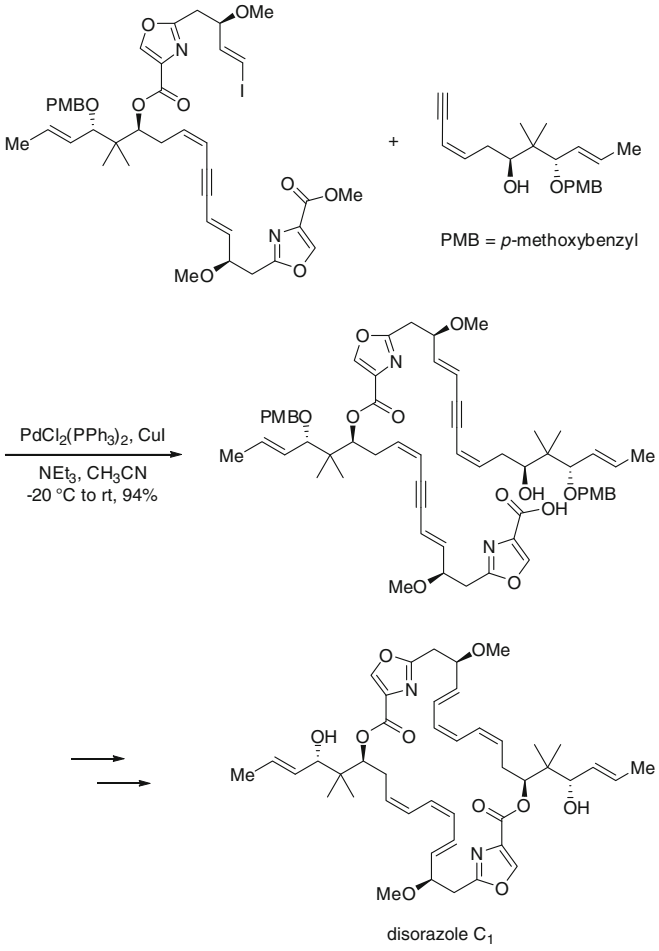
3.3 Sonogashira–Hagihara Coupling (sp–sp^2)

Sonogashira–Hagihara coupling is often employed in the natural product syntheses owing to its ability to construct enyne frameworks through the formation of carbon(sp)–carbon(sp^2) bonds. In general, in the natural product synthesis, the reactive substrates are first masked by a protecting group and economical bases such as triethylamine or diisopropylamine and copper iodide (CuI) are often used as essential reagents. Sonogashira–Hagihara coupling proceeds with high functional group tolerance under mild conditions, and often gives excellent results to afford molecules with complex structures. The total synthesis of paracentrone, shown in Scheme 3.4, is a representative example showing that Sonogashira–Hagihara coupling can be applied to a substrate bearing a reactive epoxide moiety which remains intact during the reaction [6].



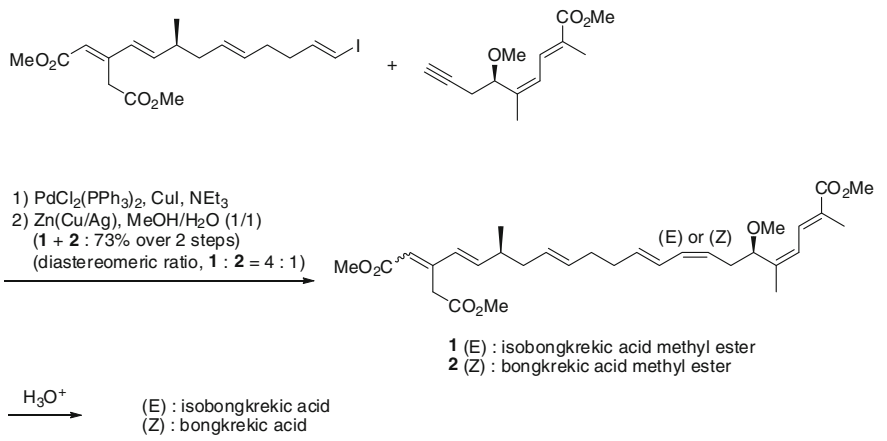
Scheme 3.4 A synthetic route to paracentrone

The air-stable $PdCl_2(PPh_3)_2$ is often used for the palladium catalyst of Sonogashira–Hagihara coupling, instead of a Pd(0) complex, because $PdCl_2(PPh_3)_2$ is reduced promptly during the reaction to form the Pd(0) species. Scheme 3.5 shows the demonstration of $PdCl_2(PPh_3)_2$ as a Pd precursor in the total synthesis of (−)-disorazole C_1 [7].



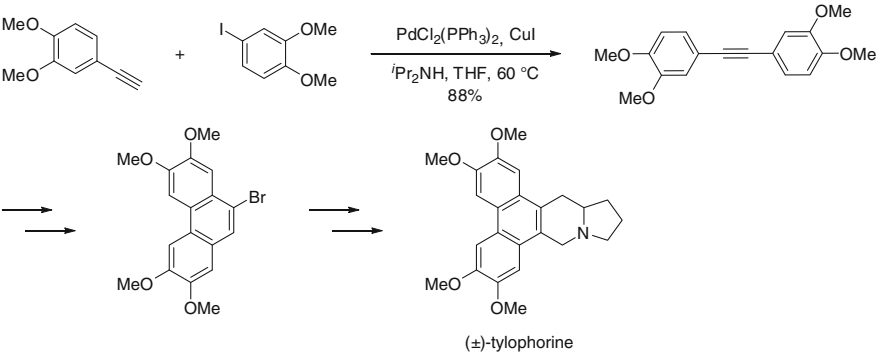
Scheme 3.5 A synthetic route to (–)-disorazole C_1

In the total synthesis of bongkrekic and isobongkrekic acids shown in Scheme 3.6, conjugate enynes were first synthesized by Sonogashira–Hagihara coupling. Then, chemoselective reduction of the alkyne moiety transformed the coupled product into the conjugate diene **1** and **2** [8]. In this reductive reaction, an excess amount of copper/silver activated with zinc was found to be the best synthetic method, since the chemoselectivity was fairly low when the *syn* reduction of the conjugate enyne by Lindlar's catalyst was attempted [9, 10].



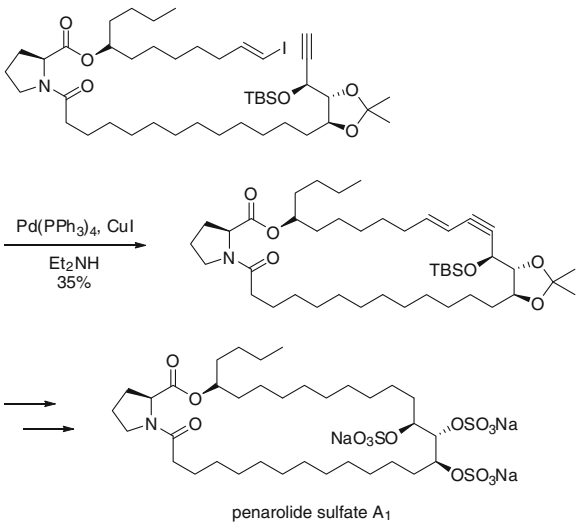
Scheme 3.6 A synthetic route to iso- and bongkrekic acids

Sonogashira–Hagihara coupling of aryl halides/triflates with terminal arylethynes is one of the most useful synthetic methods to afford an array of diarylethynes which are important frameworks applicable to liquid crystals and pharmaceuticals. The total synthesis of (±)-tylophorine shown in Scheme 3.7 is a representative example using diarylethynes as a synthetic intermediate [11].



Scheme 3.7 A synthetic route to (±)-tylophorine

Moreover, an intramolecular Sonogashira–Hagihara coupling enables the construction of large-membered rings; however, the yields of the cross-coupled products are generally very low, as shown in Scheme 3.8 [12]. Therefore, for the construction of large-membered rings, ring-closing metathesis by the Ru or Mo catalysts [13, 14] and macrolactonization [15] is often used rather than intramolecular Sonogashira–Hagihara couplings.



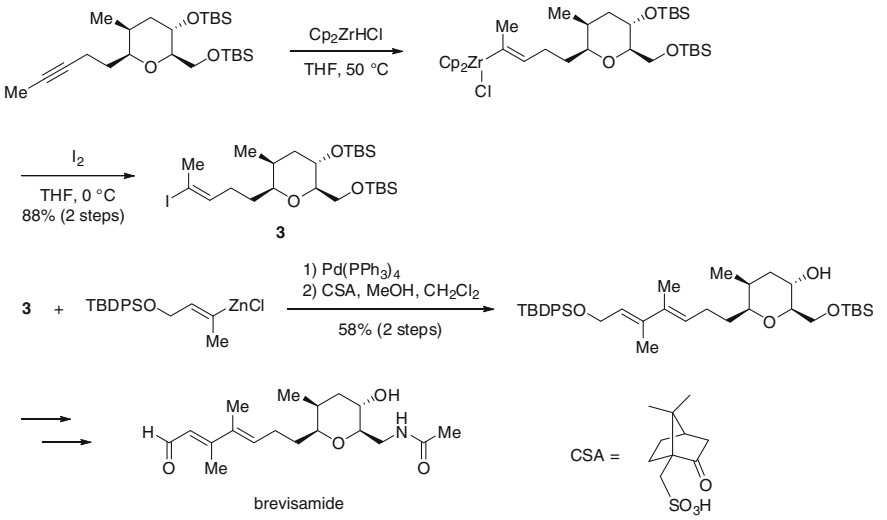
Scheme 3.8 A synthetic route to penarolide sulfate A_1

Additionally, the following are examples of total syntheses utilizing Sonogashira–Hagihara coupling reported after 2000: frondosin B [16], callipeltoside A [17], mucocin [18], borrelidin [19], tetrodotoxin [20], 34-hydroxyasimicin [21], oximidine II [22], (−)-siphonodiol, (−)-tetrahydrosiphonodiol [23], peroxyacarnoates A and D [24], leucascandrolide A [25], macbecin I [26], moracin O, moracin P [27] (+)-neopeltolide [28], furopyrans [29], leiodolide B [30], iso- and bongkrekic acids [31], *cis*- and *trans*- bupleurynol [32], and lukianol A [33].

3.4 Negishi Coupling

3.4.1 sp^2–sp^2 Negishi Coupling

Negishi coupling has also been widely used as a highly selective, efficient cross-coupling reaction in the natural product syntheses. The total synthesis of brevisamide as a natural product can be accomplished using the sp^2–sp^2 Negishi coupling (Scheme 3.9) [34]. Negishi coupling is often used in combination with hydrozirconation of alkynes by a Schwartz reagent, because hydrozirconation of alkynes generates an alkenylzirconium complex in a highly regioselective manner; the iodination and treatment with zinc salts of that complex yield the corresponding alkenyl iodides and alkenylzinc reagents, respectively, in one pot.

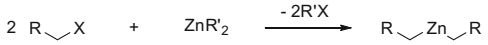


Scheme 3.9 A synthetic route to brevisamide

The sp^2–sp^2 Negishi coupling has been recently reported as applicable to other total syntheses: *cis* and *trans* bupleurynol [32] (−)-motuporin [35], xerulin [36], pitiamide A [37], FR901464 [38, 39], eunicenone A [40], bisabolene [41], xerulinic acid [42], callystatin A [43, 44], anguinomycin C [45], anguinomycin C and D [46], and 6,7-dehydrostipiamide [47].

3.4.2 sp^3–sp^2 Negishi Coupling

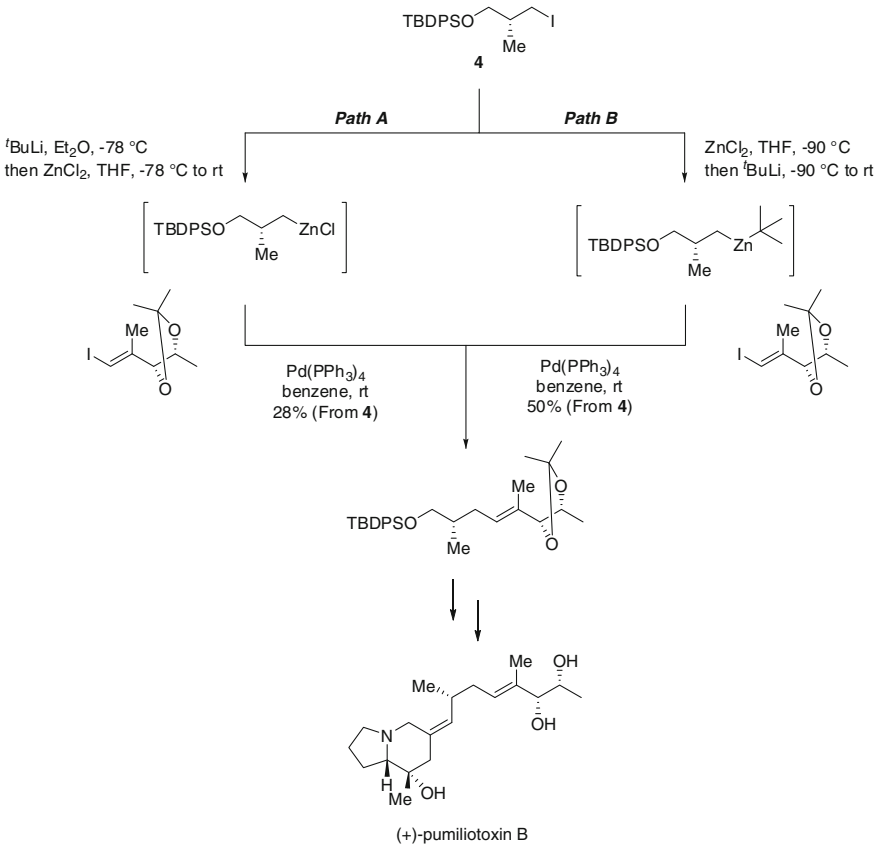
Herein, the natural product syntheses by Negishi cross-coupling of alkenyl or aryl halides (pseudo-halides) (sp^2) with alkylzinc reagents (sp^3) are described. In general, alkyl halides are converted into alkylzinc compounds by halogen–zinc exchange, as shown in Eq.3.1. In addition, a transformation with *tert*-BuLi of alkylzinc halides into dialkylzinc compounds is widely used, because the *tert*-butyl functionality can be used as a dummy group for Negishi coupling, leading to the selective formation of the desired cross-coupled products by carbon(sp^2)–carbon(sp^3) bond formation (See Chap. 8 for the details of carbon(sp^2)–carbon(sp^3) bond formation).



(3.1)

As shown in Scheme 3.10, reactivity between the dialkylzinc compound and alkylzinc chloride was compared to the total synthesis of (+)-pumiliotoxin B [48]. Starting from substrate **4** in Path A, alkylzinc chloride was prepared by halogen–lithium exchange with *tert*-BuLi and the subsequent transmetalation using zinc

chloride. On the other hand, in Path B the dialkylzinc reagent was synthesized from iodine–zinc exchange between substrate **4** and zinc chloride, followed by addition of *tert*-BuLi. As a result, Path B of Negishi coupling with the dialkylzinc reagent was found to give the desired product in better yield (50 vs 28 %).



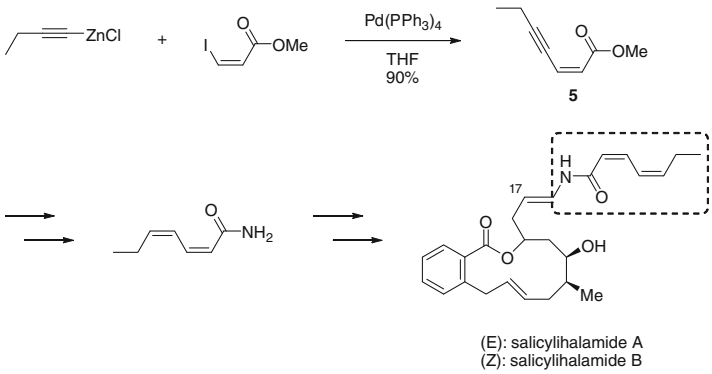
Scheme 3.10 Synthetic strategies of (+)-pumiliotoxin B

In recent years, the sp^3–sp^2 Negishi cross-coupling has been a frequently used synthetic method for multi-substituted aliphatic olefins and the substituted aryl or heteroaryl compounds. Furthermore, the utility of the sp^3–sp^2 Negishi cross-coupling has been recently observed in other total syntheses: borrelidin [19] (−)-callystatin A [43], anguinomycin C [45], anguinomycin C, D [46], (+)-discodermolide [49], dysiherbaine [50], bisabolene [41, 51], (–)-4a, 5-dihydrostreptazolin [52], a core structure of mycolactones [53], coenzyme Q_{10}, (*E*,*Z*,*E*)-geranylgeranoil [54], *trans*-epothilone A [55], oleandolide [56], sphingofungin F [57], ionomycin [58], (–)-longithorone A [59], (−)-delactonmycin [60], capensifuranone [61], (+)-murisolin [62], a side chain of scyphostatin [63],

(+)-scyphostatin [64], (−)-stemoamide [65], dysiherbaine [66], maleic anhydride, maleimide [67], OF4949-III, K-13 [68], harveynone, tricholomenyn A [69], and in the synthesis of important intermediates of ionomycin and borrelidin [70].

3.4.3 sp–sp^2 Negishi Coupling

In Negishi coupling, the coupling partners (alkenyl or aryl halides/triflates and alkynylzinc reagents) are employed to form carbon(sp)–carbon(sp^2) bonds. In the total synthesis of (–)-salicylihalamide shown in Scheme 3.11, Negishi coupling with the combination of the aforementioned substrates afforded the intermediate **5** in 90 % yield while retaining the *Z*-configuration [71].



Scheme 3.11 A synthetic route to salicylihalamide A and B

As shown above, the sp–sp^2 Negishi coupling is highly effective for the construction of the conjugate enyne frameworks. Although conjugate enynes can be synthesized by Sonogashira–Hagihara coupling, the functional group tolerance is dramatically improved with Negishi coupling because the addition of bases is not required. Other natural product syntheses by the sp–sp^2 Negishi coupling are known for the total syntheses of *cis*- and *trans*-bupleurynol [32], xerulin [36], 6,7-dehydrostipiamide [47], and harveynone, tricholomenyn A [69].

3.4.4 Carbometalation and Negishi Coupling Sequences

One of the applied Negishi cross-coupling reactions is the synthesis of a carotenoid having a conjugate polyene structure, e.g., *β*-carotene (Fig. 3.1). Since these compounds possess multi-substituted polyene motifs, a synthetic strategy that selectively introduces the substituents in appropriate positions is necessary.

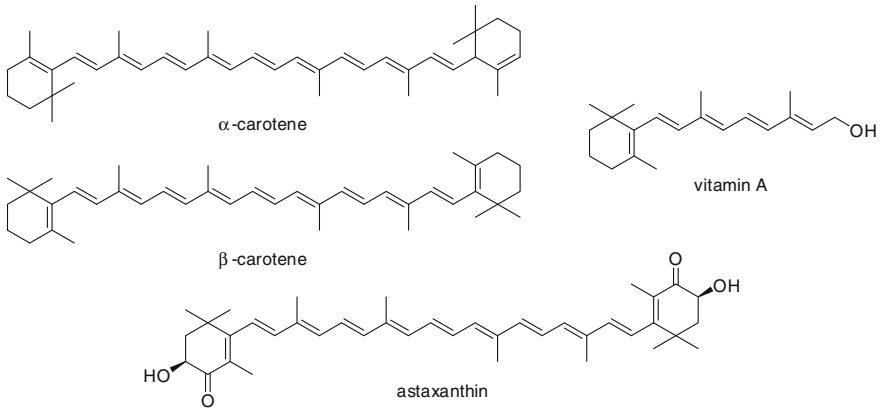
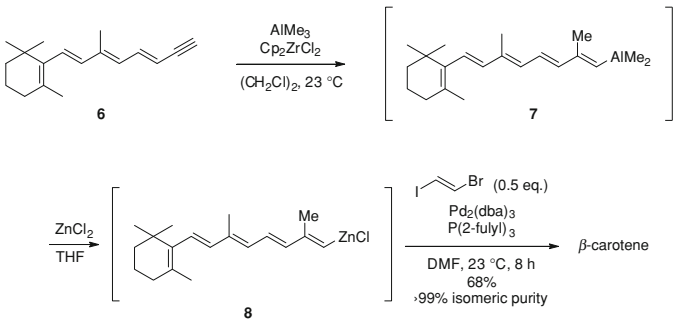


Fig. 3.1 Representative examples of carotenoids

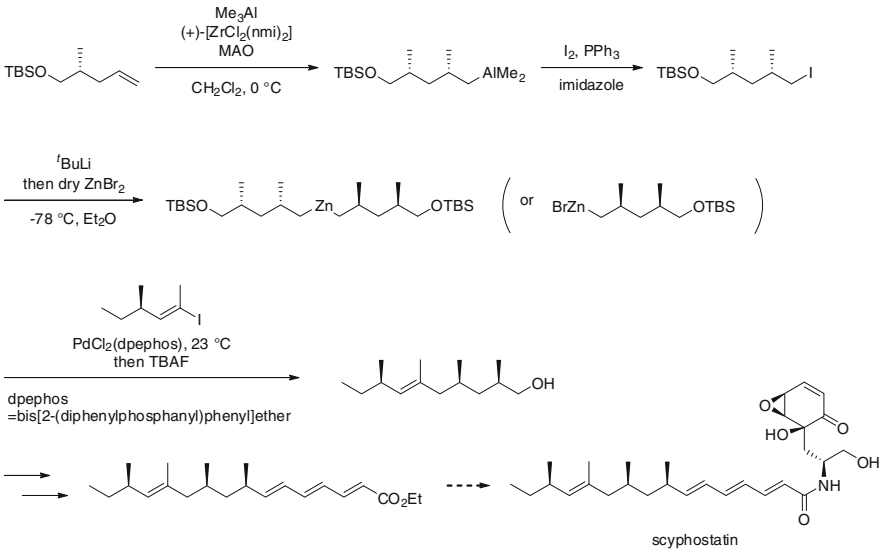
Because these conjugated polyene-type natural products are organic compounds with valuable antioxidant property, efficient and selective innovation for synthetic methods is still actively sought. It is likely that a combination of regioselective carbometalation of alkynes and sequential Negishi coupling could be used for the synthesis of such natural products.

In the syntheses of *β*-carotene and vitamin A, the Zr-catalyzed regio- and stereoselective methylalumination across the terminal alkyne in precursor **6** is the first step [72], as shown in Scheme 3.12. The formed alkenylaluminum compound **7** is transmetalated to zinc to afford the corresponding alkenylzinc compound **8**, which reacts consecutively with a half molar amount of 1-bromo-2-iodoethene leading to the successful total synthesis of *β*-carotene. This method is very advantageous from the viewpoint of the facile formation of the organozinc reagents without the addition of the bases. Using the regioselective alkylmetalation of the alkynes and sequential Negishi coupling, the total syntheses of coenzyme Q_{10}, (*E*,*Z*,*E*)-geranylgeranoil [54], and piericidin A_1 [73] have also been accomplished.



Scheme 3.12 A synthetic route to *β*-carotene

In addition, when the terminal olefins are treated with chiral reagents, regio- and stereoselective carbometalation can be achieved. The synthesis of a side chain in scyphostatin, shown in Scheme 3.13, is an applied example [63]. Moreover, the total synthesis of 6,7-dehydrostipiamide has been attained by regio- and stereoselective methylalumination and the subsequent Negishi coupling [47]. The applied synthetic methods for ionomycin, for the intermediate of borrelidin, and for the total synthesis of doliculide have also been achieved [74].



Scheme 3.13 A synthetic route to the scyphostatin side chain

3.4.5 Utility of Negishi Coupling toward Carbonyl Compound Synthesis

In Negishi coupling, acyl halides can be utilized as electrophiles to synthesize the corresponding ketones. This type of Negishi coupling has been used for the total synthesis of amphidinolide derivatives (Fig. 3.2), as shown in Scheme 3.14 [75].

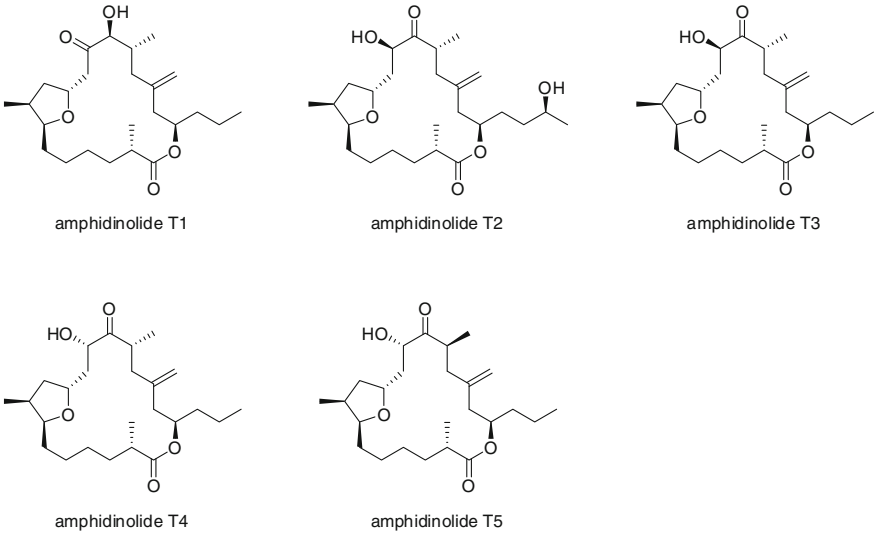
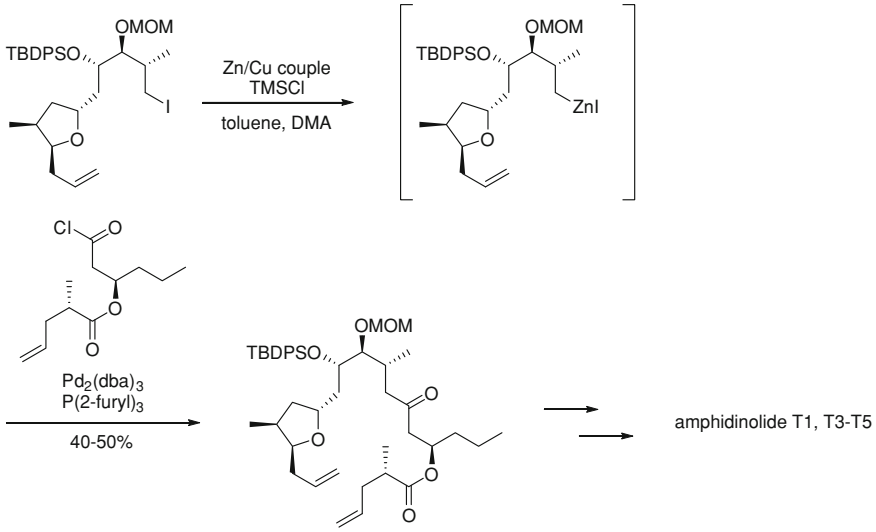


Fig. 3.2 Structures of amphidinolide derivatives



Scheme 3.14 Synthetic route for amphidinolide T1, T3–T5

As mentioned above, because Negishi coupling possesses a large number of advantages (including a wide scope of substrate options, high regio- and stereoselectivities, and preparative reactions under mild conditions), it can be a very powerful tool in the natural product syntheses through its combination with the alkylmetalation of the terminal alkynes and alkenes.

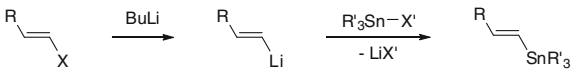
3.5 Migita–Kosugi–Stille Coupling

Although some cross-couplings might not be useful for highly reactive substrates bearing functional groups such as epoxides which are sensitive to both acids and bases, the mild and neutral Migita–Kosugi–Stille coupling has often been used in the key steps of the natural product syntheses. This section introduces representative examples of how Migita–Kosugi–Stille coupling can be used in natural product synthesis.

3.5.1 Synthetic Methods of Organotin Compounds

When Migita–Kosugi–Stille is employed as a coupling reaction, synthesis of organotin compounds is required. Since the preparation of organotin compounds can be achieved by various synthetic methods, the reaction conditions and the reagents used in the natural product synthesis offer many choices for stannation. First, some recently reported stannation reactions used in the natural product synthesis will be introduced.

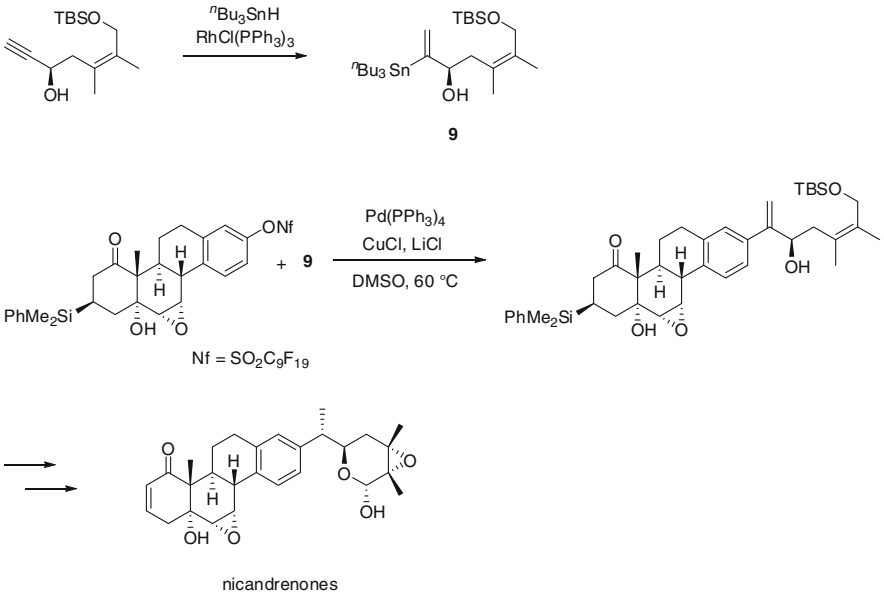
One well-known method for the preparation of organotin is via organolithium reagents; organotin reagents can be prepared by halogen–lithium exchange of alkenyl halides with n-BuLi, followed by treatment of the intermediate organolithium reagents with tin halides, as shown in Scheme 3.15. These organotin reagents can be conveniently synthesized due to the commercial availability of tin chlorides and organolithium compounds, but this synthetic method cannot be used for the substrates that have base-sensitive functional groups.



Scheme 3.15 Preparation of organostannanes from organolithium reagents

On the other hand, tin-containing functional groups can be introduced into unsaturated organic molecules in a highly regioselective fashion through hydrostannation and carbostannation reactions catalyzed by the transition metal

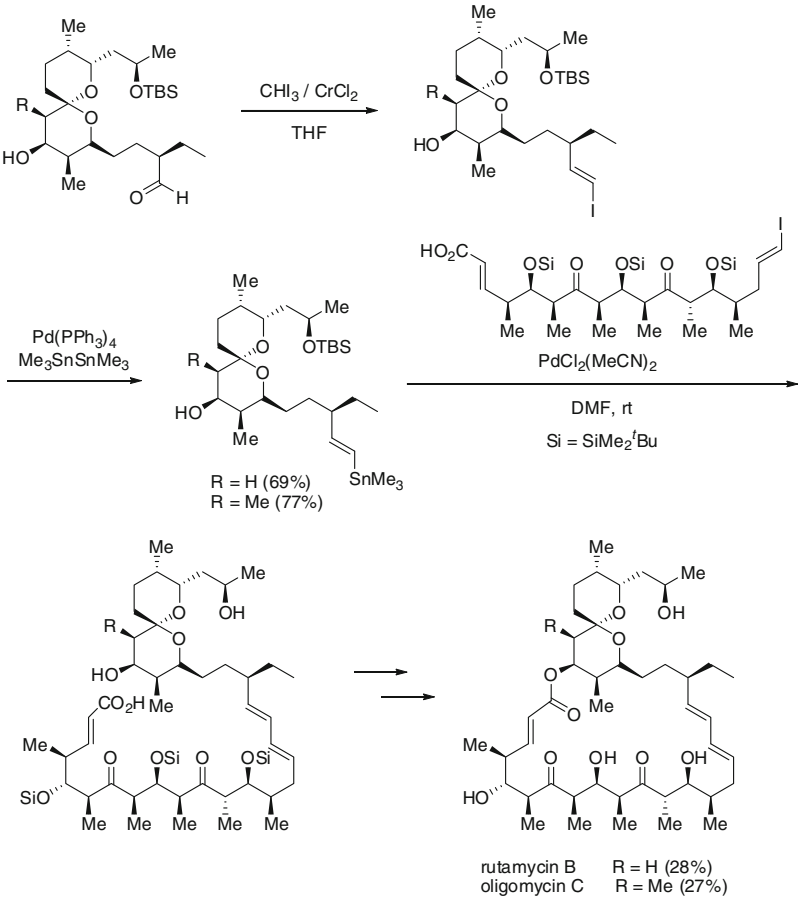
complexes. A synthetic example of a precursor of nicandrenones by the Rh-catalyzed regioselective hydrostannation and the subsequent Migita–Kosugi–Stille coupling is shown in Scheme 3.16 [76].



Scheme 3.16 A synthetic route to nicandrenones

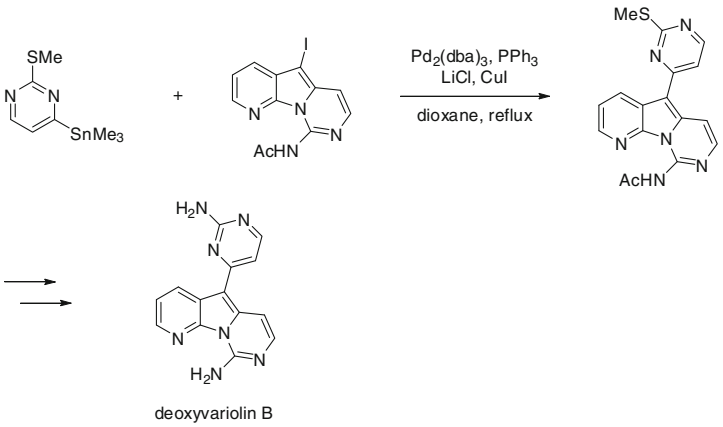
3.5.2 sp^2–sp^2 Migita–Kosugi–Stille Coupling

Migita–Kosugi–Stille coupling is often used at the key stage when the convergently synthesized fragments are bonded in natural product syntheses. Most of the reactions involve sp^2–sp^2 coupling to give the conjugate dienes and polyenes. The total syntheses of rutamycin B and oligomycin C are shown in Scheme 3.17 [77].



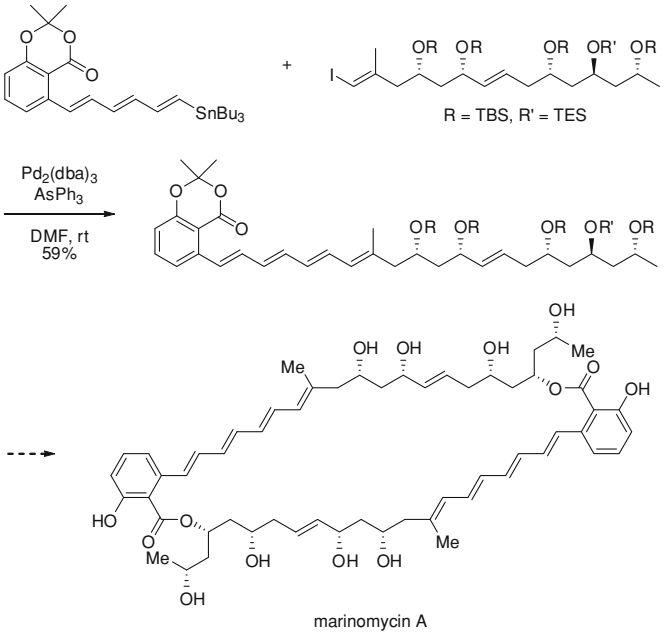
Scheme 3.17 A synthetic route to rutamycin B and oligomycin C

In Migita–Kosugi–Stille coupling, LiCl and CuI are added to promote transmetalation (see, Chap. 2). In regard to the effect of these additives, it is assumed that the added copper salt can trap the excess phosphine ligands retarding transmetalation. The more nucleophilic organocopper species, generated via transmetalation from tin to copper, accelerate the transmetalation [78]. The total synthesis of deoxyvariolin B can be achieved by applying these reaction conditions (Scheme 3.18) [79, 80].



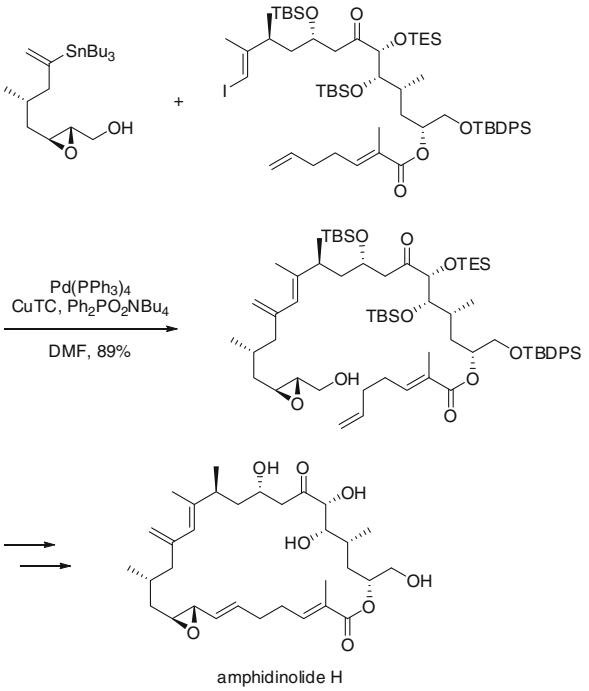
Scheme 3.18 A synthetic route to deoxyvariolin B

In some cases $AsPh_3$, which has a moderate electron-donating ability, gives better results for the construction of sp^2–sp^2 carbon–carbon bonds in Migita–Kosugi–Stille coupling. For instance, such a ligand is used in the total synthesis of marinomycin A (Scheme 3.19) [81, 82].



Scheme 3.19 A synthetic route to a monomer of marinomycin A

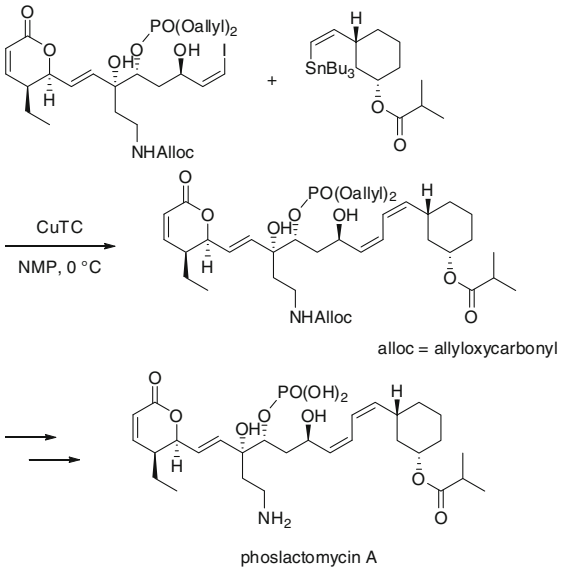
As mentioned above, the mild Migita–Kosugi–Stille coupling enables application to the substrates that are unstable under acidic and basic condition. Hence, this reaction is useful for the total synthesis of amphidinolide H, which bears an epoxide functionality (Scheme 3.20) [83]. A stoichiometric amount of copper(I)-thiophene-2-carboxylate (CuTC) can enhance Migita–Kosugi–Stille coupling as an activator [84].



Scheme 3.20 A synthetic route to amphidinolide H

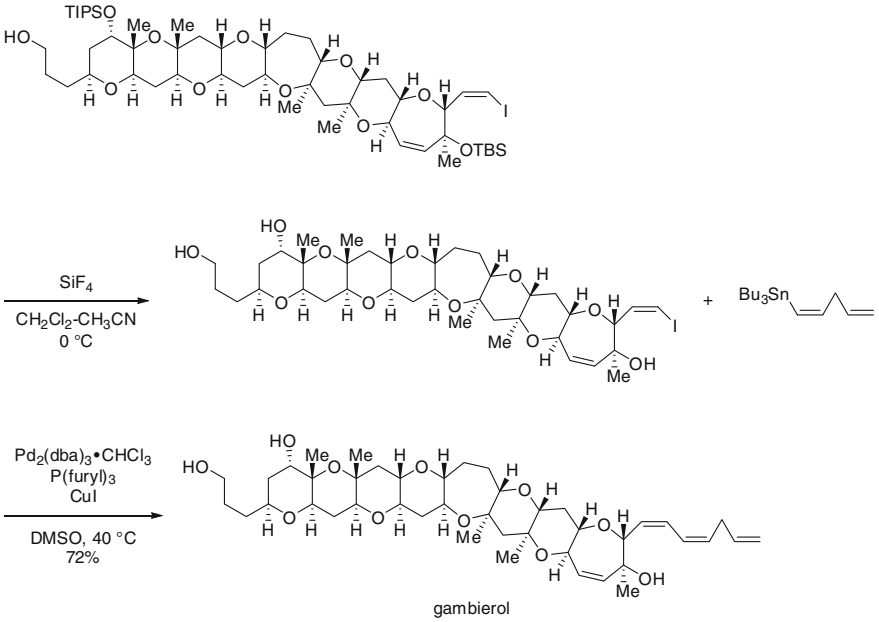
Migita–Kosugi–Stille coupling, using a stoichiometric amount of CuTC, can be used in the total synthesis of phoslactomycin A, while avoiding the side reaction of allylphosphate with the Pd catalyst (Scheme 3.21) [85]. Other stoichiometric

reactions mediated by a copper compound have been reported for the total synthesis of dictyostatin [86], formamicin [87], and amphidinolide A [88].



Scheme 3.21 A synthetic route to phoslactomycin A

The total synthesis of gambierol, shown in Scheme 3.22, is another example of a synthetic strategy utilizing Migita–Kosugi–Stille coupling [89–92]. An important aspect of this synthesis is that a silyl protecting group was removed *before* the cross-coupling. This underscores the fact that Migita–Kosugi–Stille coupling will not take place if the reaction site of the cross-coupling is sterically hindered by the presence of a bulky TBS group. Deprotection of the silyl group counteracts the steric congestion to smoothly accelerate the cross-coupling.

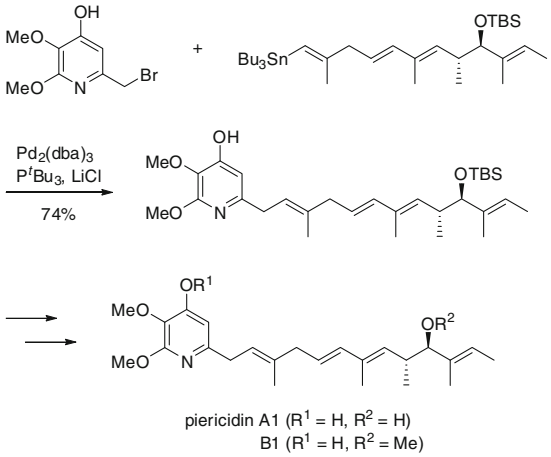


Scheme 3.22 A synthetic route to gambierol

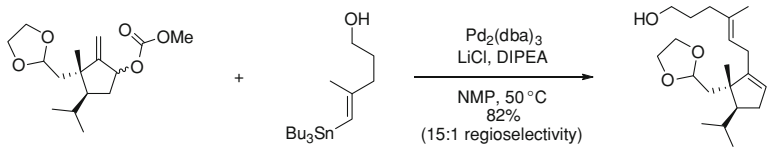
The following are known examples of the utility of the sp^2–sp^2 Migita–Kosugi–Stille coupling reactions for the natural product syntheses: paracentrone [6], iso- and bongkrekic acids [8], leiodolide B [30], (−)-callystatin A [43], sanglifehrin A [93–95], a biaryl moiety of TMC-95 [96], (−)-reveromycin B [97], manzamine A [98], quadrigemine C, psycholeine [99], pentacyclic skeletons [100], SNF4435 C, SNF4435 D [101], (−)-crispatene [102], (–)-SNF4435 C, (+)-SNF4435 D [103], 28-^{19}F-amphotericin B methyl ester [104], FR252921, pseudotrienic acid B [105, 106], (−)-spirangien A and its methyl ester [107], amphidinolide H1 [108], (+)-crocacin C [109], amphidinolides B1, B4, G1, H1 [110], (±)-havellockate [111], (±)-goniomitine [112], amphidinolide A [113], CD-D' rings in angelmicin B (hibarimicin B) [114], and brevenal [115, 116].

3.5.3 Other Migita–Kosugi–Stille Couplings

In addition to the sp^2–sp^2 coupling, sp^2–sp^3 Migita–Kosugi–Stille coupling is also utilized for natural product syntheses. The total syntheses of piericidin A1 and B1 [117] and (±)-neodolabellane-type diterpenoids [118] are shown in Schemes 3.23 and 3.24, respectively.



Scheme 3.23 A synthetic route to piericidin A1 and B1



Scheme 3.24 A synthetic route to (±)-neodolabellane-type diterpenoids

Because stable π-benzyl- and π -allylpalladium complexes are generated, these sp^2–sp^3 Migita–Kosugi–Stille couplings can be utilized with a low risk of β-hydrogen elimination. The sp^3 organotin reagents have rarely been utilized in Migita–Kosugi–Stille coupling because they cause β-hydrogen elimination (See also Chap. 8).

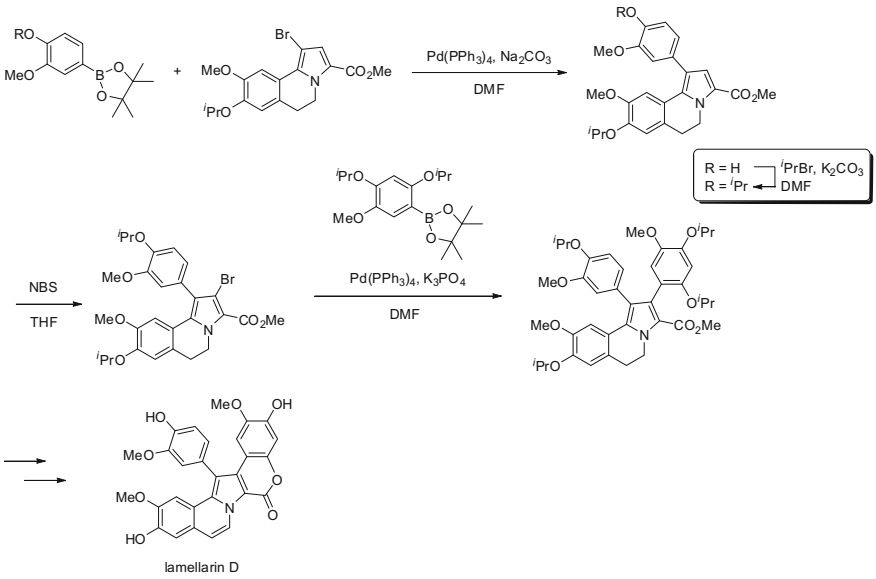
In addition, using the sp^3–sp^2 Migita–Kosugi–Stille coupling, the total syntheses of amphidinolide A [113], azaspiracid-1 [119, 120], tardioxopiperazine A, isoechinulin A, and variecolorin C [121] have been reported.

3.6 Suzuki–Miyaura Coupling

Suzuki–Miyaura coupling is extremely advantageous because the organoboron compounds have low toxicity and have stability toward water and air; this cross-coupling has been used extensively in natural product syntheses. However, Suzuki–Miyaura coupling requires the use of bases, thus functional groups that are unstable under basic conditions are incompatible. Herein, the applications of Suzuki–Miyaura coupling to natural product syntheses are described.

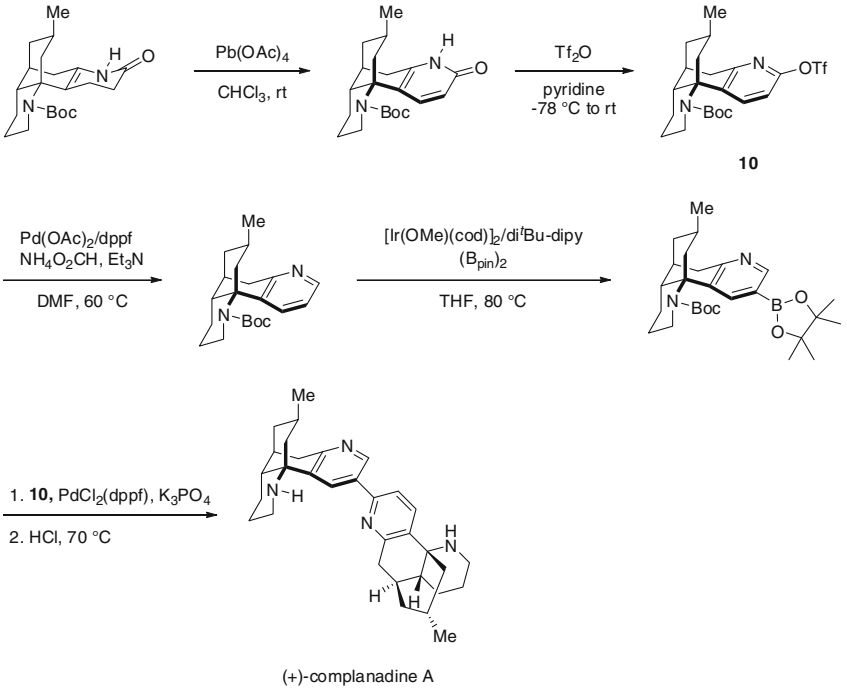
3.6.1 sp^2–sp^2 Suzuki–Miyaura Coupling

Construction of biaryl and conjugate diene motifs using the sp^2–sp^2 Suzuki–Miyaura coupling is particularly important in the natural product syntheses. Some examples include: 5,6-DiHETE methyl esters [122], (−)-chlorothricolide [123], and rutamycin B [124]. Although Negishi and Migita–Kosugi–Stille couplings can be used for sp^2–sp^2 carbon–carbon bond formation, Suzuki–Miyaura coupling is more widely utilized owing to its versatility of ligands and its various types of boron-containing reagents. The total synthesis of lamellarin D shown in Scheme 3.25 is one such example employing pinacolborane as the boron moiety [125].



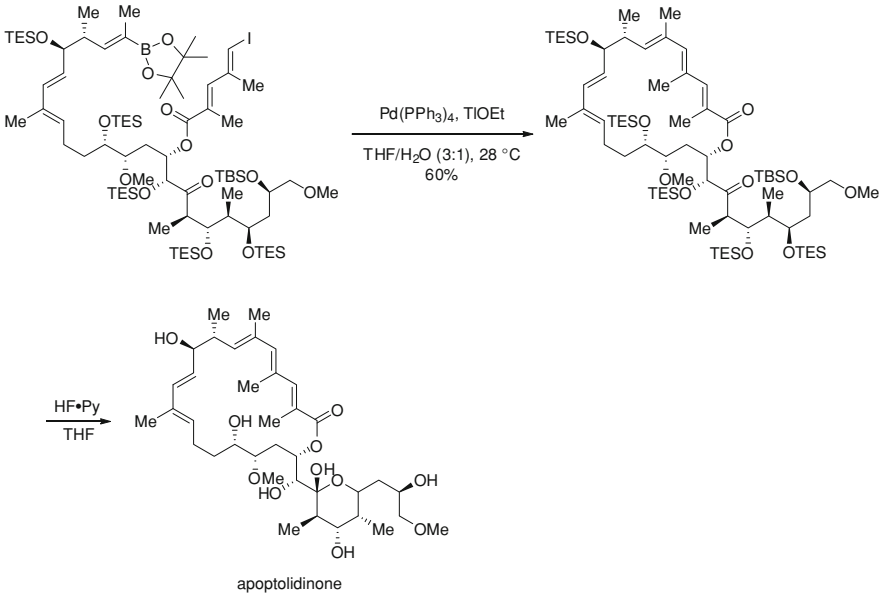
Scheme 3.25 A synthetic route to lamellarin D

$Pd(PPh_3)_4$ is generally the most frequently used Pd(0) complex in Suzuki–Miyaura coupling, but $PdCl_2$(dppf) also shows high catalytic activity in the synthesis of (+)-complanadine A (Scheme 3.26) [126].



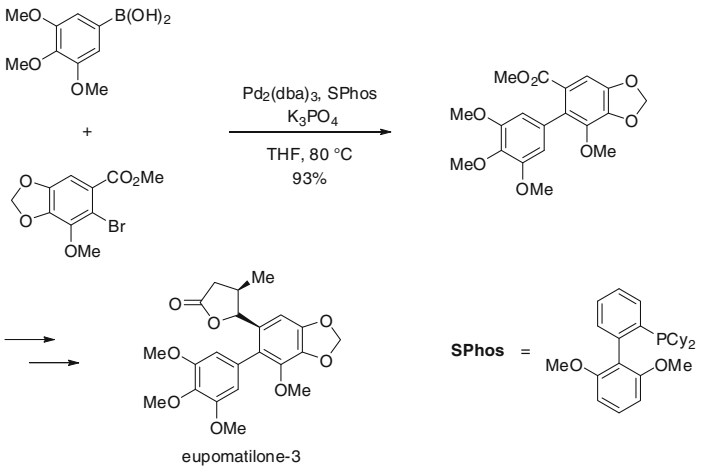
Scheme 3.26 A synthetic route to (+)-complanadine A

In general, as the substrate becomes larger, the achievement of cross-coupling becomes more difficult due to poor access to the reaction sites. However, Kishi reported in 1989 that the reactivity of a congested substrate was drastically improved by the use of thallium hydroxide as the base in the total synthesis of palytoxin [127]. More recently, TlOEt and Tl_2CO_3 have been utilized as a precursor of thallium hydroxide because thallium hydroxide is difficult to handle due to its instability to light and air [128]. The example of the synthesis of apoptolidinone via Suzuki–Miyaura coupling with TlOEt as the base is shown in Scheme 3.27 [129].



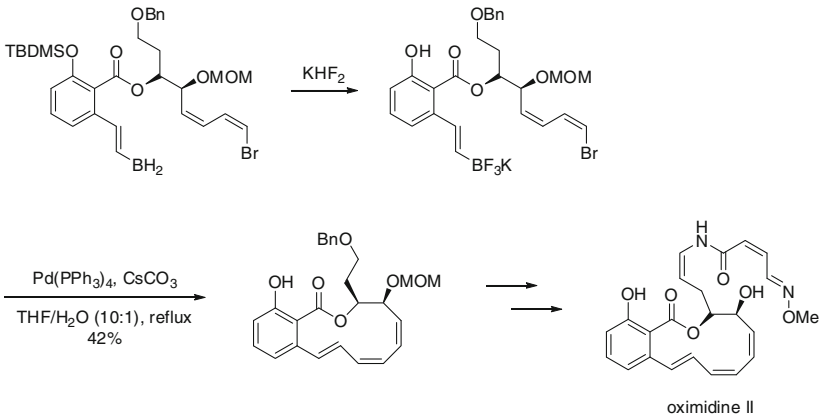
Scheme 3.27 A synthetic route to apoptolidinone

Buchwald reported that the bulky phosphine ligands with a biaryl backbone such as SPhos have a high activity in Suzuki–Miyaura coupling [130]. In the total synthesis of eupomatilones, as little as 0.005 mol % of the Pd catalyst can afford the cross-coupled products in 93 % yield (Scheme 3.28) [131, 132].



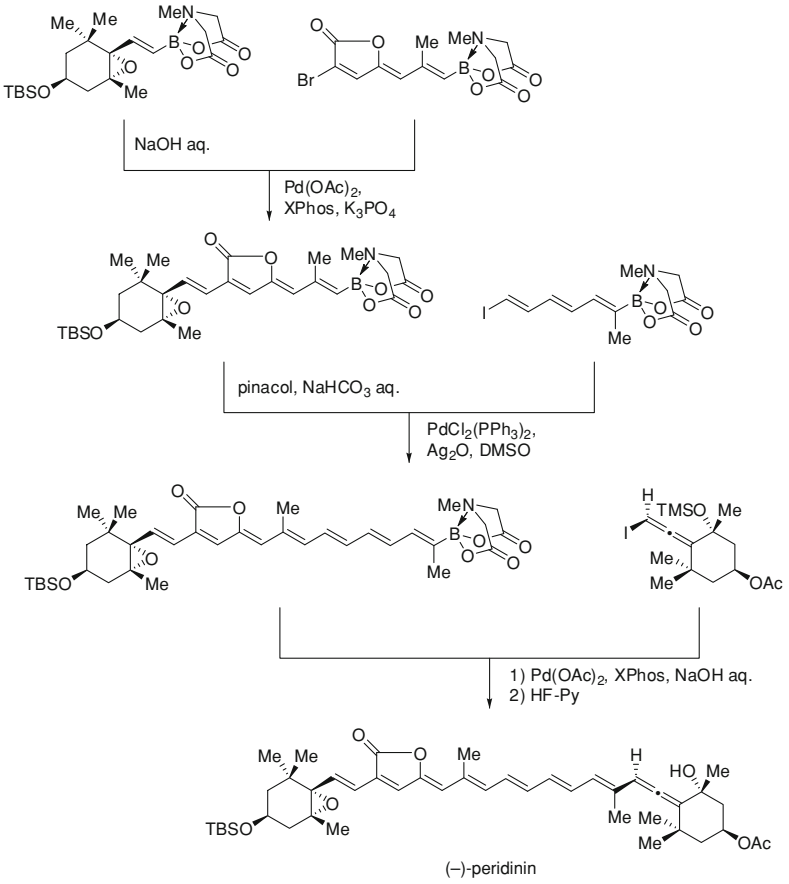
Scheme 3.28 A synthetic route to eupomatilones

Furthermore, Suzuki–Miyaura coupling is practical because it offers a superior selection of bases and ligands. As the result of recent research utilizing the benefits of organoboronic acids, many progressive synthetic routes have been established. Herein, some examples of modified organoboron compounds used in natural product syntheses are introduced. As shown in Scheme 3.29, the total synthesis of oximidine II [22] is an example of the application of organotrifluoroborates [133] to the natural product synthesis. The construction of an unsaturated 12-membered ring with a large strain was achieved.



Scheme 3.29 A synthesis route to oximidine II

In addition, Suzuki–Miyaura couplings using *N*-methyliminodiacetic acid (MIDA) have been invented [134]. (–)-Peridinin has been synthesized by repeated reactions with MIDA-containing organoborates (Scheme 3.30) [135].



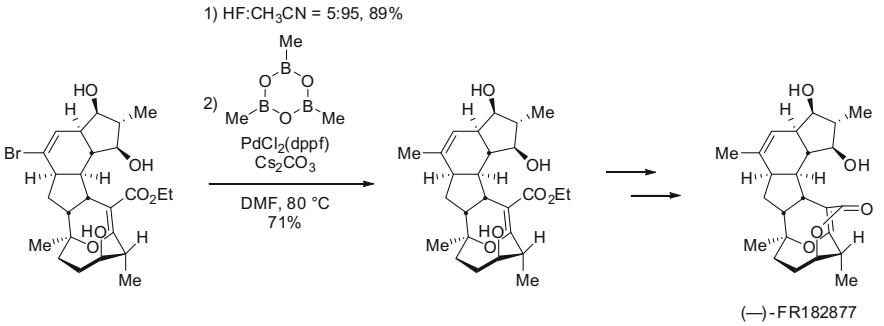
Scheme 3.30 A synthesis route to (–)-peridinin

Thus, the sp^2–sp^2 Suzuki–Miyaura coupling has achieved selective and efficient carbon–carbon bond formation in natural product syntheses through the use of a wide variety of substrates. The following examples of natural product syntheses using sp^2–sp^2 Suzuki–Miyaura coupling have been recently reported: iso- and bongkrekic acids [8, 31], furopyrans [29], lukianol A [33], maleic anhydride, maleimide [67], (+)-crocacin C [109], CD-D′ rings in angelmicin B (hibarimicin B) [114], (+)-fostriecin [136], dragmacidin D [137], (−)-FR182877 [138, 139], nakadomarin A [140], styelsamine C [141], (±)-spiroxin C [142], diazonamide A [143], quinine, quinidine [144], lamellarin G trimethyl ether [145], (+)-dragmacidin F [146], eupomatilone diastereomers [147], biphenomycin B [148], (−)-

spirofungin A, (+)-spirofungin B [149], pulvinic acids [150], N-shifted and ring-expanded buflavine [151, 152], (±)-hasubanonine [153], altenuene, isoaltenuene [154], C-15 vindoline analogs [155], (−)-erythramine and 3-*epi*-(+)-erythramine [156], biaryl hybrids of allocolchicine and steganacin [157], ratanhine [158], palmerolide A [159], eupomatilones [160], butylcycloheptylprodigiosin [161], isotetronic acids [162], 1/2 of amphotericin B macrolide [163], GEX1A [164], (±)-cyclocolorenone, (±)-α-gurjunene [165], withasomnines [166], the vacidin A (*E*,*E*,*E*,*Z*,*E*,*E*)-heptaene framework [167], fortuneanoside E [168], (–)-exiguolide [169], dunnianol [170], and hirtellanine A [171].

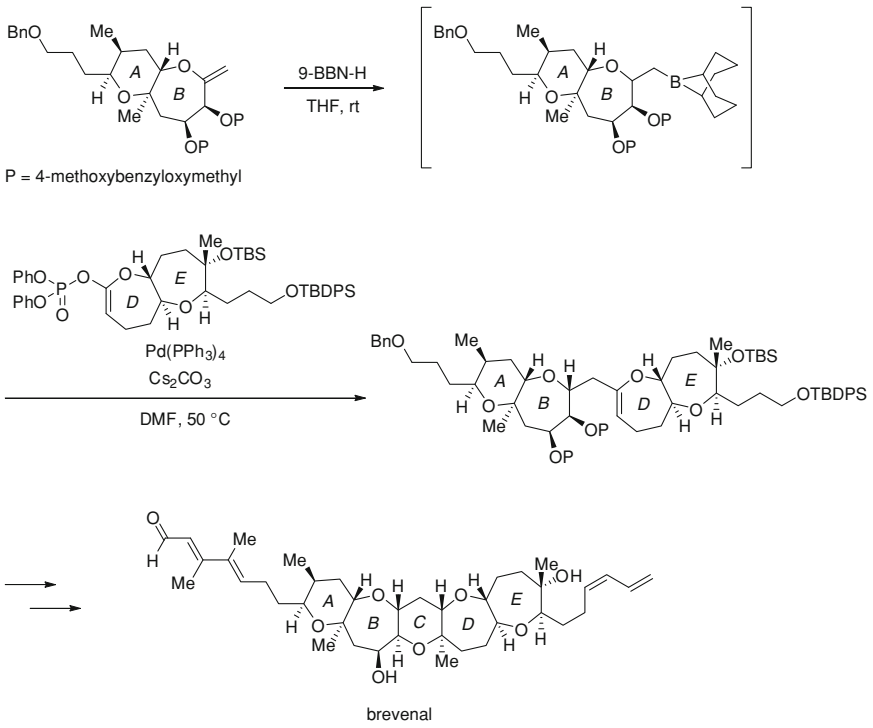
3.6.2 sp^3–sp^2 Suzuki–Miyaura Coupling

Suzuki–Miyaura coupling has also been used to construct sp^3–sp^2 carbon–carbon bonds (See also Chap. 8). One such example is the methylation using trimethylboroxine, which is a dehydrated trimer of methylboronic acid, toward aryl or alkenyl halides [172]. The total synthesis of (−)-FR182877 using the sp^3–sp^2 Suzuki–Miyaura coupling is shown in Scheme 3.31 [138].



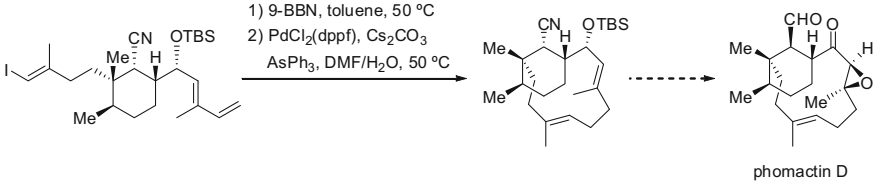
Scheme 3.31 A synthetic route to (–)-FR182877

In most cases, the sp^3–sp^2 Suzuki–Miyaura coupling employs a typical hydroboration of the terminal olefin by 9-BBN and the subsequent B-alkyl Suzuki–Miyaura coupling. Since hydroboration using a bulky 9-BBN takes place in a highly regioselective fashion [173], B-alkyl Suzuki–Miyaura coupling has been widely utilized for the connection of fragments in the natural product syntheses, e.g., the total synthesis of brevenal (Scheme 3.32) [115, 116, 174].



Scheme 3.32 A synthetic route to brevenal

In addition, the B-alkyl Suzuki–Miyaura coupling can be applied to the intramolecular cyclization in the total synthesis of phomactin D; compared with other sp^3–sp^2 cross-coupling reactions, the organoboron compounds have low toxicity and are highly stable (Scheme 3.33) [175].



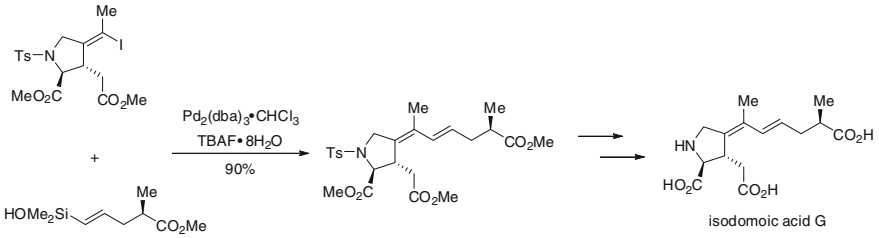
Scheme 3.33 A synthetic route to phomactin D

Other synthetic examples using the sp^3–sp^2 Suzuki–Miyaura coupling include the total synthesis of: anguinomycin C [45], anguinomycin C and D [46], transepothilone A [55], oleandolide [56], salicylihalamide [71], CP-225,917, CP-263,114 [176], epothilone A [55, 177], 12,13-desoxyepothilone F [178], FGH ring fragments of gambierol [179], sphingofungin E [180], GHIJKLM ring fragments in ciguatoxin (CTX1B) [181], ABCD ring fragments of ciguatoxin (CTX3C) and

ciguatoxin (51-hydroxyCTX3C) [182], (−)-ebelactone A [183], gymnocin-A [184–187], (+)-phomactin [188], the C6–C21 segment of amphidinolide E [189], (±)-geigerin [190], (+)-oocydin A [191], 4-hydroxydictyolactone [192], jatrophane diterpenes [193], (+)-brefeldin C, (+)-nor-Me brefeldin A, (+)-4-*epi*-nor-Me brefeldin A [194], ABC ring fragments of brevesin [195], and (−)-brevisin [196].

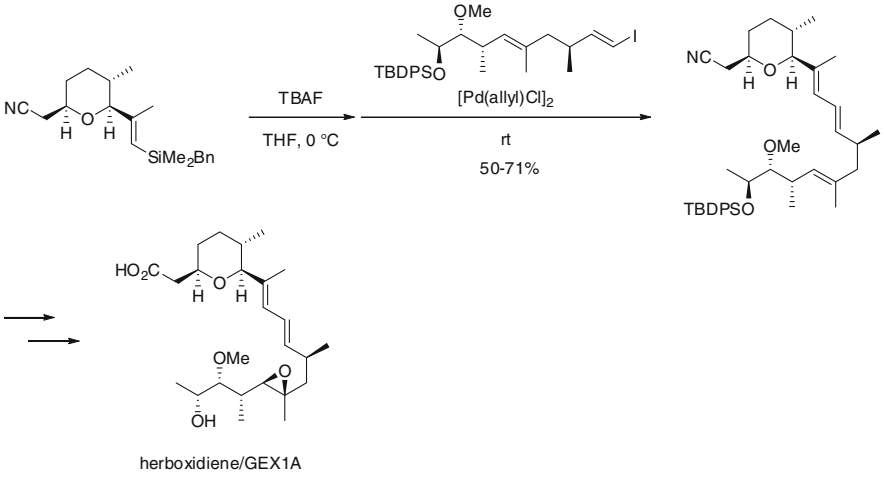
3.7 Hiyama Coupling (sp^2–sp^2)

Finally, recent examples utilizing the sp^2–sp^2 Hiyama coupling in the natural product syntheses will be briefly introduced. As shown in Scheme 3.34, silanol (the substrate bearing a hydroxyl group on silicon) is activated by TBAF to react with an alkenyl iodide in the total synthesis of isodomoic acid G [197].



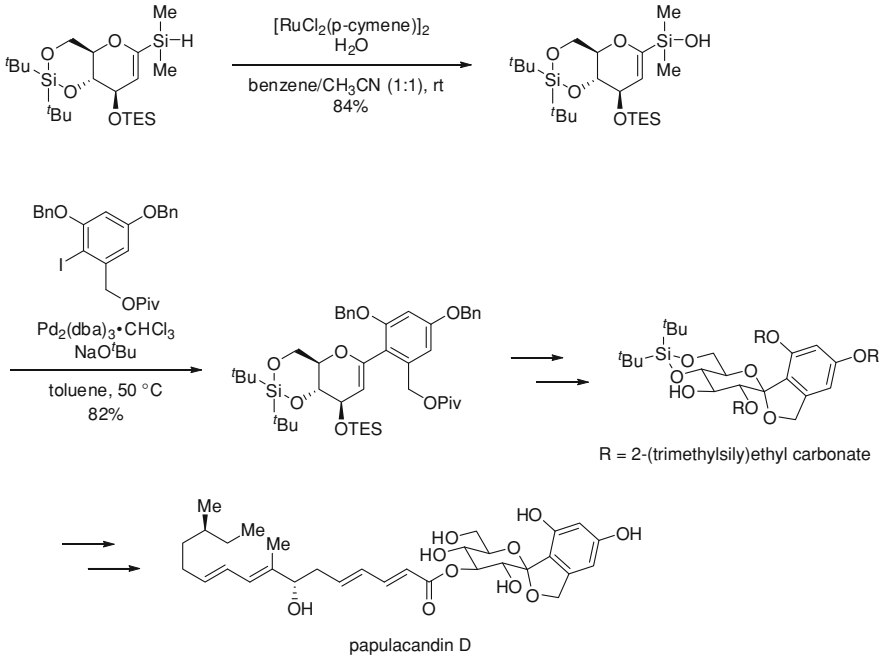
Scheme 3.34 A synthetic route to isodomoic acid G

Another alkenylsilane substituted with a benzyldimethylsilyl group was successfully subjected to Hiyama coupling for the synthesis of a precursor of herboxidiene/GEX 1A (Scheme 3.35) [198]. It should be noted that in this synthetic example, during the Hiyama coupling, the alcohol was protected by a silyl protecting group.



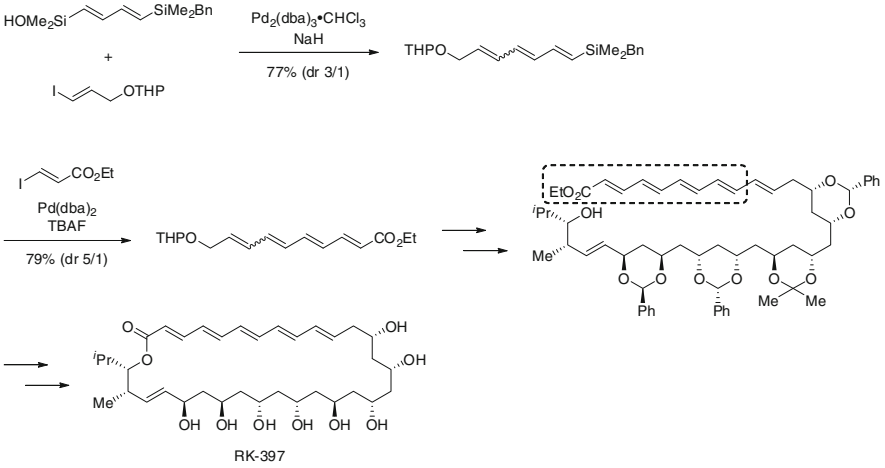
Scheme 3.35 A synthetic route to herboxidiene/GEX 1A

In the total synthesis of papulacandin D, after a hydrosilane was converted into a silanol using the Ru catalyst, Hiyama cross-coupling of silanol was applied (Scheme 3.36) [199].



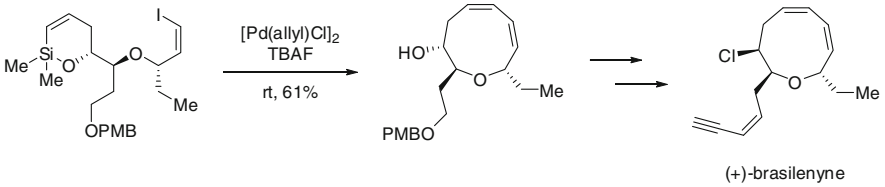
Scheme 3.36 A synthetic route to papulacandin D

In addition, a conjugate diene bearing two different silicon functional groups was subjected to the successive Hiyama coupling, achieving the total synthesis of RK-397, as shown in Scheme 3.37 [200].



Scheme 3.37 A synthetic route to RK-397

Moreover, the total synthesis of a highly strained 9-membered compound, (+)-brasilenyne, has been achieved through intramolecular Hiyama coupling (Scheme 3.38) [201, 202].



Scheme 3.38 A synthetic route to (+)-brasilenyne

Thus, Hiyama coupling has a large number of advantages from the viewpoints of high stability, low toxicity, and natural abundance of the organosilicon

compounds. Thus, Hiyama coupling can be a powerful tool in the natural product syntheses. However, Hiyama coupling has not been advanced much, because the silyl functionalities require the introduction of hydroxyl or fluoride substituents to be activated, which limits the selection of substrates.

3.8 Summary

The cross-coupling reactions have facilitated the synthesis of complex organic compounds with high selectivity and reactivity in the natural product syntheses. In addition, recent advancement of technologies for cross-couplings includes: the expansion of organometallic reagents, increased reactivity and safety by the improvement of catalysts, and the reduction of chemical wastes. This remarkable progress has made the cross-coupling reactions increasingly easy to utilize. Complicated natural product syntheses that have not yet been achieved will likely be artificially synthesized by using the cross-coupling reactions in the future. More technological development is expected toward clarification and application of the biologically active compounds.

References

1. Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70:461–477
2. Nicolaou KC, Bulger PG, Sarlah D (2005) Palladium-catalyzed cross-coupling reactions in total synthesis. Angew Chem Int Ed 44:4442–4489
3. Yokokawa F, Asano T, Shioiri T (2000) Total synthesis of the antiviral marine natural product (−)-hennoxazole A. Org Lett 2:4169–4172
4. Uenishi J, Iwamoto T, Tanaka J (2009) Total synthesis of (−)-zampanolide and questionable existence of (−)-dactylolide as the elusive biosynthetic precursor of (−)-zampanolide in an okinawan sponge. Org Lett 11:3262–3265
5. Enamorado MF, Ondachi PW, Comins DL (2010) A five-step synthesis of (S)-macrostomine from (S)-nicotine. Org Lett 12:4513–4515
6. Murakami Y, Nakano M, Shimofusa T, Furuichi N, Katsumura S (2005) Total synthesis of paracentrone, C31-allenic *apo*-carotenoid. Org Biomol Chem 3:1372–1374
7. Wipf P, Graham TH (2004) Total synthesis of (−)-disorazole C1. J Am Chem Soc 126:15346–15347
8. Francais A, Leyva A, Etxebarria-Jardi G, Ley SV (2010) Total synthesis of the anti-apoptotic agents iso- and bongkrekic acids. Org Lett 12:340–343
9. Boland W, Schroer N, Sieler C, Feigel M (1987) Sterospecific syntheses and spectroscopic properties of isomeric 2,4,6,8-undecatetraenes. New hydrocarbons from the marine brown alga giffordia mitchellae. Part IV. Helv Chim Acta 70:1025–1040
10. Avignon-Tropis M, Pougny JR (1989) Improved stereoselective reduction of a E, E, conjugated dienyne to a E, E, Z conjugated triene. Tetrahedron Lett 30:4951–4952
11. Rossiter LM, Slater ML, Giesert RE, Sakwa SA (2009) A concise palladium-catalyzed carboamination route to (±)-tylophorine. J Org Chem 74:9554–9557

12. Mohapatra DK, Bhattasali D, Gurjar MK, Khan MI, Shashidhara KS (2008) First asymmetric total synthesis of penarolide sulfate A1. Eur J Org Chem, 6213–6224
13. Mori M (2007) Synthesis of natural products and related compounds using enyne metathesis. Adv Synth Catal 349:121–135
14. Maier ME (2000) Synthesis of medium-sized rings by the ring-closing metathesis reaction. Angew Chem Int Ed 39:2073–2077
15. Parenty A, Moreau X, Campagne JM (2006) Macrolactonizations in the total synthesis of natural products. Chem Rev 106:911–939
16. Inoue M, Carson MW, Frontier AJ, Danishefsky SJ (2001) Total synthesis and determination of the absolute configuration of frondosin B. J Am Chem Soc 123:1878–1889
17. Trost BM, Gunzner JL, Dirat O, Rhee YH (2002) Callipeltoside A: total synthesis, assignment of the absolute and relative configuration, and evaluation of synthetic analogues. J Am Chem Soc 124:10396–10415
18. Takahashi S, Nakata T (2002) Total synthesis of an antitumor agent, mucocin, based on the "chiron approach". J Org Chem 67:5739–5752
19. Duffey MO, LeTiran A, Morken JP (2003) Enantioselective total synthesis of borrelidin. J Am Chem Soc 125:1458–1459
20. Ohyabu N, Nishikawa T, Isobe M (2003) First asymmetric total synthesis of tetrodotoxin. J Am Chem Soc 125:8798–8805
21. Han H, Sinha MK, D'Souza LJ, Keinan E, Sinha SC (2004) Total synthesis of 34-hydroxyasimicin and its photoactive derivative for affinity labeling of the mitochondrial complex I. Chem Eur J 10:2149–2158
22. Molander GA, Dchmel F (2004) Formal total synthesis of oximidine II via a Suzuki-type cross-coupling macrocyclization employing potassium organotrifluoroborates. J Am Chem Soc 126:10313–10318
23. López S, Fernández-Trillo F, Midón P, Castedo L, Saá C (2005) First stereoselective syntheses of (−)-siphonodiol and (−)-tetrahydrosiphonodiol, bioactive polyacetylenes from marine sponges. J Org Chem 70:6346–6352
24. Xu C, Raible JM, Dussault PH (2005) Total synthesis of peroxyacarnoates A and D: metal-mediated couplings as a convergent approach to polyunsaturated peroxides. Org Lett 7:2509–2511
25. Su Q, Dakin LA, Panek JS (2007) [4+2]-annulations of chiral organosilanes: application to the total synthesis of leucascandrolide A. J Org Chem 72:2–24
26. Belardi JK, Micalizio GC (2008) Total synthesis of macbecin I. Angew Chem Int Ed 47:4005–4008
27. Kaur N, Xia Y, Jin Y, Dat NT, Gajulapati K, Choi Y, Hong YS, Lee JJ, Lee K (2009) The first total synthesis of moracin O and moracin P, and establishment of the absolute configuration of moracin O. Chem Commun, 1879–1881
28. Guinchard X, Roulland E (2009) Total synthesis of the antiproliferative macrolide (+)-neopeltolide. Org Lett 11:4700–4703
29. Gockel B, Krause N (2010) Synthesis of bicyclic ethers by a gold/palladium/gold-catalyzed cyclization/cross coupling sequence. Eur J Org Chem, 311–316
30. Larivée A, Unger JB, Thomas M, Wirtz C, Dubost C, Handa S, Fürstner A (2011) The leiodolide B puzzle. Angew Chem Int Ed 50:304–309
31. Français A, LeyvaPérez A, Etxebarria-Jardi G, Peńa J, Ley SV (2011) Total synthesis of iso- and bongkrekic acids: natural antibiotics displaying potent antiapoptotic properties. Chem Eur J 17:329–343
32. Ghasemi H, Antunes LM, Organ MG (2004) Use of olefin templates in queued chemical transformations using late transition metal catalysis. Total synthesis of *cis* and *trans* bupleurynol via a single multireaction sequence. Org Lett 6:2913–2916

33. Liu J-H, Yang Q-C, Mak T-CW, Wong H-NC (2000) Highly regioselective synthesis of 2,3,4-trisubstituted 1H-pyrroles: a formal total synthesis of lukianol A. J Org Chem 65:3587–3595
34. Lee J, Panek JS (2009) Total synthesis of brevisamide. Org Lett 11:4390–4393
35. Hu T, Panek JS (2002) Enantioselective synthesis of the protein phosphatase inhibitor (−)-motuporin. J Am Chem Soc 124:11368–11378
36. Negishi E, Alimardanov A, Xu C (2000) An efficient and stereoselective synthesis of xerulin via Pd-catalyzed cross coupling and lactonization featuring (*E*)-iodobromoethylene as a novel two-carbon synthon. Org Lett 2:65–67
37. Ribe S, Kondru RK, Beratan DN, Wipf P (2000) Optical rotation computation, total synthesis, and stereochemistry assignment of the marine natural product pitiamide A. J Am Chem Soc 122:4608–4617
38. Thompson CF, Jamison TF, Jacobsen EN (2000) Total synthesis of FR901464. Convergent assembly of chiral components prepared by asymmetric catalysis. J Am Chem Soc 122:10482–10483
39. Thompson CF, Jamison TF, Jacobsen EN (2001) FR901464: total synthesis, proof of structure, and evaluation of synthetic analogues. J Am Chem Soc 123:9974–9983
40. Lee TW, Corey EJ (2001) Enantioselective total synthesis of eunicenone A. J Am Chem Soc 123:1872–1877
41. Vyvyan JR, Loitz C, Looper RE, Mattingly CS, Peterson EA, Staben ST (2004) Synthesis of aromatic bisabolene natural products via palladium-catalyzed cross-couplings of organozinc reagents. J Org Chem 69:2461–2468
42. Sorg A, Brückner R (2004) Total synthesis of xerulinic acid. Angew Chem Int Ed 43: 4523–4526
43. Langille NF, Panek JS (2004) Total synthesis of (−)-callystatin A. Org Lett 6:3203–3206
44. Reichard HA, Rieger JC, Micalizio GC (2008) Total synthesis of callystatin A by titanium-mediated reductive alkyne–alkyne cross-coupling. Angew Chem Int Ed 47:7837–7840
45. Bonazzi S, Güttinger S, Zemp I, Kutay U, Gademann K (2007) Total synthesis, configuration, and biological evaluation of anguinomycin C. Angew Chem Int Ed 46:8707–8710
46. Bonazzi S, Eidam O, Güttinger S, Wach J-Y, Zemp I, Kutay U, Gademann K (2010) Anguinomycins and derivatives: total syntheses, modeling, and biological evaluation of the inhibition of nucleocytoplasmic transport. J Am Chem Soc 132:1432–1442
47. Zeng X, Zeng F, Negishi E (2004) Efficient and selective synthesis of 6, 7-dehydrostipiamide via Zr-catalyzed asymmetric carboalumination and Pd-catalyzed cross-coupling of organozincs. Org Lett 6:3245–3248
48. Aoyagi S, Hirashima S, Saito K, Kibayashi C (2002) Convergent approach to pumiliotoxin alkaloids. asymmetric total synthesis of (+)-pumiliotoxins A, B, and 225F. J Org Chem 67:5517–5526
49. Smith AB III, Beauchamp TJ, LaMarche MJ, Kaufman MD, Qiu Y, Arimoto H, Jones DR, Kobayasi K (2000) Evolution of a gram-scale synthesis of (+)-discodermolide. J Am Chem Soc 122:8654–8664
50. Masaki H, Maeyama J, Kamada K, Esumi T, Iwabuchi Y, Hatakeyama S (2000) Total synthesis of (−)-dysiherbaine. J Am Chem Soc 122:5216–5217
51. Anastasia L, Dumond YR, Negishi E (2001) Stereoselective synthesis of exocyclic alkenes by Cu-catalyzed allylmagnesiation, Pd-catalyzed alkylation, and Ru-catalyzed ring-closing metathesis: highly stereoselective synthesis of (*Z*)- and (*E*)-γ-bisabolenes. Eur J Org Chem, 3039–3043
52. Cossy J, Pévet I, Meyer C (2001) Total synthesis of (−)-4a,5-dihydrostreptazolin. Eur J Org Chem, 2841–2850
53. Benowitz AB, Fidanze S, Small PLC, Kishi Y (2001) Stereochemistry of the core structure of the mycolactones. J Am Chem Soc 123:5128–5129
54. Negishi E, Liou S-Y, Xu C, Huo S (2002) A novel, highly selective, and general methodology for the synthesis of 1,5-diene-containing oligoisoprenoids of all possible

geometrical combinations exemplified by an iterative and convergent synthesis of coenzyme Q10. Org Lett 4:261–264
55. Altmann K-H, Bold G, Caravatti G, Denni D, Flörsheimer A, Schmidt A, Rihs G, Wartmann M (2002) The total synthesis and biological assessment of trans-epothilone A. Helv Chim Acta 85:4086–4110
56. Hu T, Takenaka N, Panek JS (2002) Asymmetric crotylation reactions in synthesis of polypropionate-derived macrolides: application to total synthesis of oleandolide. J Am Chem Soc 124:12806–12815
57. Lee K-Y, Oh C-Y, Ham W-H (2002) Total synthesis of sphingofungin F. Org Lett 4: 4403–4405
58. Lautens M, Colucci JT, Hiebert S, Smith ND, Bouchain G (2002) Total synthesis of ionomycin using ring-opening strategies. Org Lett 4:1879–1882
59. Layton ME, Morales CA, Shair MD (2002) Biomimetic synthesis of (−)-longithorone A. J Am Chem Soc 124:773–775
60. Corrêa IR Jr, Pilli RA (2003) Total synthesis and structural elucidation of (−)-delactonmycin. Angew Chem Int Ed 42:3017–3020
61. Williams DR, Nold AL, Mullins RJ (2004) Asymmetric conjugate addition for the preparation of *syn*-1,3-dimethyl arrays: synthesis and structure elucidation of capensifuranone. J Org Chem 69:5374–5382
62. Zhang Q, Lu H, Richard C, Curran DP (2004) Fluorous mixture synthesis of stereoisomer libraries: total syntheses of (+)-murisolin and fifteen diastereoisomers. J Am Chem Soc 126:36–37
63. Tan Z, Negishi E (2004) An efficient and general method for the synthesis of α, ω-difunctional reduced polypropionates by Zr-catalyzed asymmetric carboalumination: synthesis of the scyphostatin side chain. Angew Chem Int Ed 43:2911–2914
64. Inoue M, Yokota W, Murugesh MG, Izuhara T, Katoh T (2004) Total synthesis of (+)-scyphostatin, a potent and specific inhibitor of neutral sphingomyelinase. Angew Chem Int Ed 43:4207–4209
65. Torssell S, Wanngren E, Somfai P (2007) Total synthesis of (−)-stemoamide. J Org Chem 72:4246–4249
66. Takahashi K, Matsumura T, Ishihara J, Hatakeyama S (2007) A highly stereocontrolled total synthesis of dysiherbaine. Chem Commun, 4158–4160
67. Stewart SG, Polomska ME, Lim RW (2007) A concise synthesis of maleic anhydride and maleimide natural products found in antrodia camphorate. Tetrahedron Lett 48:2241–2244
68. Nolasco L, Gonzalez MP, Caggiano L, Jackson RFW (2009) Application of Negishi cross-coupling to the synthesis of the cyclic tripeptides OF4949-III and K-13. J Org Chem 74:8280–8289
69. Negishi E, Tan Z, Liou S-Y, Liao B (2000) Strictly regiocontrolled a-monosubstitution of cyclic carbonyl compounds with alkynyl and alkyl groups via Pd-catalyzed coupling of cyclic α-iodoenones with organozincs. Tetrahedron 56:10197–10207
70. Novak T, Tan Z, Liang B, Negishi E (2005) All-catalytic, efficient, and asymmetric synthesis of α, ω-diheterofunctional reduced polypropionates via "one-pot" Zr-catalyzed asymmetric arboalumination-Pd-catalyzed cross-coupling tandem process. J Am Chem Soc 127:2838–2839
71. Fürstner A, Dierkes T, Thiel OR, Blanda G (2001) Total synthesis of (−)-salicylihalamide. Chem Eur J 7:5286–5298
72. Zeng F, Negishi E (2001) A novel, selective, and efficient route to carotenoids and related natural products via Zr-catalyzed carboalumination and Pd- and Zn-catalyzed cross coupling. Org Lett 3:719–722
73. Lipshutz BH, Amorelli B (2009) Total synthesis of piericidin A1. Application of a modified Negishi carboalumination-nickel-catalyzed cross-coupling. J Am Chem Soc 131:1396–1397
74. Liang B, Novak T, Tan Z, Negishi E (2006) Catalytic, efficient, and *syn*-selective construction of deoxypolypropionates and other chiral compounds via Zr-catalyzed asymmetric carboalumination of allyl alcohol. J Am Chem Soc 128:2770–2771

75. A C, Riveiros R, Ragot J, Fürstner A (2003) Total syntheses of amphidinolide T1, T3, T4, and T5. J Am Chem Soc 125:15512–15520
76. Stoltz BM, Kano T, Corey EJ (2000) Enantioselective total synthesis of nicandrenones. J Am Chem Soc 122:9044–9045
77. Panek JS, Jain NF (2001) Total synthesis of rutamycin B and oligomycin C. J Org Chem 66:2747–2756
78. Fürstner A, Funel JA, Tremblay M, Bouchez LC, Nevado C, Waser M, Ackerstaff J, Stimson CC (2008) A versatile protocol for Stille–Migita cross coupling reactions. Chem Commun, 2873–2875
79. Ahaidar A, Fernández D, Danelón G, Cuevas C, Manzanares I, Albericio F, Joule JA, Álvarez M (2003) Total syntheses of variolin B and deoxyvariolin B. J Org Chem 68:10020–10029
80. Fernández D, Ahaidar A, Danelón G, Cironi P, Marfil M, Pérez O, Cuevas C, Albericio F, Joule JA, Álvarez M (2004) Synthesis of polyheterocyclic nitrogen-containing marine natural products. Monatsh Chem 135:615–627
81. Amans D, Bellosta V, Cossy J (2007) An efficient and stereoselective synthesis of the monomeric counterpart of marinomycin A. Org Lett 9:1453–1456
82. Amans D, Bareille L, Bellosta V, Cossy J (2009) Synthesis of the monomeric counterpart of marinomycin A. J Org Chem 74:7665–7674
83. Fürstner A, Bouchez LC, Funel J-A, Liepins V, Porée F-H, Gilmour R, Beaufils F, Laurich D, Tamiya M (2007) Total syntheses of amphidinolide H and G. Angew Chem Int Ed 46:9265–9270
84. Allred GD, Liebeskind LS (1996) Copper-mediated cross-coupling of organostannanes with organic iodides at or below room temperature. J Am Chem Soc 118:2748–2749
85. König CM, Gebhardt B, Schleth C, Dauber M, Koert U (2009) Total synthesis of phoslactomycin A. Org Lett 11:2728–2731
86. Paterson I, Britton R, Delgado O, Meyer A, Poullennec KG (2004) Total synthesis and configurational assignment of (−)-dictyostatin, a microtubule-stabilizing macrolide of marine sponge origin. Angew Chem Int Ed 43:4629–4633
87. Durham TB, Blanchard N, Savall BM, Powell NA, Roush WR (2004) Total synthesis of formamicin. J Am Chem Soc 126:9307–9317
88. Maleczka Jr RE, Terrell LR, Geng F, Ward III JS (2002) Total synthesis of proposed amphidinolide A via a highly selective ring-closing metathesis. Org Lett 4:2841–2844
89. Fuwa H, Kainuma N, Tachibana K, Sasaki M (2002) Total synthesis of (−)-gambierol. J Am Chem Soc 124:14983–14992
90. Kadota I, Takamura H, Sato K, Ohno A, Matsuda K, Yamamoto Y (2003) Total synthesis of (−)-gambierol. J Am Chem Soc 125:46–47
91. Kadota I, Takamura H, Sato K, Ohno A, Matsuda K, Satake M, Yamamoto Y (2003) Convergent total syntheses of gambierol and 16-*epi*-gambierol and their biological activities. J Am Chem Soc 125:11893–11899
92. Johnson HWB, Majumder U, Rainier JD (2005) The total synthesis of gambierol. J Am Chem Soc 127:848–849
93. Nicolaou KC, Murphy F, Barluenga S, Ohshima T, Wei H, Xu J, Gray DLF, Baudoin O (2000) Total synthesis of the novel immunosuppressant canglifehrin A. J Am Chem Soc 122:3830–3838
94. Duan M, Paquette LA (2001) Enantioselective total synthesis of the cyclophilin-binding immunosuppressive agent sanglifehrin A. Angew Chem Int Ed 40:3632–3636
95. Paquette LA, Duan M, Konetzki I, Kempmann C (2002) A convergent three-component total synthesis of the powerful immunosuppressant (−)-sanglifehrin A. J Am Chem Soc 124:4257–4270
96. Albrecht BK, Williams RM (2001) Entry into the bi-aryl moiety of the TMC-95 proteasome inhibitors via the Stille protocol. Tetrahedron Lett 42:2755–2757

97. Cuzzupe AN, Hutton CA, Lilly MJ, Mann RK, McRae KJ, Zammit SC, Rizzacasa MA (2001) Total synthesis of the epidermal growth factor inhibitor (−)-reveromycin B. J Org Chem 66:2382–2393
98. Humphrey JM, Liao Y, Ali A, Rein T, Wong Y-L, Chen H-J, Courtney AC, Martin SF (2002) Enantioselective total syntheses of manzamine A and related alkaloids. J Am Chem Soc 124:8584–8592
99. Lebsack AD, Link JT, Overman LE, Stearns BA (2002) Enantioselective total synthesis of quadrigemine C and psycholeine. J Am Chem Soc 124:9008–9009
100. Brückner S, Abraham E, Klotz P, Suffert J (2002) Cascade cyclization: an easy access to highly unsaturated polycyclic ring systems through a tandem Stille/[4+2] reaction under mild conditions. Org Lett 4:3391–3393
101. Beaudry CM, Trauner D (2002) Synthetic studies toward SNF4435 C and SNF4435 D. Org Lett 4:2221–2224
102. Miller AK, Byun DH, Beaudry CM, Trauner D (2004) The total synthesis of (−)-crispatene. Proc Natl Acad Sci U S A 101:12019–12023
103. Beaudry CM, Trauner D (2005) Total synthesis of (−)-SNF4435 C and (+)-SNF4435 D. Org Lett 7:4475–4477
104. Tsuchikawa H, Matsushita N, Matsumori N, Murata M, Oishi T (2006) Synthesis of 28–19F-amphotericin B methyl ester. Tetrahedron Lett 47:6187–6191
105. Amans D, Bellosta V, Cossy J (2006) Total synthesis of pseudotrienic acid B: a bioactive metabolite from *pseudomonas* sp. MF 381-IODS. Angew Chem Int Ed 45:5870–5874
106. Amans D, Bellosta V, Cossy J (2009) Synthesis of two bioactive natural products: FR252921 and pseudotrienic acid B. Chem Eur J 15:3457–3473
107. Paterson I, Findlay AD, Noti C (2008) Total synthesis of (−)-spirangien A and its methyl ester. Chem Commun, 6408–6410
108. Deng L, Ma Z, Zhao G (2008) Synthetic studies toward the total synthesis of amphidinolide H1. Synlett, 728–732
109. Gillis EP, Burke MD (2008) Multistep synthesis of complex boronic acids from simple MIDA boronates. J Am Chem Soc 130:14084–14085
110. Fürstner A, Bouchez LC, Morency L, Funel JA, Liepins V, Porée FH, Gilmour R, Laurich D, Beaufils F, Tamiya M (2009) Total syntheses of amphidinolides B1, B4, G1, H1 and structure revision of amphidinolide H2. Chem Eur J 15:3983–4010
111. Beingessner RL, Farand JA, Barriault L (2010) Progress toward the total synthesis of (±)-havellockate. J Org Chem 75:6337–6346
112. Mizutani M, Inagaki F, Nakanishi T, Yanagihara C, Tamai I, Mukai C (2011) Total syntheses of (−)- and (+)-goniomitine. Org Lett 13:1796–1799
113. Lam HW, Pattenden G (2002) Total synthesis of the presumed amphidinolide A. Angew Chem Int Ed 41:508–511
114. Narayan S, Roush WR (2004) Studies toward the total synthesis of angelmicin B (hibarimicin B): synthesis of a model CD-D' arylnaphthoquinone. Org Lett 6:3789–3792
115. Fuwa H, Ebine M, Sasaki M (2006) Total synthesis of the proposed structure of brevenal. J Am Chem Soc 128:9648–9650
116. Fuwa H, Ebine M, Bourdelais AJ, Baden DG, Sasaki M (2006) Total synthesis, structure revision, and absolute configuration of (−)-brevenal. J Am Chem Soc 128:16989–16999
117. Schnermann MJ, Boger DL (2005) Total synthesis of piericidin A1 and B1. J Am Chem Soc 127:15704–15705
118. Valente C, Organ MG (2008) Assessing synthetic strategies: total syntheses of (±)-neodolabellane-type diterpenoids. Chem Eur J 14:8239–8245
119. Nicolaou KC, Vyskocil S, Koftis TV, Yamada YMA, Ling T, Chen DYK, Tang W, Petrovic G, Frederick MO, Li Y, Satake M (2004) Structural revision and total synthesis of azaspiracid-1, Part 1: intelligence gathering and tentative proposal. Angew Chem Int Ed 43:4312–4318

120. Nicolaou KC, Koftis TV, Vyskocil S, Petrovic G, Ling T, Yamada YMA, Tang W, Frederick MO (2004) Structural revision and total synthesis of azaspiracid-1, Part 2: definition of the ABCD domain and total synthesis. Angew Chem Int Ed 43:4318–4324
121. Dai Q, Xie X, Xu S, Ma D, Tang S, She X (2011) Total syntheses of tardioxopiperazine A, isoechinulin A, and variecolorin C. Org Lett 13:2302–2305
122. Nicolaou KC, Ramphal JY, Palazon JM, Spanevello RA (1989) Stereocontrolled total synthesis of (5S,6R)-, (5S, 6S)-, (5R,6R)-, and (5R,6S)-(7E,9E,1 1Z,14Z)-5,6-dihydroxy-7,9,11,14-icosatetraenoic acid (5,6-DiHETE) methyl esters. Angew Chem Int Ed 28:587–588
123. Roush WR, Sciotti RJ (1994) Enantioselective total synthesis of (−)-chlorothricolide. J Am Chem Soc 116:6457–6458
124. Evans DA, Ng HP, Rieger DL (1993) Total synthesis of the macrolide antibiotic rutamycin B. J Am Chem Soc 115:11446–11459
125. Pla D, Marchal A, Olsen CA, Albericio F, Álvarez M (2005) Modular total synthesis of lamellarin D. J Org Chem 70:8231–8234
126. Fischer DF, Sarpong R (2010) Total synthesis of (+)-complanadine A using an iridium-catalyzed pyridine C-H functionalization. J Am Chem Soc 132:5926–5927
127. Armstrong RW, Beau JM, Cheon SH, Christ WJ, Fujioka H, Ham W-H, Hawkins LD, Jin H, Kang SH, Kishi Y, Martinelli MJ, McWhorter Jr. WW, Mizuno M, Nakata M, Stutz AE, Talamas FX, Taniguchi M, Tino JA, Ueda K, Uenishi J, White JB, Yonaga M (1989) Total synthesis of palytoxin carboxylic acid and palytoxin amide. J Am Chem Soc 111:7525–7530
128. Frank SA, Chen H, Kunz RK, Schnaderbeck MJ, Roush WR (2000) Use of thallium(I) ethoxide in Suzuki cross coupling reactions. Org Lett 2:2691–2694
129. Wu B, Liu Q, Sulikowski GA (2004) Total synthesis of apoptolidinone. Angew Chem Int Ed 43:6673–6675
130. Wolfe JP, Singer RA, Yang BH, Buchwald SL (1999) Highly active palladium catalysts for Suzuki coupling reactions. J Am Chem Soc 121:9550–9561
131. Martin R, Buchwald SL (2008) Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions employing dialkylbiaryl phosphine ligands. Acc Chem Res 41:1461–1473
132. Rainka MP, Milne JE, Buchwald SL (2005) Dynamic kinetic resolution of α, β-unsaturated lactones through asymmetric copper-catalyzed conjugate reduction: application to the total synthesis of eupomatilone-3. Angew Chem Int Ed 44:6177–6180
133. Darses S, Genet JP (2008) Potassium organotrifluoroborates: new perspectives in organic synthesis. Chem Rev 108:288–325
134. Knapp DM, Gillis EP, Burke MD (2009) A general solution for unstable boronic acids: slow-release cross-coupling from air-stable MIDA boronates. J Am Chem Soc 131:6961–6963
135. Woerly EM, Cherney AH, Davis EK, Burke MD (2010) Stereoretentive Suzuki-Miyaura coupling of haloallenes enables fully stereocontrolled access to (−)-peridinin. J Am Chem Soc 132:6941–6943
136. Reddy YK, Falck JR (2002) Asymmetric total synthesis of (+)-fostriecin. Org Lett 4:969–971
137. Garg NK, Sarpong R, Stoltz BM (2002) The first total synthesis of dragmacidin D. J Am Chem Soc 124:13179–13184
138. Evans DA, Starr JT (2002) A cascade cycloaddition strategy leading to the total synthesis of (−)-FR182877. Angew Chem Int Ed 41:1787–1790
139. Evans DA, Starr JT (2003) A cycloaddition cascade approach to the total synthesis of (−)-FR182877. J Am Chem Soc 125:13531–13540
140. Nagata T, Nakagawa M, Nishida A (2003) The first total synthesis of nakadomarin A. J Am Chem Soc 125:7484–7485
141. Nakahara S, Kubo A (2003) Total synthesis of styelsamine C, a cytotoxic fused tetracyclic aromatic alkaloid. Heterocycles 60:2017–2018
142. Miyashita K, Sakai T, Imanishi T (2003) Total synthesis of (±)-spiroxin C. Org Lett 5:2683–2686
143. Nicolaou KC, Rao PB, Hao J, Reddy MV, Rassias G, Huang X, Chen DY-K, Snyder SA (2003) The second total synthesis of diazonamide A. Angew Chem Int Ed 42:1753–1758

144. Raheem IT, Goodman SN, Jacobsen EN (2004) Catalytic asymmetric total syntheses of quinine and quinidine. J Am Chem Soc 126:706–707
145. Handy ST, Zhang Y, Bregman H (2004) A modular synthesis of the lamellarins: total synthesis of lamellarin G trimethyl ether. J Org Chem 69:2362–2366
146. Garg NK, Caspi DD, Stoltz BM (2004) The total synthesis of (+)-dragmacidin F. J Am Chem Soc 126:9552–9553
147. Yu SH, Ferguson MJ, McDonald R, Hall DG (2005) Brønsted acid-catalyzed allylboration: short and stereodivergent synthesis of all four eupomatilone diastereomers with crystallographic assignments. J Am Chem Soc 127:12808–12809
148. Lépine R, Zhu J (2005) Microwave-assisted intramolecular Suzuki-Miyaura reaction to macrocycle, a concise asymmetric total synthesis of biphenomycin B. Org Lett 7:2981–2984
149. Shimizu T, Satoh T, Murakoshi K, Sodeoka M (2005) Asymmetric total synthesis of (−)-spirofungin A and (+)-spirofungin B. Org Lett 7:5573–5576
150. Ahmed Z, Langer P (2005) Synthesis of natural pulvinic acids based on a '[3+2] cyclization–Suzuki cross-coupling' strategy. Tetrahedron 61:2055–2063
151. Appukkuttan P, Dehaen W, Van der Eycken E (2005) Microwave-enhanced synthesis of N-shifted buflavine analogues via a Suzuki-ring-closing metathesis protocol. Org Lett 7: 2723–2726
152. Appukkuttan P, Dehaen W, Van der Eycken E (2007) Microwave-assisted transition-metal-catalyzed synthesis of N-shifted and ring-expanded buflavine analogues. Chem Eur J 13:6452–6460
153. Jones SB, He L, Castle SL (2006) Total synthesis of (±)-hasubanonine. Org Lett 8:3757–3760
154. Altemöller M, Podlech J, Fenske D (2006) Total synthesis of altenuene and isoaltenuene. Eur J Org Chem, 1678–1684
155. Johnson PD, Sohn J-H, Rawal VH (2006) Synthesis of C-15 vindoline analogues by palladium-catalyzed cross-coupling reactions. J Org Chem 71:7899–7902
156. Stanislawski PC, Willis AC, Banwell MG (2007) Gem-dihalocyclopropanes as building blocks in natural-product synthesis: enantioselective total syntheses of ent-erythramine and 3-epi-erythramine. Chem Asian J 2:1127–1136
157. Joncour A, Décor A, Dau METH, Baudoin O (2007) Asymmetric synthesis of antimicrotubule biaryl hybrids of allocolchicine and steganacin. Chem Eur J 13:5450–5465
158. Gillis EP, Burke MD (2007) A simple and modular strategy for small molecule synthesis: iterative Suzuki-Miyaura coupling of B-protected haloboronic acid building blocks. J Am Chem Soc 129:6716–6717
159. Jiang X, Liu B, Lebreton S, De Brabander JK (2007) Total synthesis and structure revision of the marine metabolite palmerolide A. J Am Chem Soc 129:6386–6387
160. Mitra S, Gurrala SR, Coleman RS (2007) Total synthesis of the eupomatilones. J Org Chem 72:8724–8736
161. Reeves JT (2007) A concise synthesis of butylcycloheptylprodigiosin. Org Lett 9:1879–1881
162. Chen HS, Ma XP, Li ZM, Wang QR, Tao FG (2008) An effective synthesis of β-aryl substituted isotetronic acids via Suzuki coupling. Chin Chem Lett 19:1309–1311
163. Lee SJ, Gray KC, Paek JS, Burke MD (2008) Simple, efficient, and modular syntheses of polyene natural products via iterative cross-coupling. J Am Chem Soc 130:466–468
164. Murray TJ, Forsyth CJ (2008) Total synthesis of GEX1A. Org Lett 10:3429–3431
165. Calancea M, Carret S, Deprés J-P (2009) Short access to the aromadendrane family: highly efficient stereocontrolled total synthesis of (±)-cyclocolorenone and (±)-α-gurjunene. Eur J Org Chem, 3134–3137
166. Foster RS, Huang J, Vivat JF, Browne DL, Harrity JPA (2009) A divergent strategy to the withasomnines. Org Biomol Chem 7:4052–4056
167. Lee SJ, Anderson TM, Burke MD (2010) A simple and general platform for generating stereochemically complex polyene frameworks by iterative cross-coupling. Angew Chem Int Ed 49:8860–8863

168. Bao K, Dai Y, Zhu Z-B, Tu F-J, Zhang W-G, Yao X-S (2010) Design and synthesis of biphenyl derivatives as mushroom tyrosinase inhibitors. Bioorg Med Chem 18:6708–6714
169. Fuwa H, Sasaki M (2010) Total synthesis of (−)-exiguolide. Org Lett 12:584–587
170. Denton RM, Scragg JT (2010) A concise synthesis of dunnianol. Synlett, 633–635
171. Zheng S-Y, Shen Z-W (2010) Total synthesis of hirtellanine A. Tetrahedron Lett 51:2883–2887
172. Gray M, Andrews IP, Hook DF, Kitteringham J, Voyle M (2000) Practical methylation of aryl halides by Suzuki-Miyaura coupling. Tetrahedron Lett 41:6237–6240
173. Chemler SR, Trauner D, Danishefsky SJ (2001) The B-alkyl Suzuki-Miyaura cross-coupling reaction: Development, mechanistic study, and applications in natural product synthesis. Angew Chem Int Ed 40:4544–4568
174. Ebine M, Fuwa H, Sasaki M (2008) Total synthesis of (−)-brevenal: A concise synthetic entry to the pentacyclic polyether core. Org Lett 10:2275–2278
175. Kallan NC, Halcomb RL (2000) Synthesis of the ring system of phomactin D using a Suzuki macrocyclization. Org Lett 2:2687–2690
176. Starr JT, Carreira EM (2000) Synthesis of CP-225,917 and CP-263,114. Angew Chem Int Ed 39:1415–1421
177. Zhu B, Panek JS (2000) Total synthesis of epothilone A. Org Lett 2:2575–2578
178. Lee CB, Chou T-C, Zhang X-G, Wang Z-G, Kuduk SD, Chappell MD, Stachel SJ, Danishefsky SJ (2000) Total synthesis and antitumor activity of 12,13-desoxyepothilone F: An unexpected solvolysis problem at C15, mediated by remote substitution at C21. J Org Chem 65:6525–6533
179. Fuwa H, Sasaki M, Tachibana K (2000) Synthetic studies on a marine polyether toxin, gambierol: stereoselective synthesis of the FGH ring system via *B*-alkyl Suzuki coupling. Tetrahedron Lett 41:8371–8375
180. Nakamura T, Shiozaki M (2001) Total synthesis of sphingofungin E. Tetrahedron Lett 42:2701–2704
181. Takakura H, Noguchi K, Sasaki M, Tachibana K (2001) Synthetic studies on ciguatoxin: a highly convergent synthesis of the GHIJKLM ring system based on *B*-alkyl Suzuki coupling. Angew Chem Int Ed 40:1090–1093
182. Sasaki M, Ishikawa M, Fuwa H, Tachibana K (2002) A general strategy for the convergent synthesis of fused polycyclic ethers via *B*-alkyl Suzuki coupling:synthesis of the ABCD ring fragment of ciguatoxins. Tetrahedron 58:1889–1911
183. Mandal AK (2002) Stereocontrolled total synthesis of (–)-ebelactone A. Org Lett 4:2043–2045
184. Sasaki M, Tsukano C, Tachibana K (2002) Studies toward the total synthesis of gymnocin A, a cytotoxic polyether: a highly convergent entry to the F-N ring fragment. Org Lett 4:1747–1750
185. Sasaki M, Tsukano C, Tachibana K (2003) Synthetic entry to the ABCD ring fragment of gymnocin-A, a cytotoxic marine polyether. Tetrahedron Lett 44:4351–4354
186. Tsukano C, Sasaki M (2003) Total synthesis of gymnocin-A. J Am Chem Soc 125:14294–14295
187. Tsukano C, Ebine M, Sasaki M (2005) Convergent total synthesis of gymnocin-A and evaluation of synthetic analogues. J Am Chem Soc 127:4326–4335
188. Mohr PJ, Halcomb RL (2003) Total synthesis of (+)-phomactin A using a *B*-alkyl Suzuki macrocyclization. J Am Chem Soc 125:1712–1713
189. Marshall JA, Schaaf G, Nolting A (2005) Synthesis of the C6–C21 segment of amphidinolide E. Org Lett 7:5331–5333
190. Carret S, Deprés J-P (2007) Access to guaianolides: highly efficient stereocontrolled total synthesis of (±)-geigerin. Angew Chem Int Ed 46:6870–6873
191. Roulland E, Dr. (2008) Total synthesis of (+)-oocydin A: application of the Suzuki–Miyaura cross-coupling of 1,1-dichloro-1-alkenes with 9-alkyl 9-BBN. Angew Chem Int Ed 47:3762–3765

192. Williams DR, Walsh MJ, Miller NA (2009) Studies for the synthesis of xenicane diterpenes. A stereocontrolled total synthesis of 4- hydroxydictyo-lactone. J Am Chem Soc 131:9038–9045
193. Schnabel C, Hiersemann M (2009) Total synthesis of jatrophane diterpenes from *euphorbia characias*. Org Lett 11:2555–2558
194. Archambaud S, Legrand F, Aphecetche-J K, Collet S, Guingant A, Evain M (2010) Total synthesis of (+)-brefeldin C, (+)-nor-Me brefeldin A and (+)-4-*epi*-nor-Me brefeldin A. Eur J Org Chem, 1364–1380
195. Ohtani N, Tsutsumi R, Kuranaga T, Shirai T, Wright JLC, Baden DG, Satake M, Tachibana K (2010) Synthesis of the ABC ring fragment of brevisin, a new dinoflagellate polycyclic ether. Heterocycles 80:825–830
196. Kuranaga T, Ohtani N, Tsutsumi R, Baden DG, Wright JLC, Satake M, Tachibana K (2011) Total synthesis of (−)-brevisin: a concise synthesis of a new marine polycyclic ether. Org Lett 13:696–699
197. Denmark SE, Liu JHC, Muhuhi JM (2009) Total syntheses of isodomoic acids G and H. J Am Chem Soc 131:14188–14189
198. Zhang Y, Panek JS (2007) Total synthesis of herboxidiene/GEX 1A. Org Lett 9:3141–3143
199. Denmark SE, Regens CS, Kobayashi T (2007) Total synthesis of papulacandin D. J Am Chem Soc 129:2774–2776
200. Denmark SE, Fujimori S (2005) Total synthesis of RK-397. J Am Chem Soc 127:8971–8973
201. Denmark SE, Yang S-M (2002) Intramolecular silicon-assisted cross-coupling: total synthesis of (+)-brasilenyne. J Am Chem Soc 124:15196–15197
202. Denmark SE, Yang S-M (2004) Total synthesis of (+)-brasilenyne. Application of an intramolecular silicon-assisted cross-coupling reaction. J Am Chem Soc 126:12432–12440