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# Recent developments of the Stille reaction as a revolutionized method in total synthesis

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**John Kenneth Stille** (May 8, 1930–July 19, 1989), who was an American chemist, discovered the Stille reaction, which is a key part of palladium-catalyzed cross-coupling chemistry. He received his bachelor degree before serving in the Navy during the Korean War, and received his master degree from the University of Arizona. He got his Ph.D. from the University of Illinois, under the direction of Carl Marvel. Unfortunately, Stille was killed in the United Airlines flight 232 crash in 1989 when he was only 59 years old. Awarding of 2010 Nobel Prize in chemistry jointly, to Richard Heck, Ei-ichi Negishi, and Akira Suzuki, for their invaluable efforts on palladium-catalyzed cross-couplings in organic synthesis underscores the importance of these classes of reactions. The authors would like to dedicate this report to the memory of J. K. Stille

*Abbreviations:* CuTC, copper(I) thiophene-2-carboxylate; DIBAL-H, diisobutylaluminum hydride; DIPEA, diisopropylethylamine; DMF, dimethylformamide; MOM, methoxymethyl; NMP, *N*-methylpyrrolidone; PMB, *p*-methoxybenzyl; TASF, tris(-dimethylamino)sulfoniumdifluoro(trimethyl)silicate; TBACl, tetrabutylammonium chloride; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TBSCl, *tert*-butyldimethylsilyl chloride; TEMPO, 2,2,6,6-tetramethylpiperidinyl-1-oxy; TFP, tri(2-furyl)phosphine; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMSBr, trimethylsilyl bromide; TMSOTf, trimethylsilyl trifluoromethanesulfonate.

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**Contents**



## 1. Introduction

Among transition metal catalyzed synthetic reactions, palladium-catalyzed cross-couplings[1] (Heck,[2] Stille,[3] Negishi,[4] Suzuki–Miyaura,[5] Sonogashira,[6] Kumada,[7] and Hiyama[8]) and Tsuji–Trost[9] allylation reaction for carbon–carbon bond construction have reached a level of sophistication to assemble complex molecular frameworks in the total synthesis of natural products, medicinal chemistry, chemical biology, industrial process, materials, and nanotechnology in a controlled and selective manner. From the discovery of these reactions in 1970s, they irreversibly changed the modern chemist's ability in organic synthesis; both in academia and in industry.[10] The joining of Richard Heck, Ei-ichi Negishi, and Akira Suzuki in 2010 to the prestigious circle of Nobel Laureate chemists for their roles in developing these practical methodologies emphasizes on this claim.[11]

The Stille reaction as a Pd-coupling was originally discovered by Kosugi[12] in the late 1970s, and was afterward developed as a significant tool in organic paradigms by Stille.[3] This protocol not only has the milder reaction conditions than the older Heck coupling, but also has more functional-group tolerant, which remains that as a popular pathway, which is particularly effective for transformations of highly functionalized molecules in organic synthesis. In addition, the Stille coupling as a powerful intermolecular carbon–carbon (C–C) bond formation process is an excellent candidate in generation of carbocyclic and heterocyclic rings especially five- and six-members like in macrocyclic systems. Although, the toxicity of the tin compounds, and their low polarity, which creates them poorly soluble in water is the main drawback of this protocol, for the synthesis of complex molecules, especially natural product synthesis, the Stille coupling is usually superior, displaying high selectivity and extensive scope.[13]

The Stille coupling as a versatile C–C bond forming reaction between stannanes and halides or pseudohalides, has very few limitations on the R-groups, which allow to this sell-elaborated methods the synthesis of various products from all of the combinations of halides and stannanes. In the generalized mechanism, based on the coupling of bromobenzene with tributyl(vinyl)stannane, the active catalytic species was assumed to be a [$PdL_2$] (L=$PPh_3$) complex. This complex reacts with the organic electrophile R–X to form complex **I** (Fig. 1). This complex was the only observable species in the catalytic cycle (even in the presence of excess organostannane), which displayed that the slow step was the transmetallation reaction with the organostannane. The transmetallation was believed to convert to complex **II**. A trans to cis isomerization to give **III**, thought to be very fast, was then required for the reductive elimination to provide the coupling product R–R′.[13] In addition, the description of the mechanistic details of this process specially with emphasizing on the transmetallation step was reported by Espinet and Echavarren.[14]

In the continuation of our attempts concerning the recent advances of the name reactions in organic synthesis,[15–20] herein we wish to present the applications of the Stille carbon–carbon bond-formation reaction to the science and art of total synthesis.

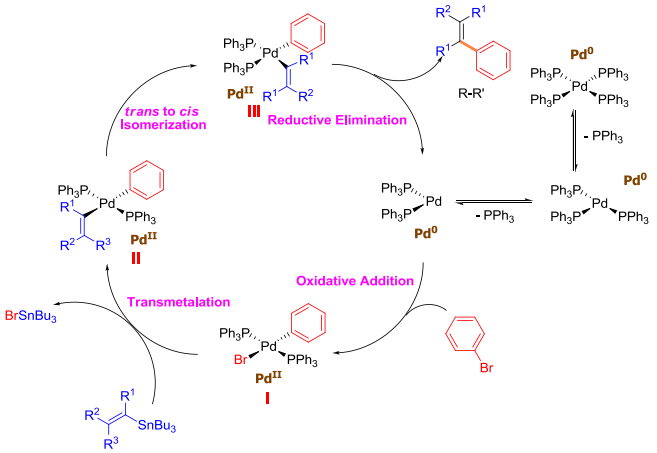
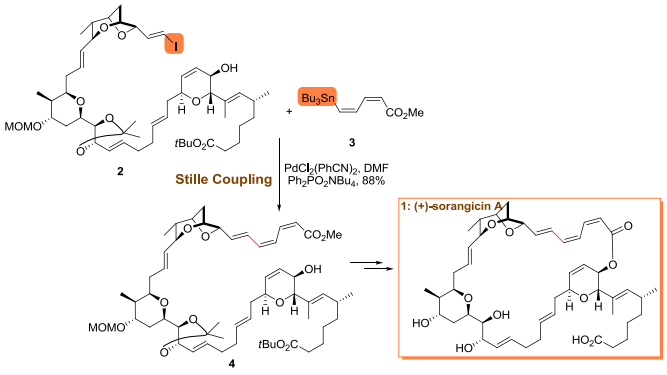



**Fig. 1.** Pd cross-coupling mechanism of the Stille reaction.

## 2. The intermolecular Stille coupling

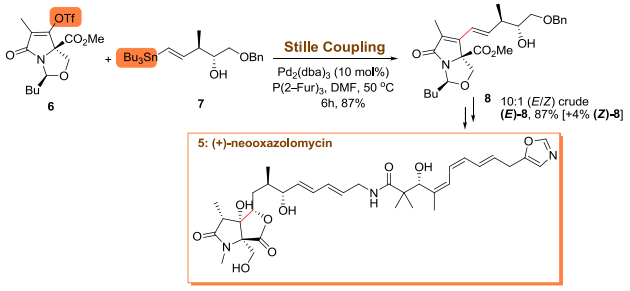
An operative asymmetric total synthesis of the macrolide antibiotics (+)-sorangicin A (**1**) has been accomplished via the Stille coupling between vinyl iodide **2** and *Z,Z*-diene stannane **3** to

furnish *Z*,*Z*,*E*-triene **4** in 88% yield (Scheme 1).[21] The requisite *Z*,*Z*,*E*-geometry of the extended unsaturation system was assigned based on coupling constants and NOE correlations. Presumably, $Ph_2PO_2NBu_4$ inhibits *Z*/*E* isomerization either by arresting formation of detrimental iodide side products, or by accelerating dissociation of the Pd catalyst after reductive elimination.



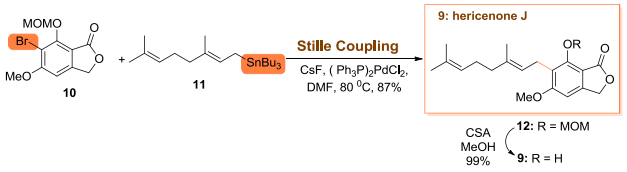

**Scheme 1.**

Formal synthesis of (−)-neooxazolomycin **5** via a Stille cross-coupling has been reported by Bastin and coworkers. The crystalline triflate **6** combined with the vinyl stannane **7** using $Pd_2(dba)_3$/P(2-fur)$_3$ in DMF at 50 °C for 6 h and afforded pure (*E*)-diene **8** in 87% yield and 4% of pure (*Z*)-**8**. Control of the temperature was essential in this reaction; if the reaction was run at higher temperatures the persistent formation of an unwanted isomer was observed (Scheme 2).[22]



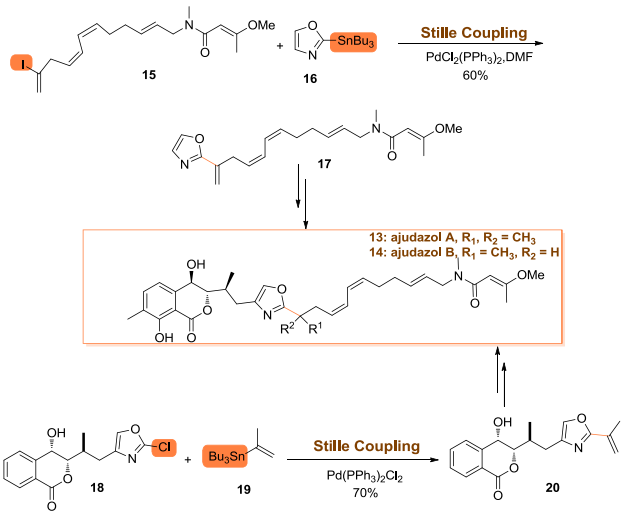

**Scheme 2.**

The total synthesis of hericenone J **9** has been reported by Kobayashi and coworkers through the Stille coupling reaction by treatment of aryl bromide **10** with coupling partner **11** in the presence of $(Ph_3P)_2PdCl_2$ and CsF to give the desired product **12** in 87% yield. Addition of CsF was crucial to obtain the product reproducibly. This is a remarkable example of a successful Stille reaction of the electron-rich, bis*ortho*-substituted aromatic bromide (Scheme 3). Natural product **9** can be produced by removal of the MOM group via acid-catalyzed condition (Scheme 3).[23]



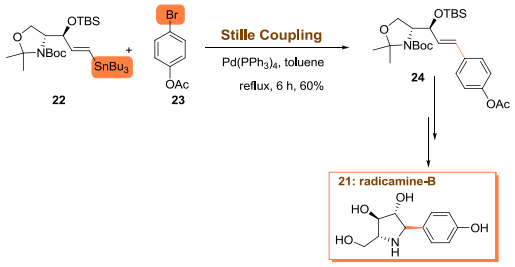

**Scheme 3.**

In the synthesis of the C1−C16 framework of the ajudazol A (**13**) and B (**14**) with significant biological activities, two kinds of key Stille cross coupling reaction in the different pathway used to introduce the C−C bond. Coupling of vinyl iodide **15** and 2-(tributylstannyl)oxazole **16** using $PdCl_2(PPh_3)_2$ furnished **17**, which can be converted to **13** and **14** after several steps. The coupling step was extremely dependent on the nature of the Pd ligands and the reaction temperature. In other hands treatment of chloroisochromanone **18** with the vinyl stannane **19** under the optimized conditions ($PdCl_2(PPh_3)_2$, degassed DMF, TFP and, P(PPh)$_3$) afforded the desired alkenyl **20** in excellent yields, which is the C1−C16 framework in synthetic route of **13** and **14** (Scheme 4).[24]



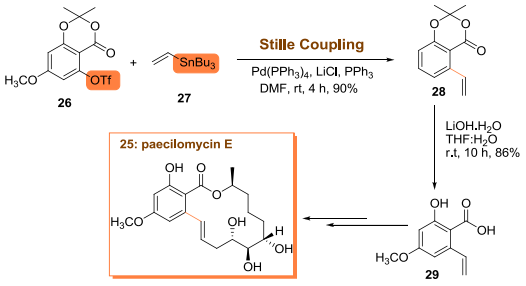

**Scheme 4.**

As illustrated in Scheme 5, the key step in the total synthesis of (−)-radicamine-B (**21**) as a potent inhibitor of α-glucosidase included the Stille coupling of the protected vinyl stannane **22** and 4-acetoxy bromobenzene **23** using $Pd(PPh_3)_4$ in toluene for affording the coupling compound **24** in the moderate yields (60%). This synthesis relied on Stille coupling as a handle for integrating the aryl group.[25]



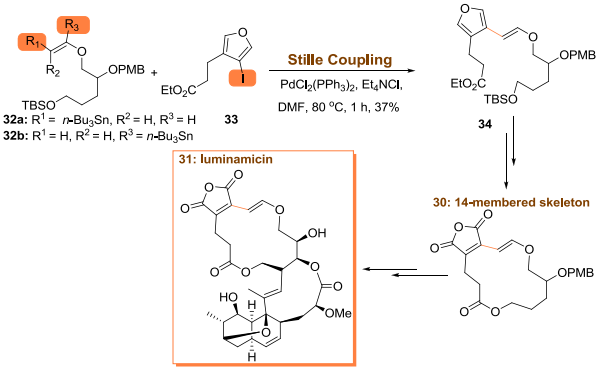

**Scheme 5.**

Srihari and coworkers synthesized paecilomycin E (**25**) with biological properties, such as antifungal, antiviral, cytotoxic, antimalarial, and protein tyrosine kinase and ATPase inhibition activities by Pd-catalyzed reaction. The coupling of triflate **26** and vinyl tributyl tin **27** afforded styrene **28**, which led to the key fragment **29** by deprotection of isoproylidene moiety with LiOH·$H_2O$, which was transformed to the natural product **25** (Scheme 6).[26]



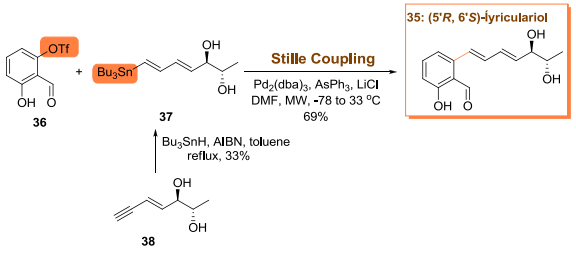

**Scheme 6.**

Kimishima and coworkers utilized the Stille coupling for the construction of the 14-membered skeleton compound **30**, which led to the luminamicin (**31**) as an antibacterial agent. With coupling partners β-*O*-vinyltin **32a** or α-*O*-vinyltin **32b** and iodofuran ester **33** in the presence of $PdCl_2(PPh_3)_2$ and $Et_4NCl$ the product **34** obtained in 37% yield (Scheme 7).[27] It is obvious that the yield of the Stille coupling was found to be considerably low, despite the high selectivity of the hydrostannylation.



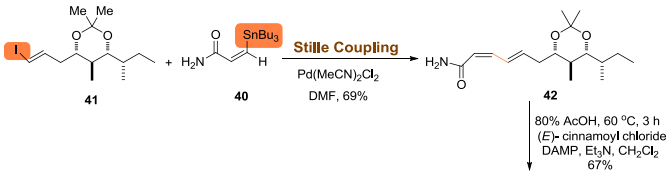

**Scheme 7.**

The key reaction in the total synthesis of (−)-pyriculariol (**35**), a phytotoxin isolated from rice blast fungus, included the Stille coupling reaction between triflate **36** and vinyl stannane **37** (was generated from enynediol **38**) under optimized conditions using microwave irradiation and finally, (5′*R*,6′*S*)-pyriculariol (**35**) formed in good yield. The effect of microwave could be direct activation of the molecule rather than immediate application of heat (Scheme 8).[28]



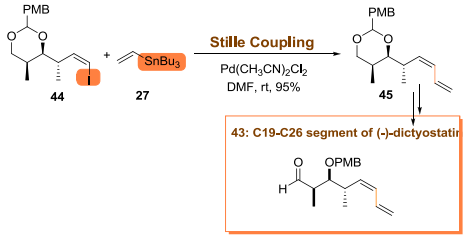

**Scheme 8.**

(−)-Basiliskamide B (**39**) a polyketide antibiotic as an attractive target for total synthesis, synthesized via the Stille cross-coupling. In one of the input step, coupling of *Z*-vinyl stannane **40** and *E*-vinyl iodide **41** utilizing $Pd(MeCN)_2Cl_2$ in DMF at ambient temperature furnished the product **42** in 69% yield after purification by silica gel column chromatography (Scheme 9). Valuable compound **42** can be converted in to **39** in 67% overall yield after removal of the isopropylidene acetal followed by selective acylation.[29,30]



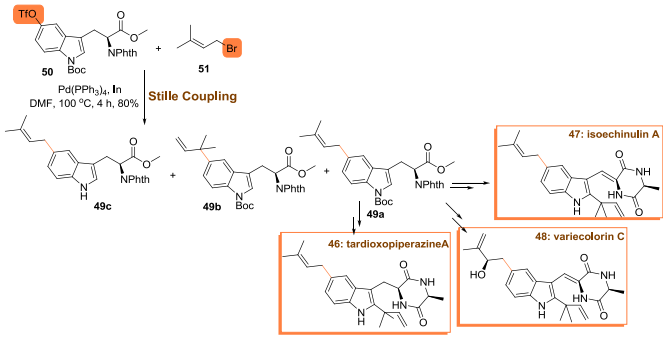

**Scheme 9.**

Yadav and Rajender developed the Stille coupling reaction for the construction of *Z*-diene core of C19–C26 segment in the total synthesis of (−)-dictyostatin (**43**) (an antimitotic marine macrolide). Cross-coupling between *Z*-vinyl iodide **44** and vinyl tributyl tin (**27**) in the presence of $Pd(CH_3CN)_2Cl_2$ in DMF at room temperature for 15 min yielded the *Z*-diene **45** in 95% (Scheme 10).[31]




**Scheme 10.**

Preparation of tardioxopiperazineA (**46**), isoechinulinA (**47**), and variecolorin C (**48**) starting from the key intermediate **49a** was derived from a regiocontrolled Stille cross-coupling reaction of coupling partner **50** and **51** (Scheme 11). The Stille coupling afforded two isomers **49a** and **49b** and the separation was very difficult.

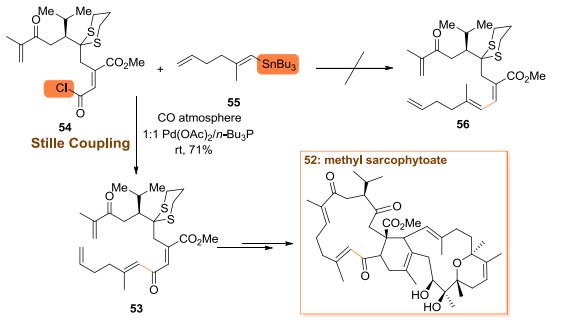



| Entry | 51 derivatives | reaction temprature/time | Yield 49a (%) | Yield 49c(%) | Yield 49b (%) |
|---|---|---|---|---|---|
| 1 | In | 100 °C, 4h | 60 | 20 | 0 |
| 2 | In | 100 °C, 4h | 50 | 5 | 0 |
| 3 | In | 100 °C, 4h | 40 | 5 | 0 |
| 4 | $SnBu_3$ | 100 °C, 4h | 60 | 0 | 25 |
| 5 | 9-BBN | 100 °C, 4h | 0 | 0 | 80 |

**Scheme 11.**

To solve this problem, various coupling partners were tested such as organomagnesium, organozinc, organolithium, and organoboron; however the identical results were obtained. providentially, when the allylindium reagent generated insitu was utilized under the optimized conditions according to the illustrated table in this reaction, was found that **49a** and Boc-deprotected product **49c** with heat in DMF were obtained in 60% and 20% yields (entry 1), respectively, which can be easily separated (Scheme 11).[32]

Among biologically active total syntheses of marine natural products, employing the Stille reaction by Ichige and coworkers stands out for the preparation of methyl sarcophytoate (**52**) (Scheme 12). By utilizing of the highly active $Pd(OAc)_2/n\text{-}Bu_3P$ catalyst, under CO atmosphere the desired product **53** was furnished in 71% from the coupling of the acid chloride **54** and vinyl stannane **55**. For avoiding the preparation of the unwanted product **56**, employing the reaction under the CO pressure is essential. When less polar toluene was used as a solvent as it was shown in table, the reaction proceeded in 3 h, and the yield of **53** was 43%. In conclusion, it was found that benzene was the best solvent for affording **53** in 71% yield in 1 h.[33]



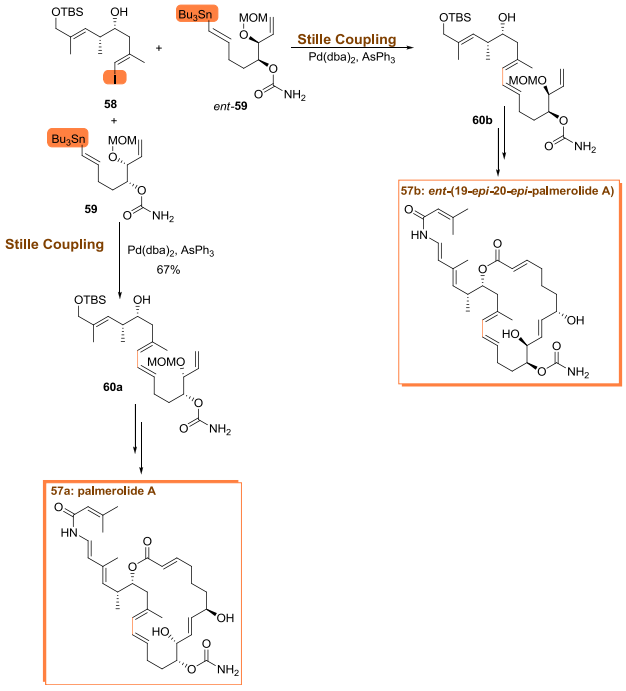

| Entry | catalyst | solvent | atmosphere | temprature (°C) | time (h) | Yield **53** (%) | Yield **56** (%) |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | THF | Ar | 60 | 36 | 0 | 28 |
| 2 | $Pd(PPh_3)_4$ | THF | CO | 50 | 16 | 0 | 27 |
| 3 | $1{:}1Pd(OAc)_2/n\text{-}Bu_3P$ | THF | CO | rt | 12 | 30 | 0 |
| 4 | $1{:}1Pd(OAc)_2/n\text{-}Bu_3P$ | THF | Ar | rt | 12 | 36 | trace |
| 5 | $1{:}1Pd(OAc)_2/n\text{-}Bu_3P$ | toluene | CO | rt | 3 | 43 | 0 |
| 6 | $1{:}1Pd(OAc)_2/n\text{-}Bu_3P$ | benzene | CO | rt | 1 | 71 | 0 |

**Scheme 12.**

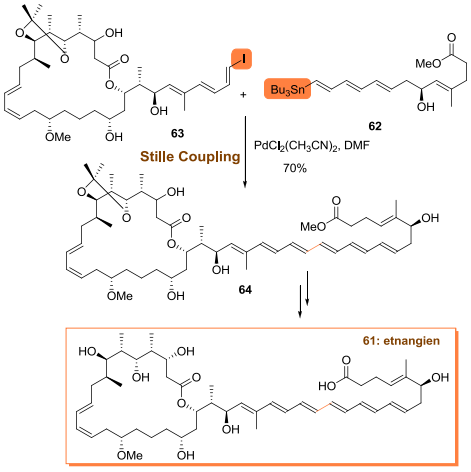
As another example of the use of the Stille coupling we consider the total synthesis of palmerolide A stereoisomers (**57a** and **57b**) with remarkable biological properties, by Nicolaou and coworkers. Coupling of vinyl iodide **58** and vinyl stannane **59** under the Pd-coupling condition ($Pd(dba)_2$, $AsPh_3$, LiCl) (Scheme 13) gave tetraene **60a** in 67% yield as a key intermediate in the synthetic rout of palmerolide A (**57a**). On the other hand, developing the same coupling condition of **58** and vinyl stannane *ent*-**59** provided hydroxyl tetraene **60b**, which led to synthesis of one of the palmerolide A stereoisomers: *ent*-(19-*epi*-20-*epi*-**57a**) (**57b**).[34]

In a beautiful example of the application of the Stille coupling, the potent antibiotic etnangien **61** was synthesized (Scheme 14) via the reaction between compound **62** and iodide **63** with $PdCl_2(CH_3CN)_2$ in degassed DMF for preparing the desired intermediate **64** in good yields (70%).[35]

A highly convergent second-generation total synthesis of (+)-phorboxazole A and B (**65a** and **65b**) with excellent biologically active properties was reported by Smith teams. A key Stille coupling reaction of macrocycle vinyl iodide (+)-**66** with **67** was applied for the formation of the full phorboxazole carbon backbone coupling product (+)-**68** in 68% yield (Scheme 15). Searching a variety of ligands, bases, solvents, and temperature ranges, catalyst system comprising $Pd_2(dba)_3{\cdot}CHCl_3$with $AsPh_3$ in combination with diisopropylamine, $Ph_2PO_2NBu_4$, and DMF at room temperature was selected. $Ph_2PO_2NBu_4$ gave a dramatic increase in yield.[36]




**Scheme 13.**

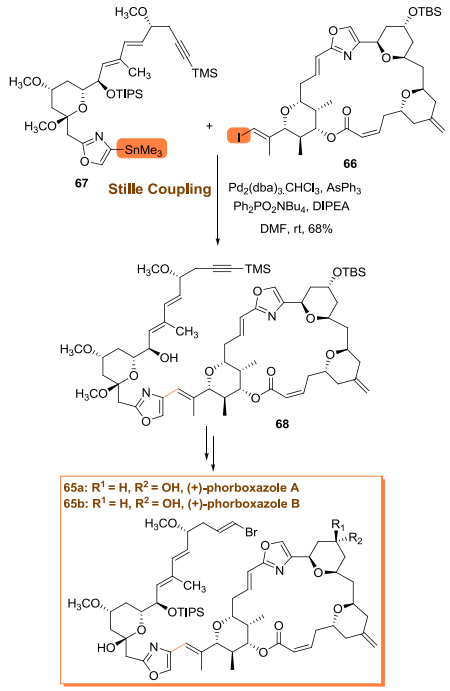



**Scheme 14.**

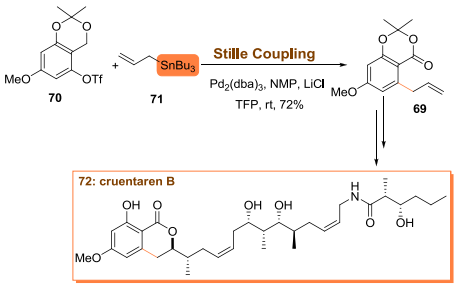
The key intermediate **69** in 65% yield obtained by the Pd-coupling of triflate **70** and allylstannane **71** in the presence of LiCl and tri(2-furyl)phosphine (TFP) in *N*-methylpyrrolidine (NMP) (Scheme 16) in the total synthesis of cytotoxic natural product cruentaren B (**72**).[37]

Leustroducsin B (**73**) with thrombopoiesis, anti-infective and antimetastatic activity was synthesized through the Stille coupling (Scheme 17) of triol **74** and segment **75** for the preparation the product **76** (included the entire carbon skeleton of **73**) in 61% yield.[38]

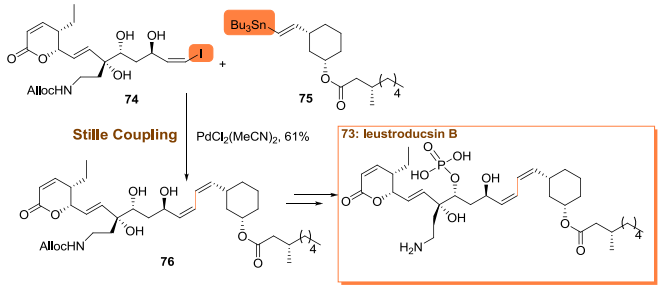
As shown in Scheme 18, the optimized Stille cross coupling condition, as an important step, was applied by Herrmann and coworkers to install the conjugated (*E*,*E*)-dieneal for the reaction of the compound **77** (prepared by hydrostannylation of 2-butyn-1-ol) and *E*-iodoalkene **78** with the copper(I) bromide dimethylsulfide complex (CuBr·DMS) without any detrimental effect on the $Pd_2(dba)_3/Ph_3As$-catalyzed cross-coupling process to produce **79** in 78% yield in asymmetric total synthesis of (+)-brevisamide (**80**).[39]



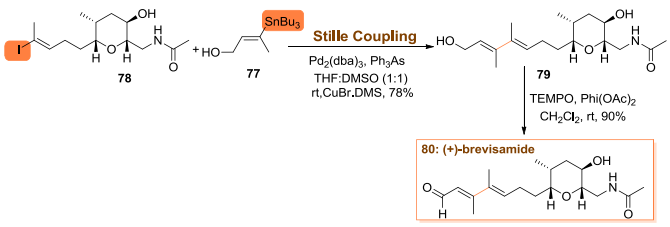

Scheme 15.




Scheme 16.

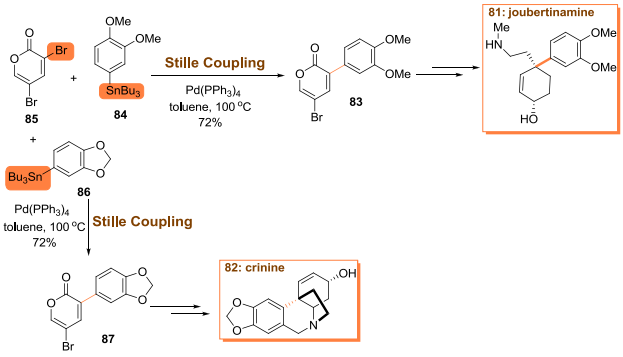



Scheme 17.



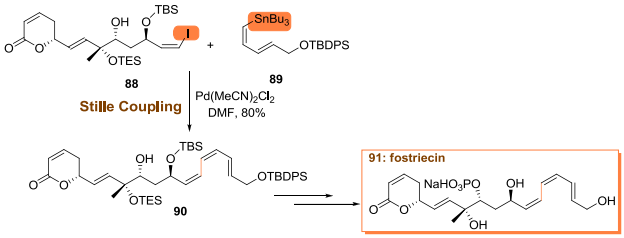

Scheme 18.

Crinane alkaloids, such as (±)-joubertinamine (**81**) and (±)-crinine (**82**) can be produced via the Stille coupling. In the total synthetic protocol of **81**, regioselectively 2-pyrone diene **83** was synthesized in good yield via the Pd-coupling of aryltin **84** with 3,5-dibromo-2-pyrone **85**. Furthermore the C3-selective Stille coupling reaction of **85** with aryltin **86** furnished 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone **87** in 72% yield, which converted to **82** after several step (Scheme 19).[40]



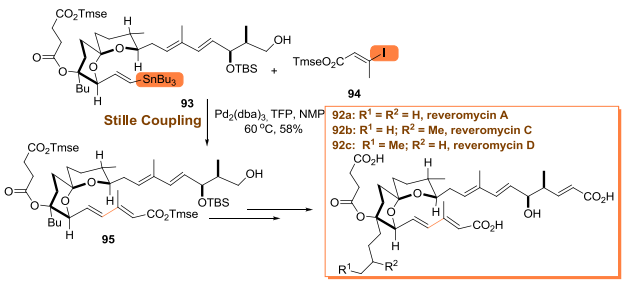

Scheme 19.

Treatment of vinyl iodide **88** with stannane compound **89** under ligand-free condition produced **90** as a key intermediate in different suggested total synthesis pathway of fostriecin (**91**) with potential cytotoxic activity in vitro and in vivo (Scheme 20) The Stille coupling was employed to prepare conjugated *Z,Z,E*-trienol unit.[41]




Scheme 20.

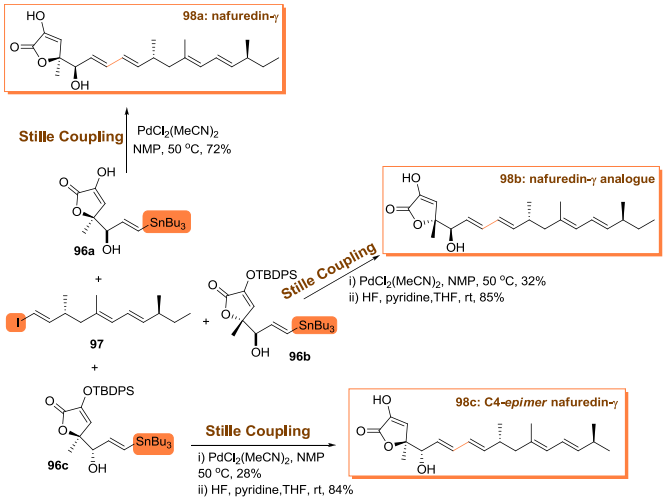
In the asymmetric synthesis of (−)-reveromycin A, C, and D (**92a**–**c**) with antifungal activity, the Stille cross coupling between stannane **93** and vinyl iodide **94** (Scheme 21) using modified Farina conditions afforded the desired tetraene **95** (58% yield) with a little amount of unfavorable geometric isomer, which could be removed by HPLC.[42]




Scheme 21.

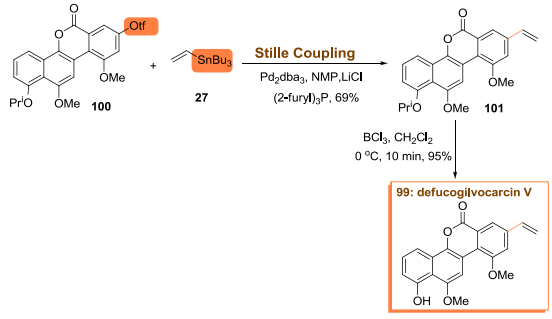
The Stille coupling between *E*-alkenylstannanes **96a** and vinyl iodide **97** in the presence of $PdCl_2(MeCN)_2$ afforded nafuredin-γ

(**98a**) in 72% yield. In addition, this route provides a simple and well-organized method to synthesize various nafuredin-γ analogues **96b** and **96c**. Coupling of **97** with **96b** and **96c** in similar condition and subsequent deprotection of the silyl enol ether was applied for the synthesis of nafuredin-γ analogue **98b** and its C4-*epimer* **98c** (Scheme 22).[43]




**Scheme 22.**

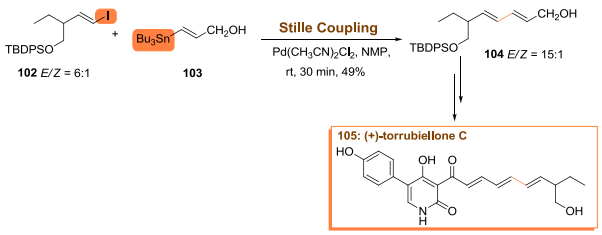
In the total synthesis of defucogilvocarcin V (**99**) a natural product with antitumor, antiviral antitopoisomerase, and anitestrogen properties James and Snieckus accomplished the modified Stille cross coupling condition for the reaction of triflate **100** with trinbutyl vinyl stannane (**27**) to afford 1-isopropoxy defucogilvocarcin V (**101**) in satisfactory yield, which provided **99** by deprotection of isopropyl ether (Scheme 23).[44]



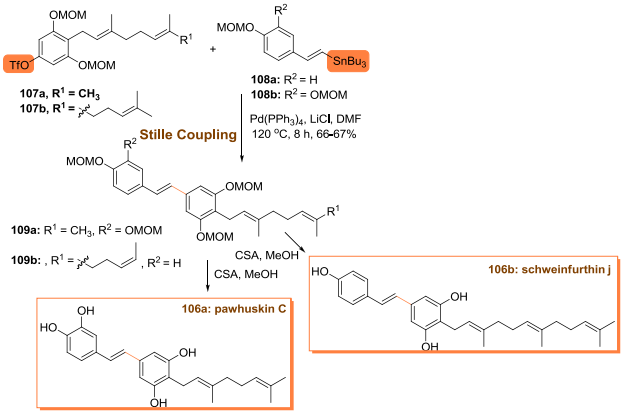

**Scheme 23.**

The Stille cross coupling of iodoolefin **102** with (*E*)-3-(tributylstannyl)-prop-2-en-1-ol (**103**) furnished homologated alcohol **104** as an important intermediate in the enantiomeric synthesis of natural product (+)-torrubiellone C (**105**) with biologically active properties. Flash chromatography on silica gel at this stage, could be increased the *E*/*Z* ratio to 15:1[45] (Scheme 24).

Argade and Singh reported the total syntheses of anticancer natural products pawhuskin C (**106a**) and Schweinfurthin J (**106b**) via the Stille cross-coupling of triflate **107a** with stannate **108b**, and **107b** with **108a** in the presence of $Pd(PPh_3)_4$ and LiCl to provide, respectively, **109a** and **109b** as a thick oil, which changed to the desired natural products **106a** and **106b** by acid deprotection of methoxymethyl groups (Scheme 25). In addition, intermediates **109a** and **109b** can be made by either of Heck coupling or Suzuki coupling.[46]

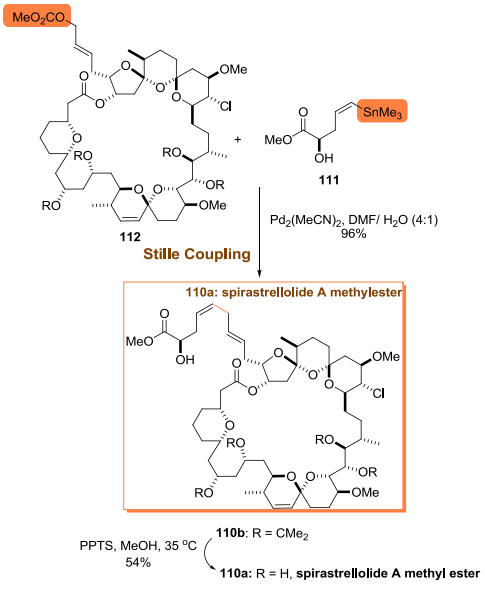



**Scheme 24.**




**Scheme 25.**

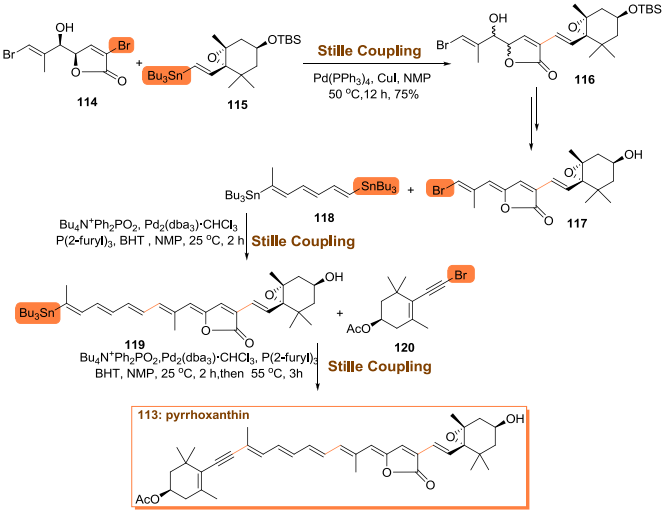
Anticancer spirastrellolide A methyl ester (**110a**) as an attractive target for total synthesis can provide through the Stille coupling between stannane **111** and allylic carbonate **112** with the correct stereochemistry in $PdCl_2(MeCN)_2$ for producing the desired coupled product **110b** in 96% yield. The key compound is precursor of the target molecule and converted to **110a** with the excess of PPTS in MeOH (Scheme 26).[47]




**Scheme 26.**

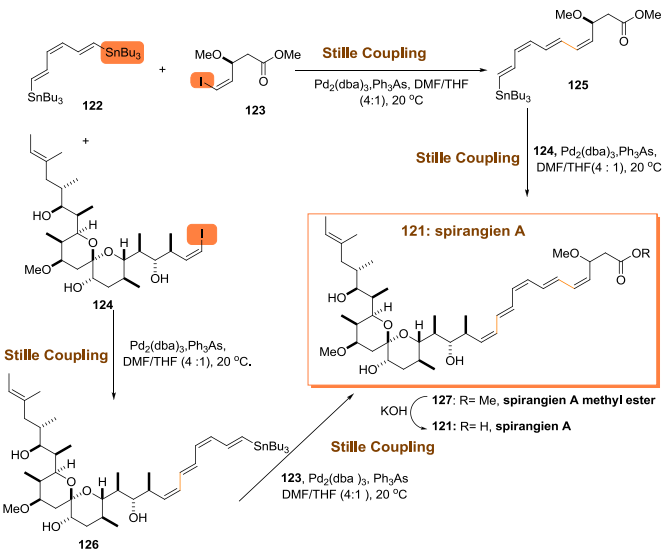
Successive Stille coupling reactions with substrates containing two or more possible reactive sites is attainable in the synthesis

pathway of pyrrhoxanthin (**113**). Pd-coupling between dibromodiolefin **114** and the six-membered-ring building block **115** under $Pd(PPh_3)_4$ and CuI afforded the coupling product **116**, which was converted to bromobutenolide **117**. Compound **117** was coupled with heptatrienyldistannane **118** in the presence of $[Pd_2(dba)_3{\cdot}CHCl_3]$, the sterically undemanding ligand P(2-furyl), and the $Bu_3Sn$ trap $Bu_4N^+Ph_2PO_2^-$ for the preparation of pyrrhoxanthin precursor **119**, which immediately coupled with bromoalkyne **120** to afford **113** in 38% yield after the purification by preparative reversed-phase HPLC (Scheme 27).[48]



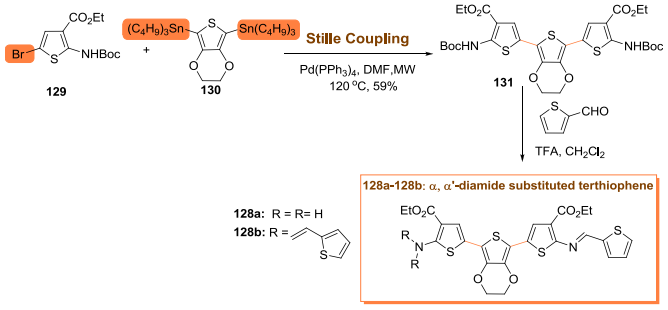

**Scheme 27.**

Successive Stille coupling reactions were successively used to install the sensitive side chain in the total synthesis of (−)-spirangien A (**121**), a cytotoxic and antifungal polyketide. In the same catalytic condition, two pathways are available (independently of the order of coupling partner). Coupling of bisstannyl triene **122** with either (*Z*)-vinyl iodides **123** or **124** provided the desired stannyl tetraenes **125** (59%) and **126** (60%), respectively (Scheme 28), which were subjected to the second coupling under the same conditions reaction with **124** or **123** to furnish spirangien A methyl ester **127** the procedure of **121**.[49]



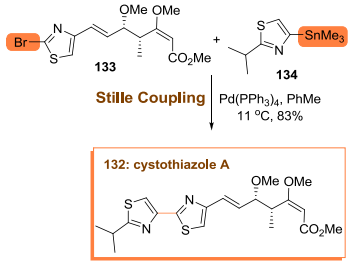

**Scheme 28.**

An early application of the Stille reaction in total synthesis can be found in the generalized synthetic route to the pharmaceutically active α,α′-diamide substituted terthiophene derivatives (**128a** and **128b**) by Dong and coworkers. As illustrated in Scheme 29, coupling of 2-amino-5-bromo derivative **129** and bis(tributylstannyl)–EDOT **130** with $Pd(PPh_3)_4$ afforded the conjugated thiophene **131** in 59% yield as a key intermediate, which can be converted in to target molecules.[50]



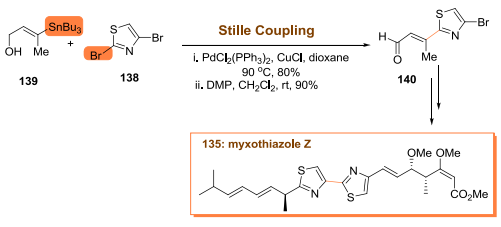

**Scheme 29.**

Cystothiazole A (**132**) as a potent antitumor agent synthesized via the Stille coupling in the short and efficient synthesis pathway (Scheme 30). By having the coupling partners **133** and **134** in hands, Pd-coupling proceeded smoothly to afford **132** as the only product in 83% yield.[51]




**Scheme 30.**

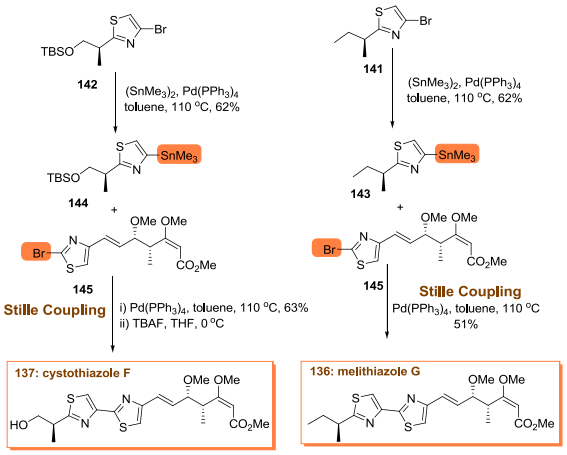
Stille reaction in myxobacterial antibiotics myxothiazole Z (**135**), melithiazole G (**136**), and cystothiazole F (**137**) total synthesis plays a key role to link the two thiazole units together. Coupling between 2,4-dibromothiazole **138** and vinyl stannane **139** using $PdCl_2(PPh_3)_4$, CuCl in dioxane followed by Dess–Martin oxidation created α,β-unsaturated aldehyde **140** in 73% yield, which was converted to **135** (Scheme 31).[52]




**Scheme 31.**

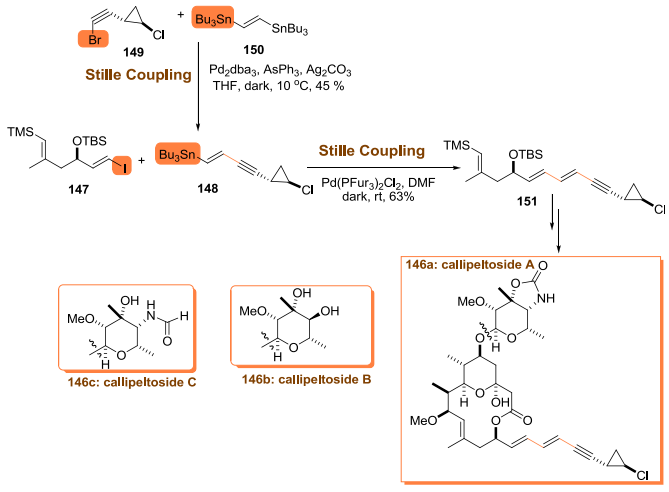
4-Bromo thiazole derivatives **141** and **142** were stannylated by $(SnMe_3)_2$, and $Pd(PPh_3)_4$ to produce compounds **143** and **144**. Then, they subjected to the Stille reaction with bromothiazole

intermediate **145** to provide **136** in 51% yield. Furthermore **137** can be obtained after TBAF-mediated deprotection of the primary alcohol[52] (Scheme 32).




**Scheme 32.**

The sequential Stille reaction was applied in the total synthesis of biologically active callipeltosides A, B, and C (**146a**–**c**). Coupling between vinyl iodide **147** and Stille coupling partner **148** (generated by treatment of bromoalkyne **149** and bisstannane **150**) using $[Pd(PFur_3)_2]Cl_2$ yielded the desired compound **151** in 63%, which is the key intermediate in total synthesis pathway of **146a**–**c** (Scheme 33).[53]

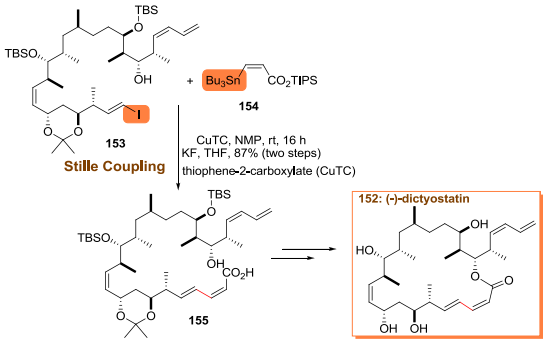



**Scheme 33.**

## 2.1. Copper-mediated Stille intermolecular reaction

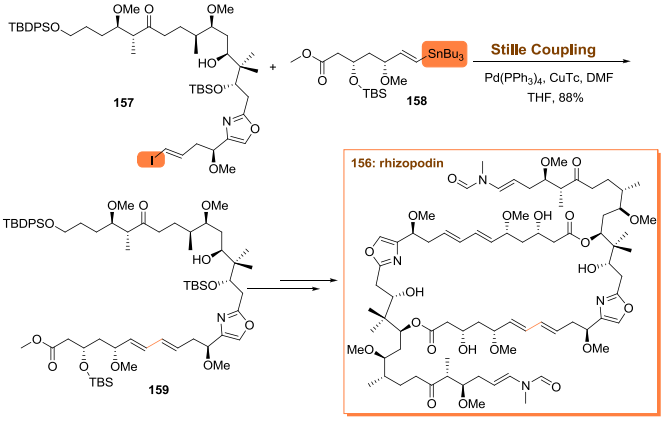
In 1990s, the practical utility of the co-catalytic Cu(I) on the Stille cross-coupling catalyzed by palladium was recognized and the beneficial influence of the 'copper effect' was quickly extended to numerous other palladium-catalyzed C–C formation reactions.[54] The transmetallation of the R group from $RSnBu_3$ to CuX could be accountable for the catalysis, a procedure portending a synthetically useful cross-coupling protocol mediated by simple copper salts alone.[55]

A copper-mediated Stille–Liebeskind[55] cross-coupling protocol employed for the synthesis of (−)-dictyostatin (**152**) as a potent cytotoxic marine macrolide, which represents an attractive template for the optimization of a new structural class of microtubule-stabilizing anticancer agent. The vinyl iodide **153** and stannane **154** was treated with CuTC in deoxygenated NMP to give an acid-sensitive TIPS ester, which was immediately deprotected with KF in THF/MeOH to yield the *seco*-acid **155**. Compound **155** can be converted into the 22-membered macrocyclic lactone **152** after some steps (Scheme 34).[56]



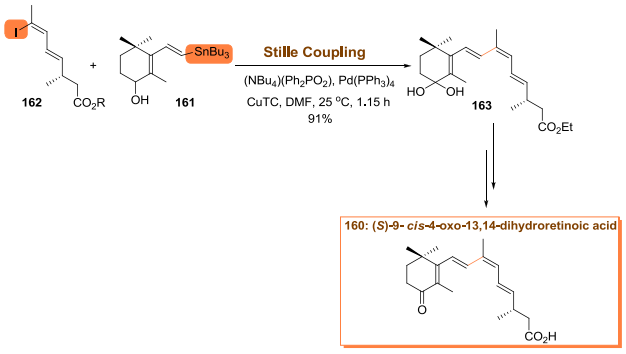

**Scheme 34.**

Rhizopodin (**156**) with potent cytotoxic activity against various cancer cells can be prepared via the Pd-cross coupling reaction. In a concise route (Scheme 35), vinyl iodide **157** was intended to the Stille coupling with vinyl stannane **158** in presence of $Pd(PPh_3)_4$ and a stoichiometric amount of CuTc in a DMF/THF(1:1) mixture to afford the coupling protected monomeric product **159** in 88% yield as a key intermediate in preparation of **156**. The Stille coupling in other conditions with 10 mol % of Pd (0, II) catalysts were less successful and afforded the desired diene only in 30% yield, along with a byproduct consequential from the homocoupling of vinyl iodide **157**.[57]



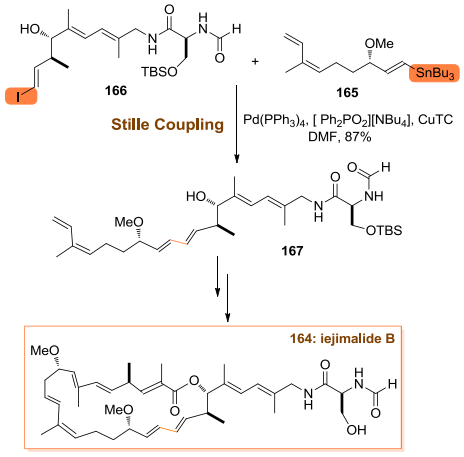

**Scheme 35.**

(*S*)-9-*cis*-4-Oxo-13,14-dihydroretinoic acid (**160**), a major endogenous vitamin A metabolite, can be stereoselectively synthesized via the Stille cross coupling between vinyl stannane **161** and dienyliodide **162** using $Pd(PPh_3)_4$ and CuTC in DMF in the presence of $(NBu_4)(Ph_2PO_2)$ to give tetraenol **163** in high yield, which can be converted in to **160** after two steps. This method was selected because that the reactions usually take place with retention of configuration of the coupling partners (Scheme 36).[58]



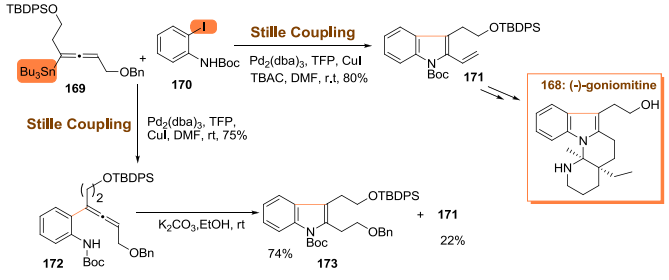

**Scheme 36.**

Using the Stille protocol contain Pd $(PPh_3)_4$, CuTC, and $Ph_2PO_2NBu_4$ in DMF make particularly mild and essentially neutral conditions, and is appropriate for delicate bond forming reactions for the synthesis of iejimalide B (**164**) with anticancer properties is achievable for the reaction of stannane **165** with alkenyl iodide **166**. The heat- and base-sensitive polyene **167** (87% yield) obtained as an important intermediate in synthesis pathway (Scheme 37).[59]




**Scheme 37.**

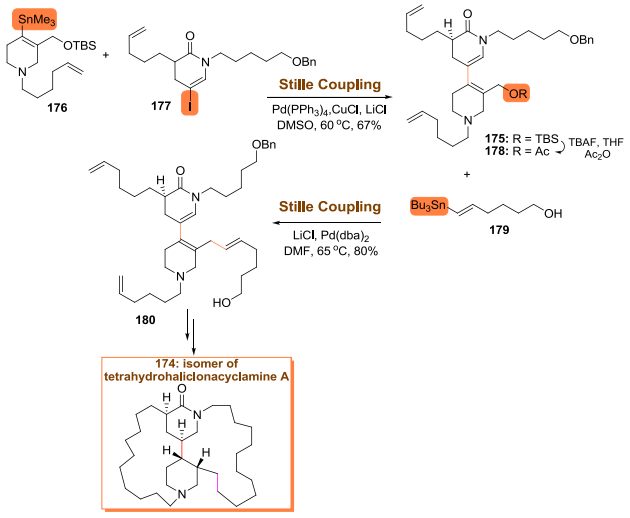
(−)-Goniomitine (**168**) with nanomolar antiproliferative effects on several tumor cell lines were directly synthesized through the Stille coupling of 3-(benzyloxymethyl)-1-(*tert*-butyldiphenylsiloxy) ethyl-1-(tributylstannyl)allene (**169**) with *N*-(*tert*-butoxycarbonyl)-2-iodoaniline **170**. As shown in Scheme 38, the 2-vinylindole derivative **171** produced in the presence of tetrabutylammonium chloride (TBAC) in one operation in 80% yield. When this ring-closing reaction was performed in the absence of TBAC, the




**Scheme 38.**

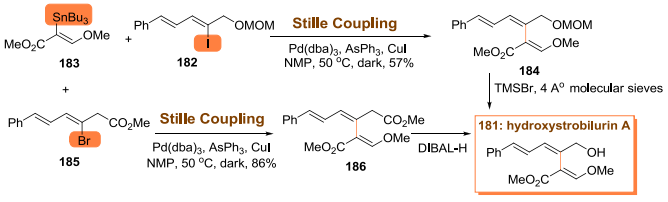
structure of the allenylaniline derivative **172** was achieved in 75% yield as the only product, which was after that changed into **171** and **173**.[60]

The Stille coupling was twice applied in the total synthesis pathway of unnatural *cis–anti-cis* isomer tetrahydrohaliclonacyclamine A (**174**) (an alkylpiperidine alkaloid with the similar potency) by Smith and coworkers. Bis-piperidine **175** in 67% yield was obtained from the coupling of the stannane **176** and iodoenamide **177** in dimethyl sulfoxide with copper chloride, lithium chloride, and tetra-kis(triphenylphosphine)Pd at room temperature. The TBS ether was then exchanged for an acetate group and the second Stille cross-coupling between compound **178** and vinyl stannane **179** provide the key intermediate **180** in 84%yield (Scheme 39).[61]




**Scheme 39.**

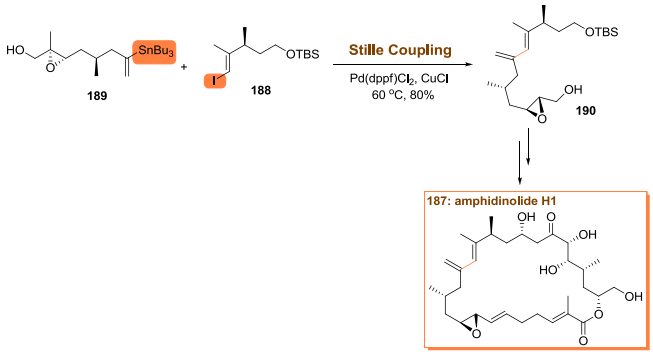
The Stille coupling as a useful approach in the total synthesis of hydroxystrobilurin A (**181**) with fungicidal activity was employed for the coupling of iodide **182** with **183** to form MOM ether **184** in 57% yield. Moreover for improving the yield of the reaction, coupling of bromide **185** and **183** under the same Pd-coupling conditions supplied triene ester **186** in 86% yield, which can be changed to **181**. The use of Stille chemistry enabled well-organized and stereocontrolled formation of the strobilurin triene system under comparatively undemanding conditions (Scheme 40).[62]




**Scheme 40.**

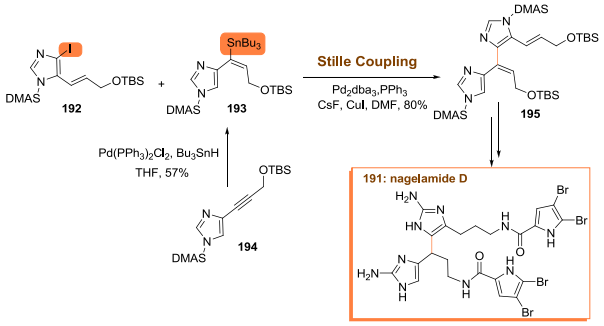
The total synthesis of the 26-membered macrocycle amphidinolide H1 (**187**) as a biologically active compound was reported by Deng and coworkers utilizing the Pd-catalyzed Stille cross-coupling between the vinyl iodide **188** and vinyl stannane **189** with catalytic amount of $PdCl_2$(dppf) in the presence of CuCl in MeCN at 60 °C to form the key conjugated diene **190** in 80% yield (Scheme 41).[63]

Application of the Stille coupling in the total synthetic route of the recognized structure of nagelamide D (**191**) was described by



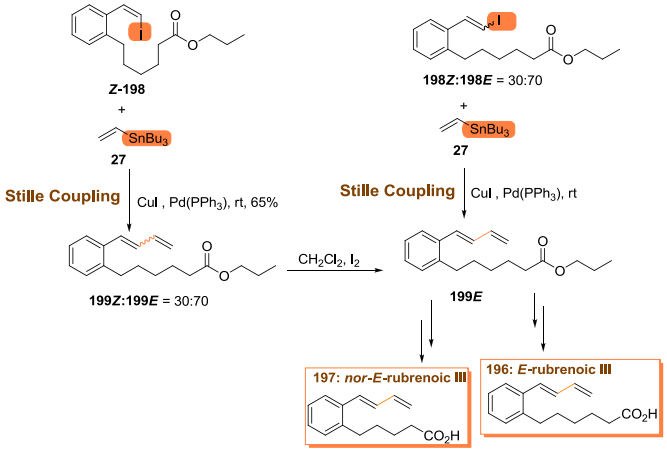

**Scheme 41.**

Bhandari and coworkers. Reaction of silyl ether **192** and *E*-vinyl stannane **193** (which produced by hydrostannylation of TBS-protected propargyl alcohol **194**) in fluoride-mediated Pd-coupling conditions created the valuable intermediate bis vinyl-imidazole **195** in good yield (Scheme 42).[64]




**Scheme 42.**

Two similar Stille cross coupling can be used for the total stereoselective synthesis of *E*-rubrenoic III (**196**) and nor-*E*-rubrenoic III (**197**) acids. Treatment of 6-[2-*Z*-(2-iodo-vinyl)-phenyl]-hexanoic acid propyl ester (**198**) with tributylvinyltin (**27**) afforded the 6-(2-*Z*-buta-1,3-dienyl-phenyl)-hexanoic acid propyl ester (*Z*-**199**) in 65% yield. Not only the cis compound spontaneously isomerizes in the presence of light to the *trans* isomer *E*-**199**, as a matter of fact, the only coupling product of the reaction of *Z*/*E* iodo-alkene **198** mixture was *E*-**199** compound. *E*-**199** was subsequently elaborated to complete the total synthesis pathway (Scheme 43).[65]

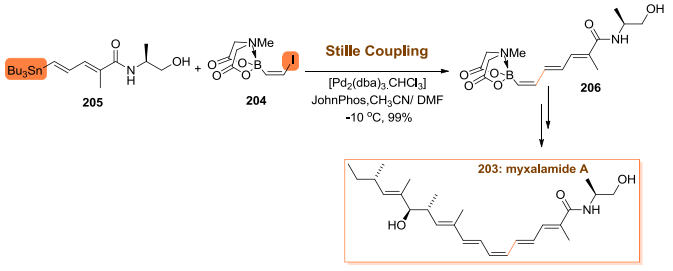



**Scheme 43.**

As illustrated in Scheme 44, C–C bond formation via the Stille reaction as a key step in the convergent synthesis of biologically active natural product (+)-crocacin C (**200**) is achievable by coupling of vinyl stannane intermediate **201** and (*E*)-iodoacrylamide **202** to afford target molecule **200** in presence of $Pd(PPh_3)$ under microwave irradiation (best obtained result from different examined conditions). When the Stille coupling was carried out without microwave irradiation in the presence of $Pd(dba)_3$ and tri-2-furylphosphine(TFP) the natural product was earned in a poor yield. The use of $PdCl_2(PPh_3)_2$ particularly improved the yield.[66]


**Scheme 44.**

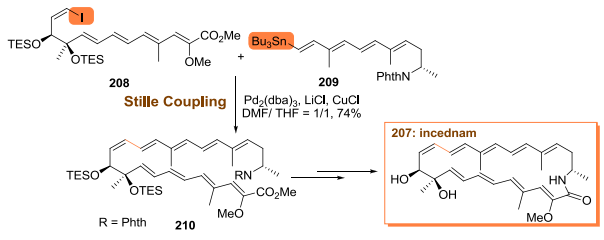
Total synthesis of (−)-myxalamide A (**203**) is feasible via a one-pot Stille/Suzuki–Miyaura cross-coupling reaction. Coupling between (*Z*)-boronate **204** and vinyl stannane **205** in MeCN and DMF in the presence of $[Pd_2(dba)_3{\cdot}CHCl_3]$ as catalyst and JohnPhos as additive furnished triene **206**, which was subjected to the sequence Suzuki–Miyaura coupling (other unsuccessful conditions was also reported in Scheme 45).[67]




| Entry | catalyst (mol%) | additive (mol%) | solvent | Yield (%) |
|---|---|---|---|---|
| 1 | $[Pd(PPh_3)_4]$ (10) | CuI (150) | THF/DMF | decomposed |
| 2 | $[Pd(PPh_3)_4]$ (10) | CuTC (150) | DMF | trace |
| 3 | $[PdCl_2(CH_3CN)_2]$ | $AsPh_3$ (20) | THF/DMF | decomposed |
| 4 | $[Pd_2(dba)_3.CHCl_3]$ (10) | dppe (40) | THF/DMF | trace |
| 5 | $[Pd_2(dba)_3.CHCl_3]$ (20) | P(2-furyl)$_3$ (50) | THF | 51 |
| 6 | $[Pd_2(dba)_3.CHCl_3]$ (10) | SPhos (40) | THF/DMF | 45 |
| 7 | $[Pd_2(dba)_3.CHCl_3]$ (5.0) | JohnPhos (20) | THF/DMF | 88 |
| 8 | $[Pd_2(dba)_3.CHCl_3]$ (5.0) | JohnPhos (20) | $CH_3CN$/DMF | 99 |

**Scheme 45.**

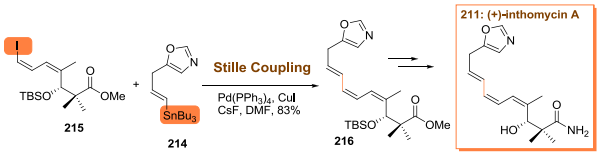
Ohtani and coworkers have disclosed the total synthesis of Incednam (**207**) with biologically active properties through the Stille reaction. Coupling of pentaenoate subunit **208** with *E*-configured tetraene **209** using Pd(0), LiCl, and CuCl (Corey's protocol) provided the desired coupling product **210** in 74% yield as an important intermediate in synthesis pathway of **207** (Scheme 46).[68]




**Scheme 46.**

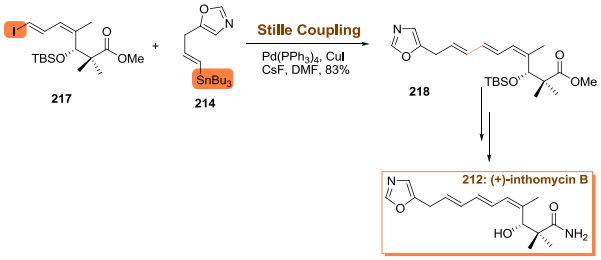
(+)-Inthomycin A (**211**), (+)-inthomycin B (**212**), and (−)-inthomycin C (**213**), oxazole-triene antibiotics, are significant

and important targets for the total synthesis via the Stille coupling. Compound **211** can be synthesized through the Stille coupling between stannane **214** and *Z,Z*-iododiene **215** using $Pd(PPh_3)_4$, CuI, and CsF to furnish *Z,Z,E*-triene **216** in geometrically pure form as a key intermediate in synthetic rout. When this coupling was performed using Pd(0) catalyst alone, some extent of isomerization of the triene system was always observed (Scheme 47).[69]



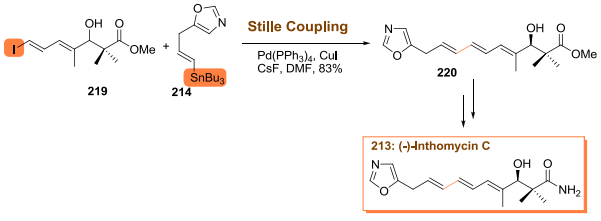

**Scheme 47.**

Moreover *Z,E*-iododiene **217** was engaged to the Stille coupling with **214** under the same conditions to afford stereoselectively *Z,E,E*-triene **218** in modest yield, which could be changed to **212** after several steps (Scheme 48).[69]




**Scheme 48.**

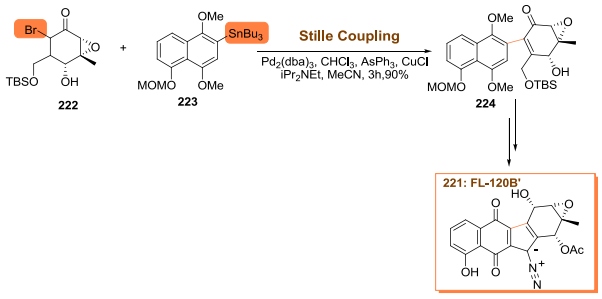
Synthesis of **213** is achievable by using the Stille coupling of *E,E*-iododiene **219** with **214** using $Pd(PPh_3)_4$, CuI, and CsF to furnish geometrically pure *E,E,E*-triene **220** in 83% yield (Scheme 49).[69]




**Scheme 49.**

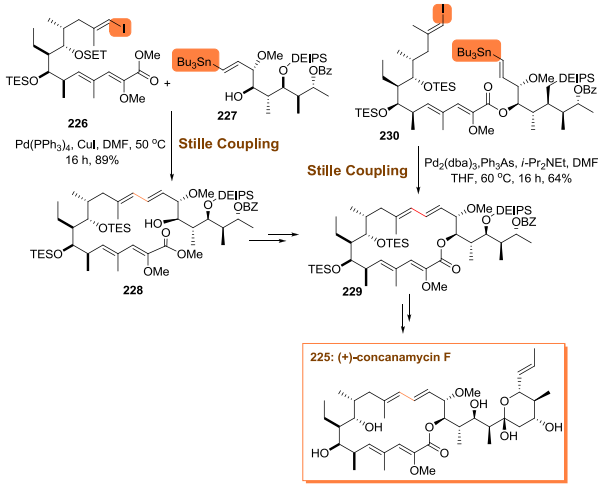
Epoxykinamycin FL-120 B′ (**221**) as powerful cytotoxicity compound in several cancer cell lines, was asymmetrically prepared by Scully and Porco Jr. The Stille coupling between stannane **222** and bromide **223** in the presence of $Pd_2(dba)_3$, $CHCl_3$, $AsPh_3$, CuCl, and *i*-$Pr_2NEt$ yielded epoxyketone **224** in excellent yield (Scheme 50).[70]

The stereocontrolled total synthesis of the 18-membered macrolide (+)-concanamycin F (**225**), an important member of the plecomacrolide antibiotic family, is described by Paterson and coworkers. The Liebeskind-Stille cross-coupling reaction between the vinyl iodide **226** and vinyl stannane fragments **227** using catalytic $Pd(PPh_3)_4$ in DMF with CuI as an additive collected the diene **228** in modest yield. But the use of stoichiometric copper(I) thiophene-2-carboxylate (CuTC) in NMP afforded coupled product **228**




**Scheme 50.**

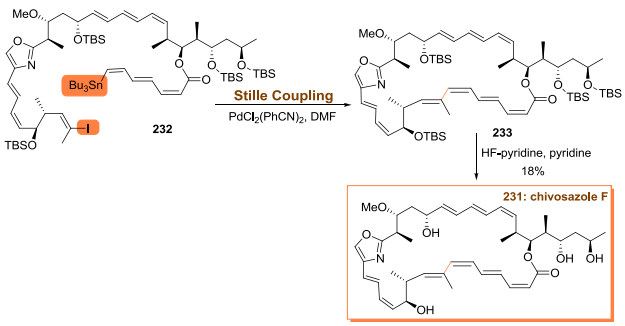
in 88% yield. 18-Membered macrocycle **229** as a key intermediate in the synthesis of **225** was obtained after several steps from the **228**. The alternative preparation of compound **229** was explored using an intramolecular Stille reaction of **230** (which was produced from some reaction on **226** and **227**) using $Pd_2(dba)_3$, $Ph_3As$, and *i*-$Pr_2NEt$. The use of CuTC resulted in only protodestannylation and recovered starting material (Scheme 51).[71]




**Scheme 51.**

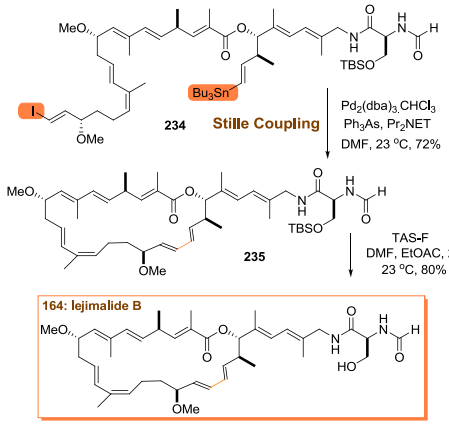
## 3. The intramolecular Stille coupling

The total synthesis of chivosazole F (**231**) with antifungal and cytotoxic activity was elaborated by Brodmann and coworkers. Synthesis relies on the use of intramolecular Stille coupling of **232** in the presence of $Pd_2(PhCN)_2$ in DMF for the formation the carbon framework of chivosazole **233** followed by deprotection with HF–pyridine in 18% yield over two steps (Scheme 52).[72]



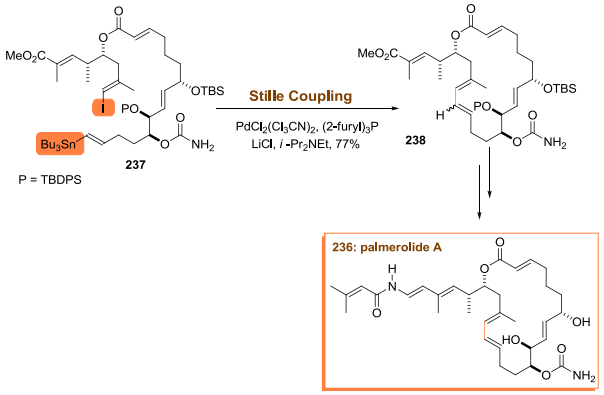

**Scheme 52.**

Chen and coworkers described the total synthesis of iejimalide B (**164**) (a structurally unique 24-membered polyene macrolide) with considerable antitumor potential through the intramolecular Stille coupling of **234** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$, $Ph_3As$, and DIPEA for the synthesis of the key intermediate **235** in 72% yield as shown in Scheme 53. The use of $(CH_3CN)_2PdCl_2$, $(Ph_3P)_4Pd$–CuCl, and $Pd_2(dba)_3$–$Ph_3As$–DIPEA was examined to intermolecular Stille coupling, but $Pd_2(dba)_3{\cdot}CHCl_3$, $Ph_3As$, and DIPEA was most effective.[73]




**Scheme 53.**

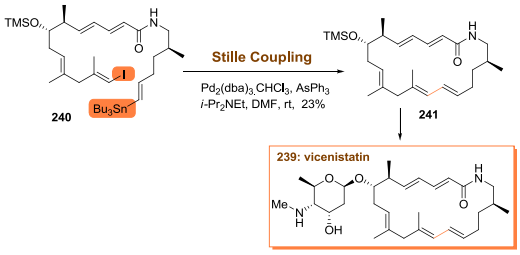
Formal total synthesis of palmerolide A (**236**) with unique cytotoxic activity was achieved by Jägel and Maier (Scheme 54). The intramolecular Stille cyclization reaction of ester **237** using $PdCl_2(Cl_3CN)_2$, (2-furyl)$_3$P as ligand, and LiCl plus *i*-$Pr_2NEt$ as additives produced an *E*/*Z* mixture of the C14–C15 double bond **238** as a key intermediate in the synthesis pathway of **236**.[74]




**Scheme 54.**

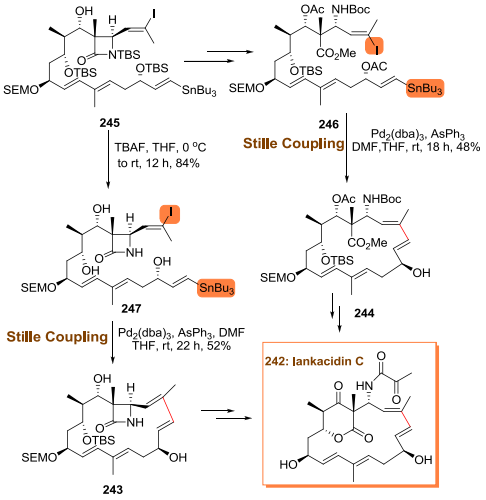
The intramolecular Stille coupling reaction was investigated and applied in the total synthesis of macrocyclic lactam glycoside vicenistatin (**239**) with antitumor activity.[75] Pentaene **240** advanced under the Nicolaou conditions[76] [$Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, *i*-$Pr_2Net$, and DMF] to afford the important macrolactam intermediate **241** in the modest yield, which could be converted to the **239** (Scheme 55).

In the framework of a total synthesis of the precursors of lankacidin C (**242**), a macrocyclic natural product with antibiotic activity, the synthesis of advanced intermediates azetidinone-fused macrocycle **243** and the 17-membered macrocyclic ester **244** via




**Scheme 55.**

intramolecular Stille reactions from the key compound **245** has been elaborated by Brain and coworkers. Cyclization of vinyl stannane **246** by tris(dibenzylideneacetone)bis-palladium(0) in the presence of triphenylarsine as catalyst give the macrocyclic intermediate **244** in 48% yield. Similarly, the Stille reaction of the hydroxyvinyl stannane **247** using bis(acetonitrile)palladium(II) chloride as the catalyst had given useful results in the intermolecular Stille reactions in modest yields but, when tris(dibenzylideneacetone)bis-palladium(0) in the presence of triphenylarsine was used as the catalyst, a considerably better yield of **243** was reported but in the best condition included the use of tris(dibenzylideneacetone)bis-palladium(0) as the catalyst for producing the 17-membered macrocycle **243** successfully in 52% yield (Scheme 56).[77]




**Scheme 56.**

## 4. Conclusions

As simply demonstrated above, the Stille coupling as marvelous tools allows the artisans of chemical synthesis to construct complex molecules with not only high stereo- and regioselectively but also tolerating an extensive variety of functional groups under comparatively mild conditions. A very wide range of aryl- and 1-alkenylstannane reagents undergo the Stille reactions with alkyl, 1-alkenyl, aryl, and 1-alkynyl substrates. In addition, usage of combination of heterogeneous catalytic systems and co-catalytic systems (Cu mediated Stille reaction) gives desired products that are not available by using one of the catalysts.

## Acknowledgements

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