Application of Copper (I) salt and Fluoride promoted Stille coupling reactions in the synthesis of bioactive molecules.

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Abstract

The Stille coupling between organostannane and organohalide is an effective catalytic method for organic synthesis. Despite of the ample amount of published results in this area, finding the optimal conditions for this transformation is often not straightforward. It was observed that this reaction could be accelerated with improved efficiency by the addition of Cu(I) salt and fluoride. This review summarises the application this simple protocol in the synthesis of natural products, their analogues and other biologically active molecules, from 2004 to 2018.

Introduction.

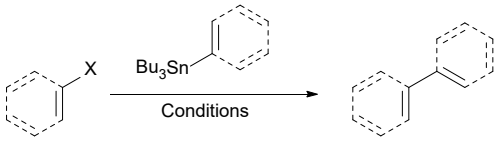
The palladium catalysed cross coupling C-C bond formation reactions are powerful methodologies in organic synthesis. Indeed, the 2010 Nobel Prize in Chemistry were awarded to three outstanding organic chemists, Richard Heck, Ei-ichi Negishi and Akira Suzuki for palladium-catalyzed cross coupling in organic synthesis.[1-2] All three individuals are well deserved winners as they have made important fundamental discoveries and contributions that enrich the field of organic synthesis. An equally important palladium catalysed C-C bond forming reaction is the coupling between organostannane and organohalide, commonly known as the Stille reaction.[3-6] Historically this reaction was first reported by the Eaborn group[3] in 1976 and then by the Kosugi-Migita group[4, 5] in 1977. However, it was the publication of Stille's 1978 paper[6] that put this reaction firmly on the synthetic organic chemists' map. To highlight the significant scientific contribution of J. K. Stille, it would be appropriate to quote the following statement from a 2015 review article by Espinet *et al.*[7] "Were it not for his premature death at the age of 59 in an airplane crash, John Kenneth Stille would have likely shared the 2010 Nobel Prize in Chemistry for the work on palladium-catalysed cross coupling reactions". No doubt all readers of this article will agree with that.

The Stille coupling reactions are usually conducted under mild conditions with good functional group compatibility. Over the years, this C-C bond forming reaction has become a powerful tool in natural product synthesis.[8, 9] Notwithstanding its versatility, some organic chemists are still hesitant to utilise the Stille coupling reaction in organic synthesis. The main concerns of these practitioners are the toxicity of organostannanes and the possible presence of tin contaminants in the coupled products. The issue about organostannanes toxicities has been discussed in Espinet's *et al.*'s recent review article[7] while various methods for the removal of tin residues from organic reactions has been

reviewed by Grognec.[10] The content of two articles will provide essential information to those who would consider including the Stille coupling reaction as part of their synthetic design.

The mechanism of the Stille reaction was previously reviewed in detail by Espinet and Echavrren[11] in 2004 and Espinet *et al.* published a follow up article[7] in 2015, discussing new mechanistic insights and practical developments in this area. Readers who are interested in mechanistic aspects of the Stille reaction should refer to these two articles.

Although the use of Stille coupling reactions in organic synthesis is well documented throughout the chemical literatures, often it is less than trivial to pinpoint the correct conditions to conduct these reactions. In 2004, Mee, Lee and Baldwin communicated a simple protocol to improve the efficiency of Stille coupling reaction, and this was followed by a full disclosure of the investigation results in the following year.[12, 13] It was observed that the addition of CsF (2 equiv.) and CuI (10%) greatly enhanced the rate and efficiency of the Stille coupling reactions between aryl/vinyl iodides or triflates with aryl/vinyl organostannanes, when $Pd(PPh_3)_4$ (5%) was used as catalyst. For the coupling reactions of the less reactive aryl/ vinyl bromides, a combination of $PdCl_2$ (2%) and P^tBu_3 (4%), together with CsF (2 equiv.) and CuI (4%) was essential to ensure the coupling reactions proceed efficiently. (Scheme 1)



Conditions A, X = I or OTf, $Pd(PPh_3)_4$ (5%), CuI (10%), CsF (2 equiv), DMF, 45 °C

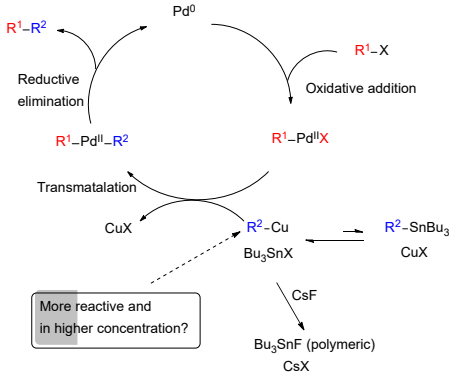
Conditions B, X = Br, $PdCl_2$ (2%), P^tBu_3 (4%), CuI (4%), CsF (2 equiv), DMF, 45 °C

Scheme 1 CsF/ CuI promoted Stille coupling reaction.

Since the disclosure of these results, this simple and effective method has been adopted both in the areas of natural product and materials synthesis. This article summarises the application of this methodology in the synthesis of natural products and other potentially biological active molecules, from 2004 to 2018. Comparisons of this protocol with other similar methods will be discussed, if such information is available in the original article. Other variants of this methodology will also be included in this review. Throughout this article the CsF/CuI promoted Stille reaction will be referred as the MLB conditions or protocol.

Possible mechanism and the role of CsF and CuI in the modified Stille reaction.

It has been documented that Cu(I) salt accelerates the Stille coupling in highly polar solvent like DMF or *N*-methylpyrrolidine. This rate enhancement effect is due to the transmetalation reaction of Cu(I) with organostannane .[14, 15] This results in the formation of a more reactive organocopper species, with Bu_3SnI as the transmetalation byproduct. If this transmetalation reaction is reversible then the removal of the byproduct Bu_3SnI from the reaction will shift the equilibrium towards the formation of the more reactive organocopper intermediate. Presumably CsF reacts with Bu_3SnI to form the polymeric Bu_3SnF which precipitates out from the solution. (Scheme 2)

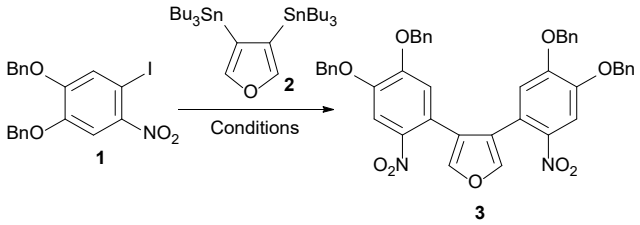


Scheme 2 Possible mechansim of the CsF/CuI promoted Stille coupling reaction.

Studies by Jutand *et al.*[16] suggested that fluoride ion plays a more complex role in the Stille coupling reaction. Previously, Wang and Burton reported the direct spectroscopic observation of organocopper formation from the corresponding organostannane reagent with CuI.[17] The mechanism depicted in Scheme 2 is likely to be much simplified but suffice to provide a reasonable working model for the observed phenomenon. One possible practical advantage of the MLB protocol is the *in situ* precipitation of the polymeric Bu_3SnF, which simplifies the purification of the coupled product.[6]

The synthesis of bioactive compounds using the modified Stille reactions.

Not surprisingly, the first application of the MLB protocol in synthesis was conducted in the Baldwin group. To investigate the synthesis of the proposed structure of a potential oxidant found in beetroot (*Beta vulgaris*), Mee, Lee and Baldwin attempted a double Stille reaction with aryliodide **1** and stannane **2**.[18] Initial attempts[19-22] of using other known Stille conditions gave the desired product in moderate yields after 15 hours. However, when both CsF and CuI were used as additives and with DMF as solvent, the coupling reaction was completed in 2 hours at 40 °C to give the desired product in 92% isolated yield. (Scheme 3)

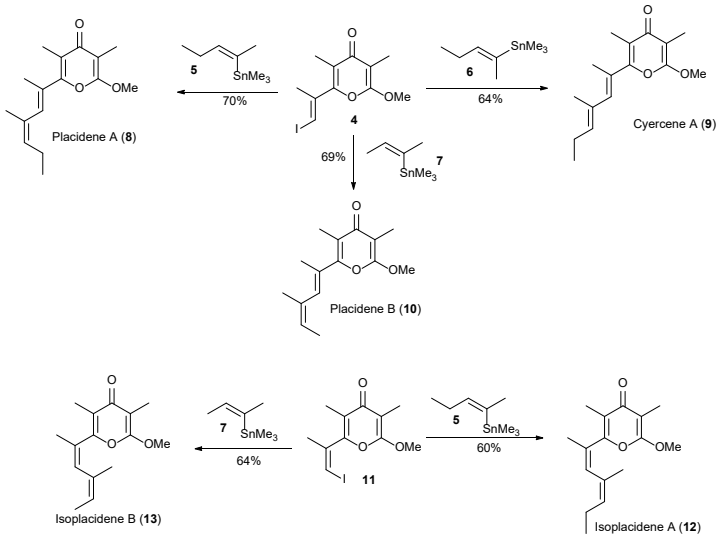


Scheme 3

Conditions	Yield/ %
$Pd(PPh_3)_4$, CuBr, THF, 60°C, 15 h	30
$Pd_2(dba)_3$, $AsPh_3$, CuI, DMF, 15h	55
$Pd(PPh_3)_4$, CuI, CsF, DMF, 40°C, 2h	**92**

In 2005, Trauner *et al.* reported the total synthesis of the ichthyotoxic natural product Cyercene A (**9**) and its structurally related compounds Placidenes.[23] These compounds are characterised by the presence of highly substituted diene sidechains, which were assembled in the final steps of their

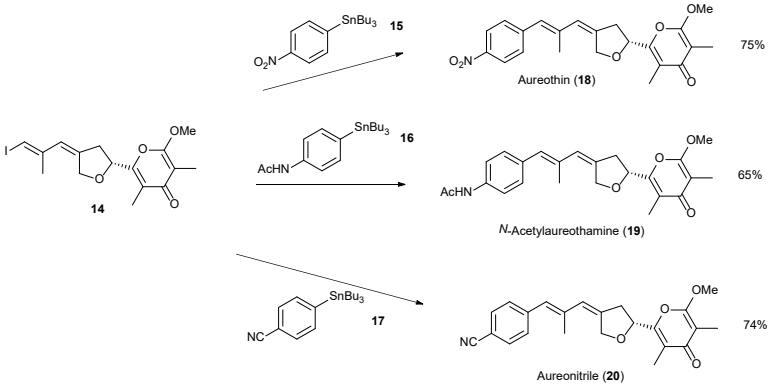
syntheses using the Stille reactions. The common intermediate **4** was coupled to vinylstannanes **5**, **6** and **7** to give Placidene A (**8**), Cyercene (**9**) and Placidene B (**10**) respectively. Similarly, the coupling of vinyl iodide **11** to vinylstannanes **5** and **7** gave Isoplacidenes A (**12**) and B (**13**) respectively. The Trauner group examined a variety of coupling conditions and found that the MLB protocol gave the best results in terms of rate and efficiency. It is noteworthy that the dienes in Isoplacidenes A (**12**) and B (**13**) are especially congested due to the *Z*- orientation of the pyrone moieties and the alkenyl groups in both natural products. (Scheme 4)



Reaction conditions: 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI, 2 equiv of CsF, DMF, 45°C

Scheme 4 Synthesis of Cyercene A (**9**), Placidenes A (**8**), B (**10**) and Isoplacidenes A (**12**) and B (**13**).

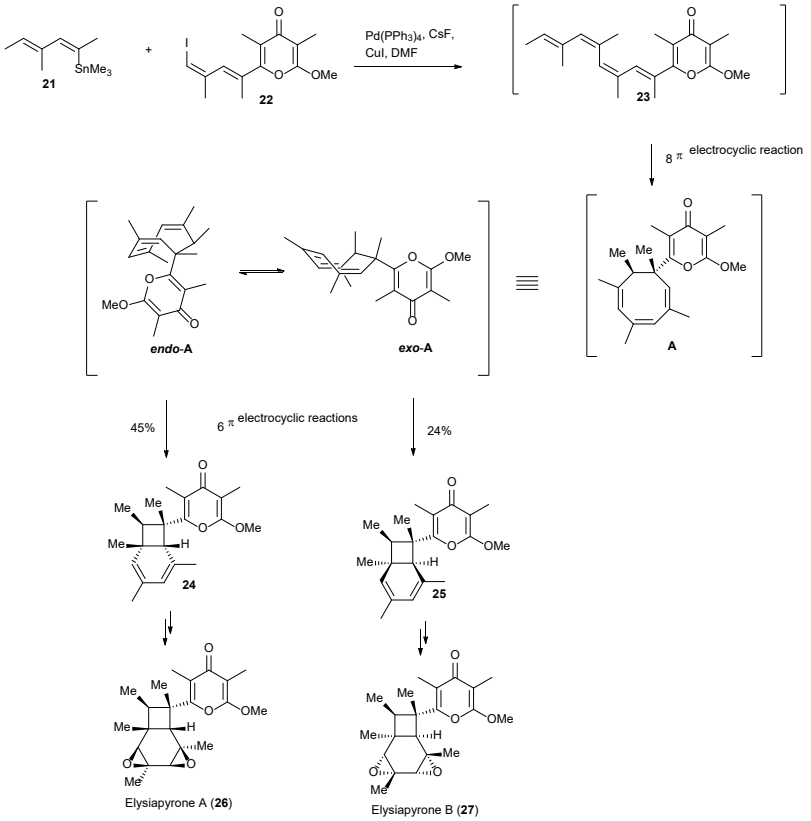
Three structurally similar natural products were synthesised using the modified Stille reaction by Trauner *et al*. Aureothin (**18**) is an antifungal and anti-tumour compound isolated from *S.* thiouteus. *N*-Acetylaureothamine (**19**) is an anti-Helicobacter pylori compound isolated from *S. netropsis*. and Aureonitrile (**20**), a mutasynthesis product of **18**, is cytotoxic against HeLa and K-562 timopur cells. The coupling of arylstannanes **15**, **16** and **17** to common building block **14** using the CsF/ CuI promoted Stille conditions gave Aureothin (**18**), *N*-Acetylaureothamine (**19**) and Aureonitrile (**20**) respectively, in respectable yields.[24] (Scheme 5)



Conditions: 5 mol % $Pd(PPh_3)_4$, 10 mol % CuI, 2 equiv of CsF, DMF, 45°C.

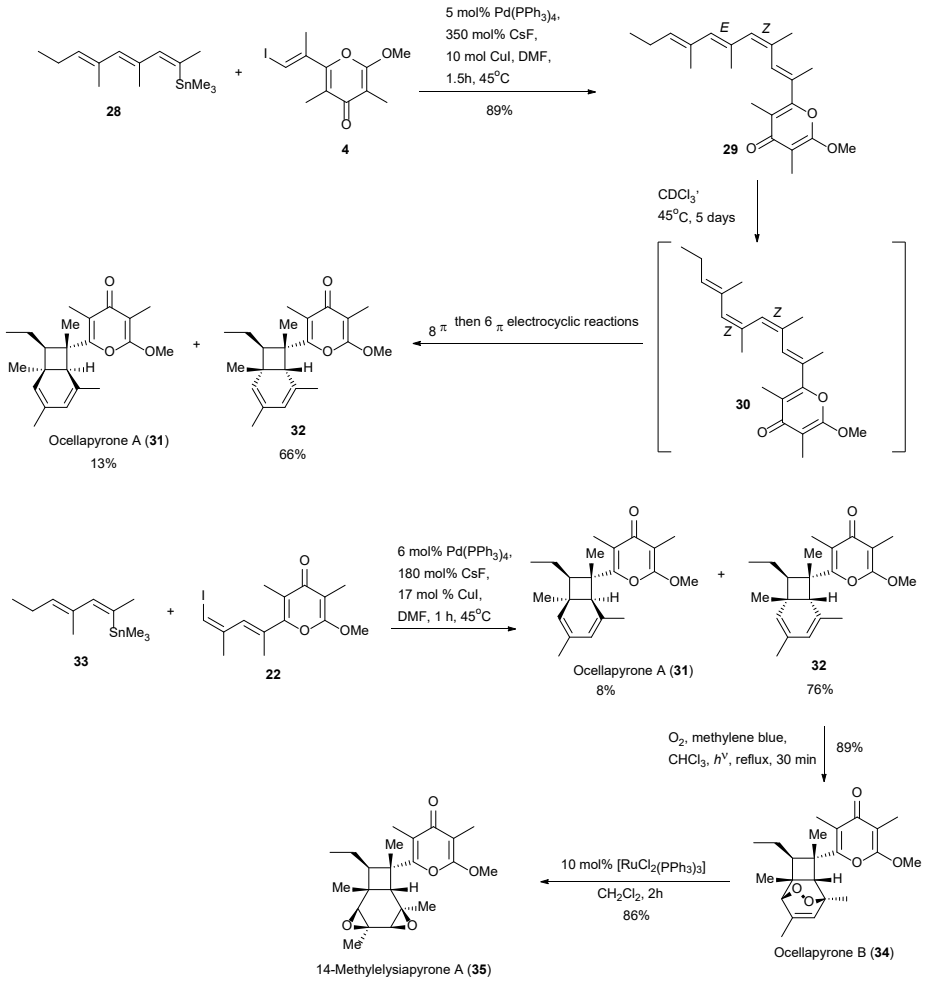
Scheme 5 Synthesis of Aureothin (**18**), *N*-Acetylaureothamine (**19**) and Aureonitrile (**20**).

Elysiapyrones A (**26**) and B (**27**) are natural products found in the saccoglossan mollusks *Placobranchus ocellatus* and *Elysia diomedea* respectively. The biomimetic synthesis of these two compounds were reported by Trauner *et al.* They achieved a remarkable transformation through initial Stille coupling of vinyl stannane **21** to vinyl iodide **22**, using the MLB conditions.[25] This reaction presumably led to the formation of tetraene **23**. This compound underwent an *in situ* 8π electrocyclic reaction to form intermediate **A**, which existed as two conformers, ***endo*-A** and ***exo*-A**. Each of these conformers further underwent a 6π electrocyclic reaction and resulted in the formation of a mixture of compounds **24** and **25**. Compounds **24** and **25** were converted to Elysiapyrone A (**26**) and Elysiapyrone B (**27**) respectively. In this spectacular tandem reaction, three C-C bonds and two rings were formed in a single operation. (Scheme 6)



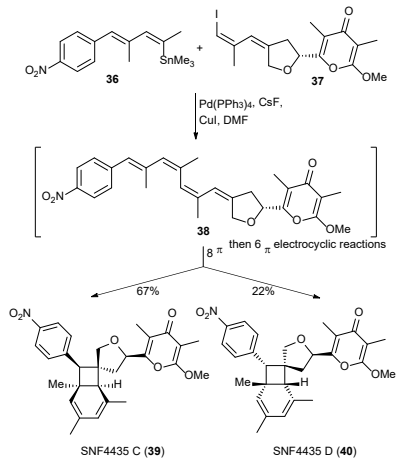
Scheme 6 Biomimetic synthesis of Elysiaptrones A (**26**) and B (**27**).

Trauner *et al.* continued to explore and apply this tandem reaction strategy in the synthesis of Ocellapyrone A (**31**), Ocellapyrone B (**34**) and 14-Methylelysiapyrone A (**35**).[26] Two synthetic routes were examined in this investigation. In the first synthesis, vinyl stannane **28** was coupled to pyrone **4** using the MLB protocol to give an unstable (*E*,*E*,*Z*,*E*)-tetraene **29**. It was observed that by heating **29** in $CDCl_3$ at 45°C for 5 days, Ocellapyrone A (**31**), a natural product found in *Placobranchus ocellatus*, and compound **32** were formed in 13% and 66% respectively. Presumably during the course of the reaction, (*E*,*E*,*Z*,*E*)-tetraene **29** first isomerised to (*E*,*Z*,*Z*,*E*)-tetraene **30** which was followed by a 8π then 6π electrocyclisation to give Ocellapyrone A (**31**) and **32**. A second synthesis of **31** and **32** was achieved through the coupling of stannane **33** and vinyl iodide **22**, again utilising the MLB protocol to give **31** and **32** in 8% and 76% yields respectively. Compound **32** was converted to Ocellapyrone B (**34**) by reaction with singlet oxygen. Treatment of this compound with $RuCl_2(PPh_3)_3$ gave 14-Methylelysiapyrone A (**35**) as product. (Scheme 7)



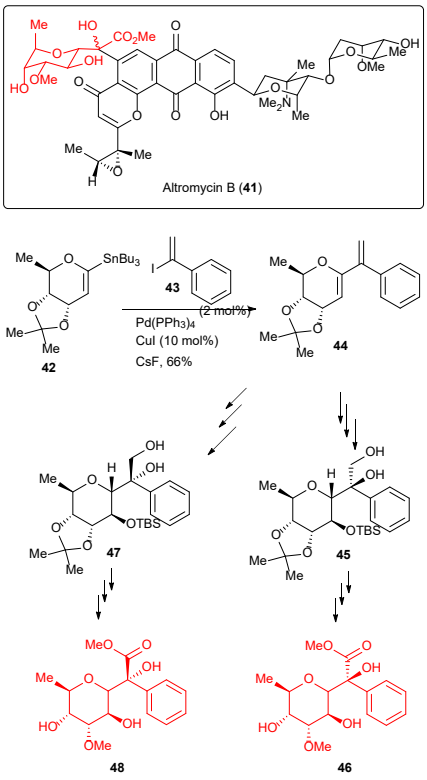
Scheme 7 Biomimetic synthesis of Ocellapyrones A (**31**), B (**34**) and14-Methylelysiapyrone A (**35**).

In the synthesis of the immunosuppressive and anticancer natural products SNF4435 C (**39**) and SNF4435 D (**40**), Trauner *et al*. performed the Stille coupling reaction of vinyl stannane **36** and vinyl iodide **37** under the MLB conditions. Presumably this reaction initially delivered tetraene **38**, which underwent an 8π con then 6π dis rotation to afford SNF4435 C (**39**) and SNF4435 D (**40**) as products in 67% and 22% yields respectively.[27] (Scheme 8)



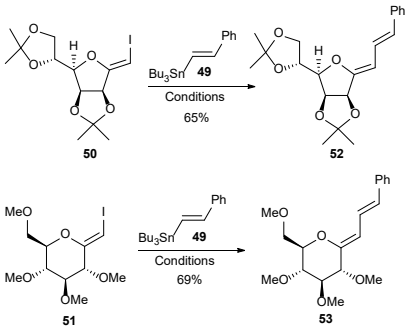
Scheme 8 Synthesis of SNF4435 C (**39**) and SNF4435 D (**40**).

Altromycin B (**41**) is an antibiotic isolated from South African bushveld soil and later found to show anticancer activity. The synthesis of the branched *C*-glycoside substructure of Altromycin B (**41**) was accomplished by Koo and McDonald. They examined the Stille coupling reaction between stannylated glycal **42** and α-iodostyrene **43** but this transformation was found to be problematic. The use of previous established Stille coupling protocols [28, 29] for stannyl glycals gave irreproducible results. Eventually this problem was solved by application of the MLB protocol, which gave compound **44** in 66% yield. Compound **44** was converted to **45** and eventually to compound **46**. Similar chemistry transformed **44** into **47** and eventually to **48**. Both **46** and **48** are analogues of the *C*- glycoside substructure of Altromycin B (**41**).[30] (Scheme 9)



Scheme 9 Synthesis of Altromycin B C-glycoside analogues **46** and **48**.

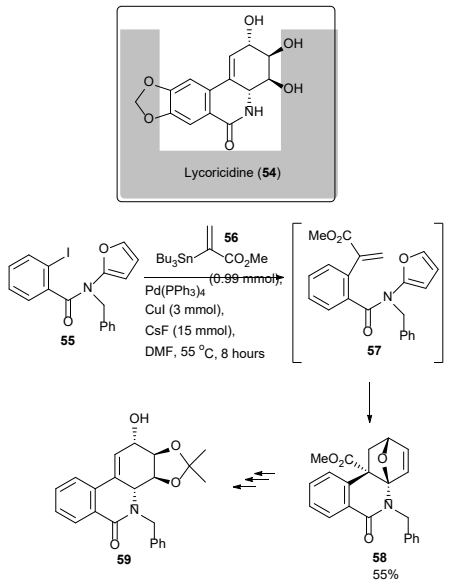
Exo-glycals are useful synthetic intermediates and have been utilised as glycosidase inhibitors. Gómez *et al.* investigated the use of Stille coupling reaction in the stereocontrolled synthesis of *exo*-glycal.[31] It was observed that for the coupling of vinylstannane **49** to *Z*-iodo-exo-glycals **50** and **51**, application of the MLB conditions in these reactions gave **52** (65%) and **53** (69%) as products respectively. (Scheme 10)



Conditions: $Pd(PPh_3)_4$ (10%), CsF (2.0 equiv), CuI (10%)

Scheme 10 Synthesis of exo-glycals **52** and **53**.

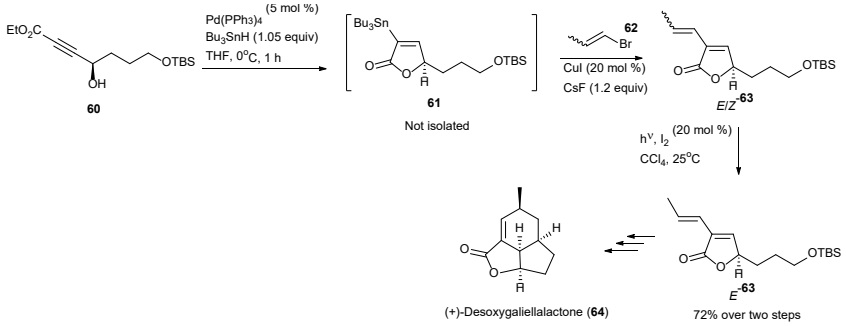
Zhang and Padwa investigated the synthesis of hydroxylated phenanthridones, which are the core structures of the *Amaryllidaceae* alkaloids, e.g. Lycoricidine (**54**). One of the C-C bond forming reaction in this work featured the Stille coupling reaction between aryl iodide **55** and stannane **56**, using the MLB protocol. The presumed coupled product **57** was not isolated as it underwent an intramolecular Diels-Alder reaction *in situ* to give **58** in 55% yield. Compound **58** was transformed into of hydroxylated phenanthridone **59**.[32, 33]



Scheme 11 Synthesis of hydroxylated phenanthridone **59**.

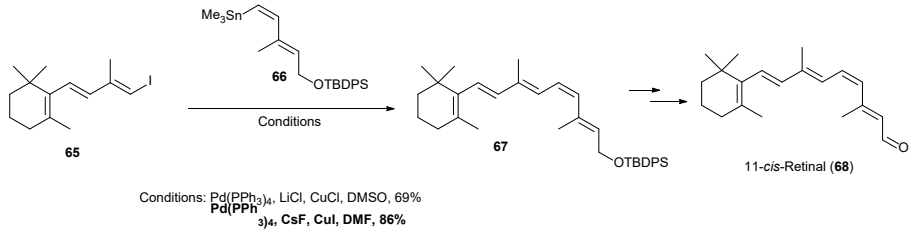
An interesting application of the MLB protocol is found in Lebel and Parmentier's synthesis of (+)-Desoxygaliellalactone (**64**).[34] The opposite enantiomer of this compound is a biologically active natural product isolated from ascomycetes *Galliela rufa*. In this work, propargylic alcohol **60** was subjected to a $Pd(PPh_3)_4$ catalysed hydrostannylation reaction, with concomitant lactonisation to form

intermediate **61**. This intermediate was not isolated but treated *in situ* with CsF, CuI and vinyl bromide **62** to form the coupled product **63** as an *E*/*Z* mixture. Photoisomerisation of *E*/*Z*-**63** gave pure *E*-**63**. The overall yield of *E*-**63** was 72% over two steps. This compound was transformed into (+)-Desoxygaliellalactone (**64**) in a few steps. (Scheme 12) An important observation was made in this work. By using a limited amount of CsF (1.2 equiv), Lebel and Parmentier were able to preserve the primary *tert*-butyldimethylsilyl protecting group in the coupling reaction. This result suggests that fluoride ion has much a higher affinity for the stannyl than the silyl group.



Scheme 12 Synthesis of (+)-Desoxygaliellalactone (**64**).

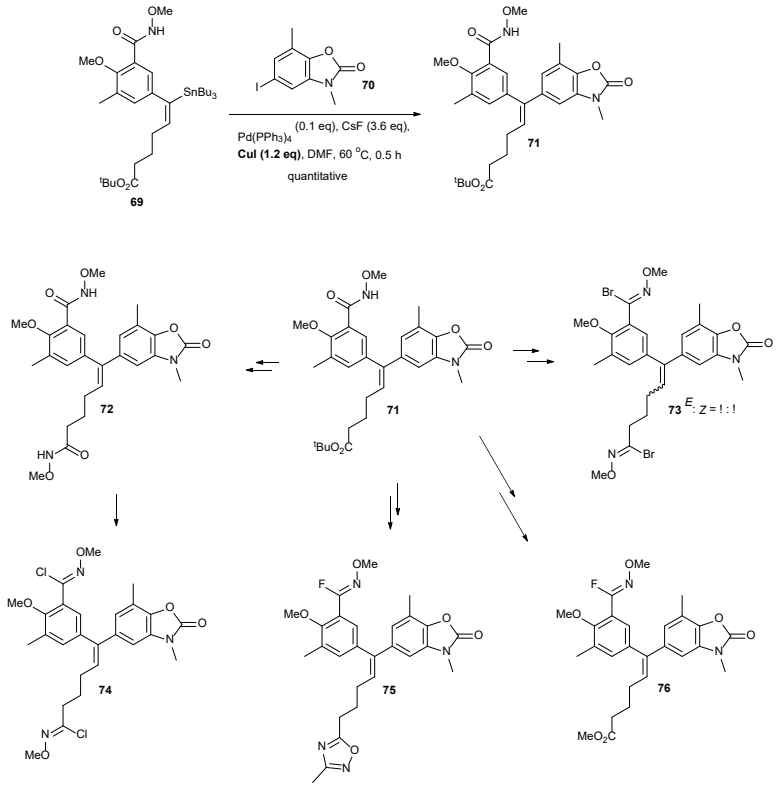
The synthesis of 11-*cis*-Retinal (**68**) was achieved by López *et al.*, using transition metal catalysed cross coupling reactions of (*Z*)-1-alkenylorganometallics.[35] As part of the investigation, the Stille coupling reaction between vinyl iodide **65** and vinyl stannane **66** was examined. The use of more reactive trimethylstannane organometallic was necessitated due to the hindered nature of both reacting partners. Initially López *et al.* observed that the use of the Corey protocol [$Pd(PPh_3)_4$, LiCl, CuCl, DMSO][36] gave the desired product **67** in 69% yield. Subsequently the MLB protocol was found to be more efficient and delivered **67** in 86% after 3 hours at room temperature. This compound was converted to 11-*cis*-Retinal (**68**). (Scheme 13)



Scheme 13 Synthesis of 11-*cis*-Retinal (**68**).

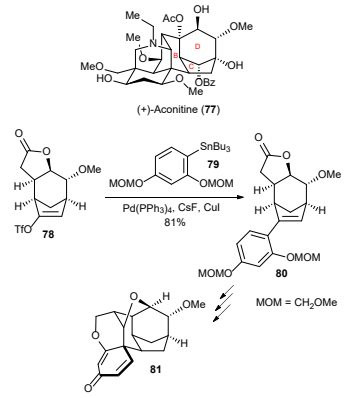
The MLB protocol was utilised by Cushman *et al.* in the synthesis of metabolically stable alkenyldiarylmethanes **72**-**76**, a class of non-nucleoside reverse transcriptase inhibitors.[37] The coupling of vinyl stannane **69** to aryl iodide **70** required some experimentations. Initially when the standard MLB protocol was applied to the coupling of **69** and **70**, no reaction was observed. Cushman *et al.* speculated that caesium fluoride might behave as a base and deprotonate the *N*-methoxyamide. The negative species formed from this process, together with the adjacent methoxy group, might chelate to Pd(II) and stop it from turning over in the catalytic cycle. However, when the quantity of CuI was increased to 1.2 equivalents, a quantitative yield of the coupled product **71** was obtained.

Cushman *et al.* did not offer any explanation for this "excess CuI" effect. This observation can be rationalised by competitive binding of the Cu(I) ion with the bidentate methoxy and the deprotonated *N*-methoxyamide group, thus leaving Pd(II) free to turn over in the catalytic cycle. Compound **71** served as a common synthetic intermediate for the synthesis of compounds **72**-**76**. These compounds were screened for reverse transcriptase inhibition activities. (Scheme 14)



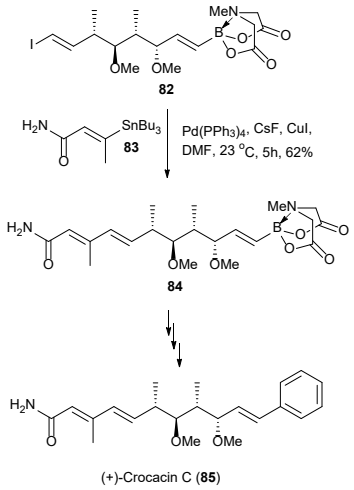
Scheme 14 Synthesis of alkenyldiarylmethanes **72**-**76**.

In the synthetic studies of the natural product Aconitine (**77**), a complex alkaloid isolated from *Aconitum* genus of plants, Conrad and Du Bois performed the coupling of vinyl triflate **78** to arylstannane **79** under the MLB conditions.[38] This transformation afforded compound **80** as product in 81% yield. Compound **80** was converted into the final product **81**, which resembles the B/ C/ D ring of Aconitine (**77**). (Scheme 15)



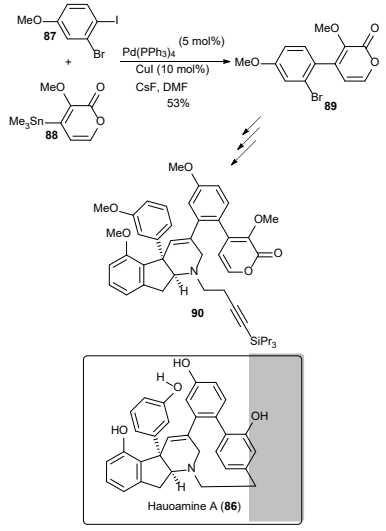
Scheme 15 Synthesis of **81**, the B/ C/ D ring analogue of (+)-Aconitine (**77**).

An interesting application of the MLB protocol was demonstrated by Gills and Burke in the synthesis of the natural product (+)-Crocacin C (**85**),[39] a cytotoxic natural product found in *Chondromyces crocatus* and *Chondromyces pediculatus*. The coupling of the vinyl iodide **82** to vinylstannane **83** gave compound **84** in 62% yield under the MLB conditions. It is noteworthy that the *N*-methyliminodiacetic acid boronate residue in vinyl iodide **82** survived in the modified Stille coupling reaction, which allowed subsequent chain enolgation. Compound **84** was transformed into (+)-Crocacin C (**85**) in a few steps. (Scheme 16)



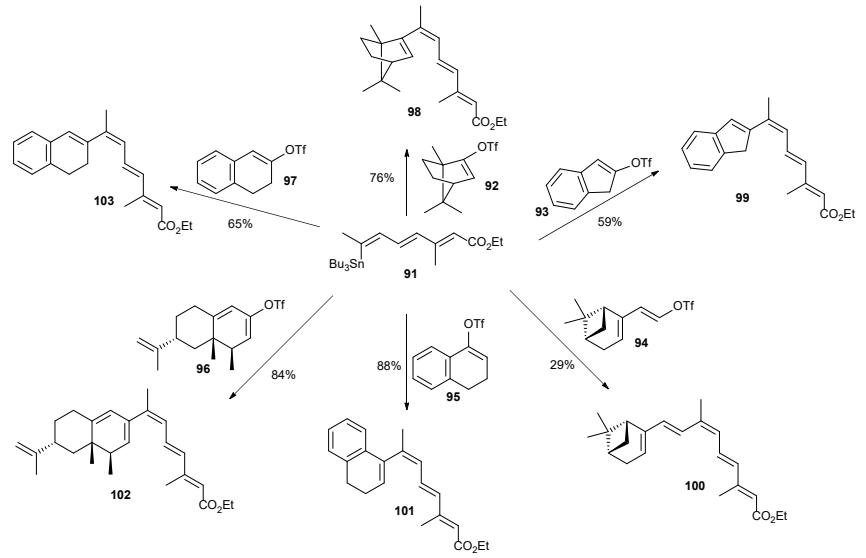
Scheme 16 Synthsis of (+)-Crocacin C (**85**).

(-)-Haouamine A (**86**) is a cytotoxic alkaloid isolated from the marine ascidian *Aplidum haouarianum*. In the formal synthesis of this natural product, Fürstner and Ackerstaff performed a chemoselective coupling reaction between aryl iodide **87** and stannane **88**, under the MLB conditions, to deliver **89** in 53% yield.[40] This compound was eventually transformed into **90**. Compound **90** is an advanced synthetic intermediate of the natural product (-)-Haouamine A (**86**). (Scheme 17)



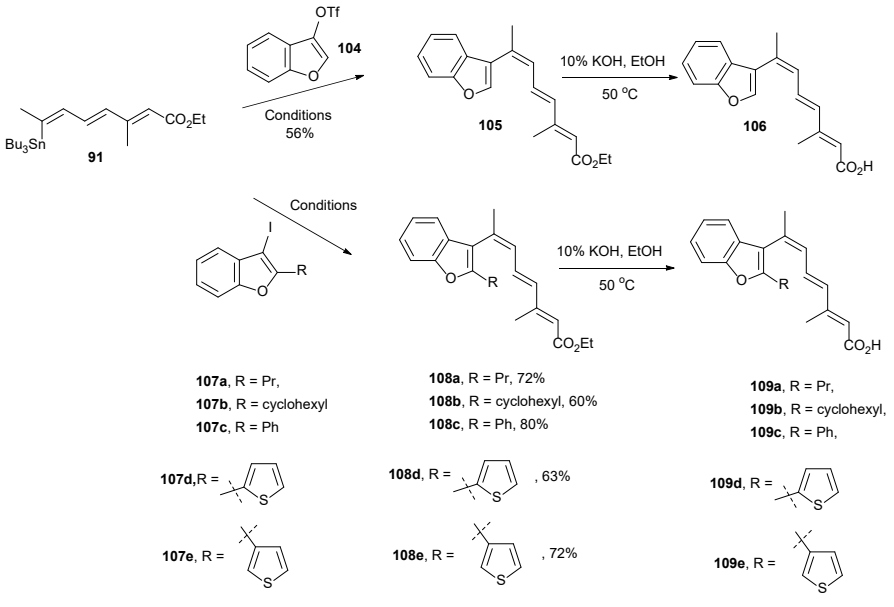
Scheme 17 Formal synthsis of Hauoamine A (**86**).

Wada *et al.* prepared 9*Z*-retinoic acid analogues **98**-**103** by coupling of a common stannyl building block **91** to different vinyl triflates **92**-**97** by using the MLB protocol.[41] (Scheme 18)



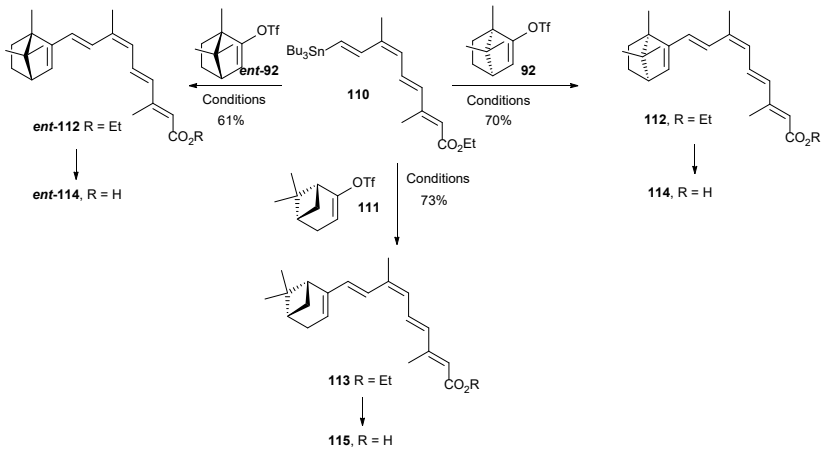
Scheme 18 Synthesis of 9*Z*-retinoic acid analogues **98-103**.

Later the same group investigated the syntheses of various 2-substituted benzo[b]furan derivatives of 9*Z*-retinoic acid **106** and **109a-e.** The coupling of stannane **91** to benzofuran triflate **104** was performed under the MLB conditions to give ester **105** as product. This compound was subjected to basic hydrolysis to afford carboxylic acid **106**. Similarly, stannane **91** reacted with 3-iodo-benzofurans **107a-e** to form esters **108a-e**. Hydrolysis of esters **108a-e** gave carboxylic acids **109a-e**.[42] (Scheme 19)



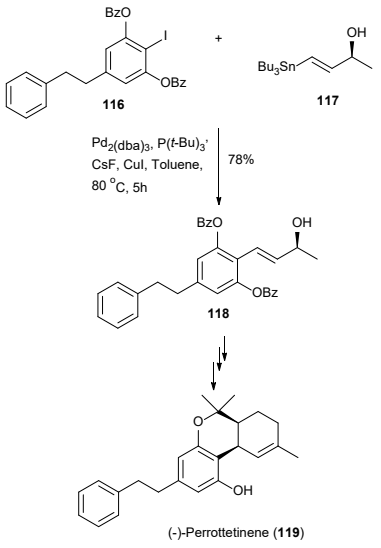
Scheme 19 Synthesis of 9*Z*-retinoic acid 2-substituted benzo[b]furan derivatives **106** and **109a-e**.

In 2011, Wada *et al*. further prepared various 9*Z*-retinoic acid derivatives in which the hydrophobic part of the natural product was replaced by other cyclic terpene moieties. Common synthetic intermediate stannane **110** was coupled to vinyl trilfates ***ent*-92**, **92** and **111**, under the MLB conditions, to give esters ***ent*-112**, **112** and **113** respectively. Esters ***ent*-112**, **112** and **113** were hydrolysed to their corresponding carboxylic acids ***ent*-114**, **114**, **115**. Some of these compounds were shown to have Retinoid X receptors-selective agonistic activities.[43] (Scheme 20)



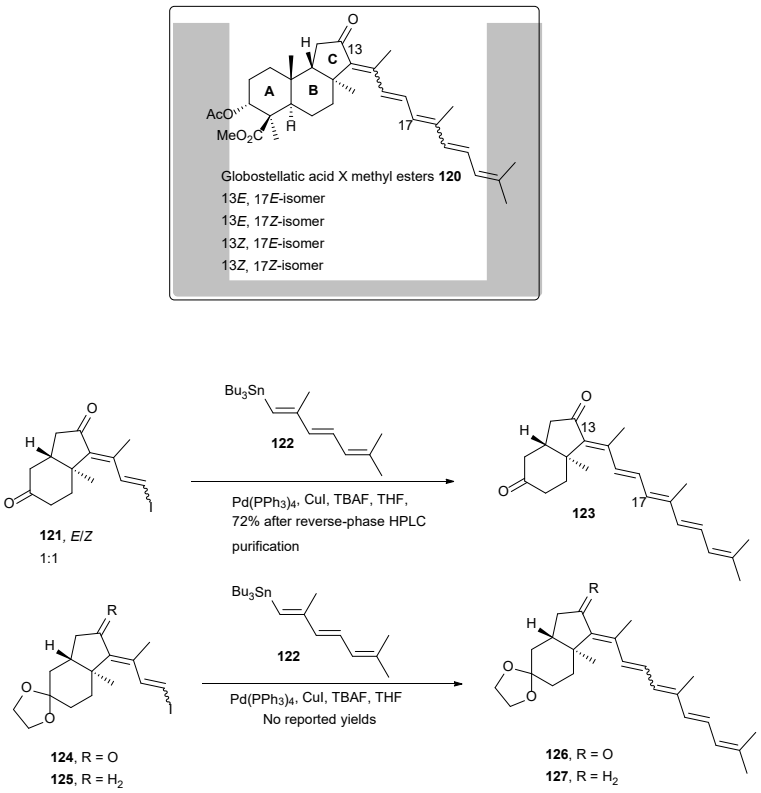
Scheme 20 Syntheis of 9-*cis*-retinoid acid analogues **114**, ***ent*-114**,**115**.

The total synthesis of (-)-Perrottetinene (**119**), a natural product isolated from the liverwort *Radula perrottettii*, was reported Kim *et al*. In this synthesis, a coupling reaction between aryl iodide **116** with vinylstannane **117** was performed under the modified MLB conditions. Interestingly, "ligandless" $Pd_2(dab)_3$ was utilised as catalyst together with P(*t*-Bu)$_3$ as ligand.[44] It is possible that the hindered nature of aryl iodide **116** lowered its reactivity towards oxidative addition. Consequently this would require a more electron rich Pd(0) species to overcome this kinetic barrier. The coupling reaction proceeded to give the desired product **118** in 78% yield. This compound was converted to (-)-Perrottetinene (**119**) in a few steps. The absolute configuration of this natural product was established through comparison of the specific rotation values. (Scheme 21)



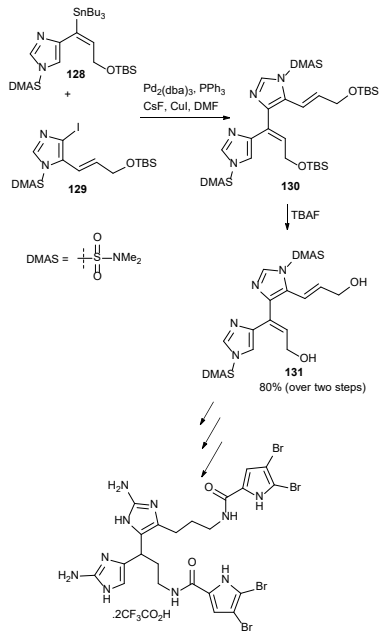
Scheme 21 Synthesis of (-)-Perrottetinene (**119**).

Globostellatic acid X methyl esters (**120**) are a group of antiangiogenic triterpene derivatives isolated from Indonesian sponge *Rhabdastrella globostellata*. Kobayashi *et al.* synthesised the B/C ring analogues of the natural product these natural products by using Stille coupling to install the polyene side chains.[45] Initially Kobayashi attempted to couple vinyl iodide **121**, a 1:1 *E*/ *Z* mixture, and stannane **122** by using palladium catalyst with no additive. They observed that the reaction was sluggish. However, inclusion of TBAF and CuI gave the all-*trans* coupled product **123** after reverse-phase HPLC purification. Similarly, coupling of **124** and **125** with **122** using the same conditions gave **126** and **127** respectively, although no yields for these products were reported. (Scheme 22)



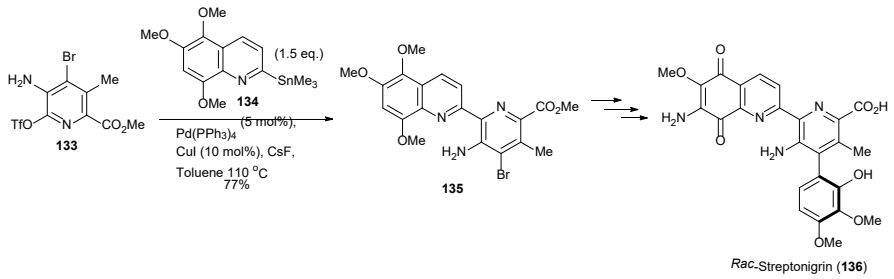
Scheme 22 Synthesis of Globostellatic acid X methyl esters analogues **123**, **126** and **127**.

In the attempted synthesis of the marine sponge alkaloid Ngaelamide D, an alkaloid isolated from the Okinawan marine sponge *Agelas* sp., Lovely *et al*. applied the MLB protocol to couple vinyl stannane **128** and iodide **129** to give **130**. Deprotection of **130** with TBAF gave the desired product **131** in 80% yield over two steps. Interestingly, $Pd_2(dba)_3$ was utilised as palladium catalyst in this reaction. Compound **131** was eventually transformed into the putative structure of Nagelaminde D (**132**). Unfortunately, the spectroscopic data of synthetic **132** did not match the literature data of the natural product, suggesting that the putative structure of Ngaelamide D is incorrect.[46] (Scheme 23)



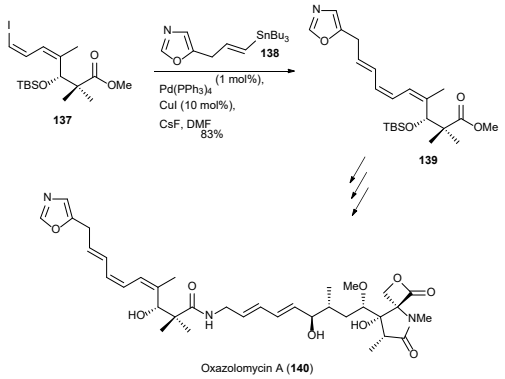
Scheme 23 Synthesis of the putative sturcture of Nagelamide D (**132**).

In the synthesis of the aminoquinone antitumor antibiotic *rac*—Streptonigrin (**136**), Donohoe *et al.* conducted the coupling of triflate **133** with stannane **134** using the MLB conditions to afford **135** in 77% yield. The coupling reaction was very site selective as oxidative addition took place only on the more electron deficient C-2 triflate rather than the more hindered 4-bromo substituent in **133**. The free amino group in **133** remains intact in the coupling reaction. Compound **135** was eventually transformed into the desired product *rac*-Streptonigrin (**136**).[47, 48] (Scheme 24)



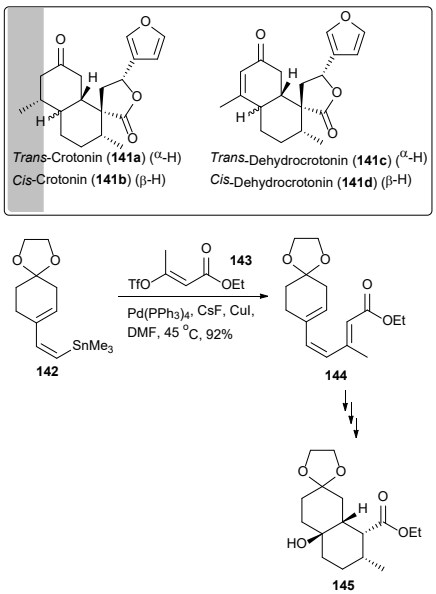
Scheme 24 Synthesis of *rac*-Streptonigrin (**136**).

The synthesis of the complex polyene γ-lactam/β-lactone antibiotic Oxazolomycin A (**140**) was accomplished by Hatakeyama *et al.* The *Z,Z,E*-triene moiety of this natural product was constructed via the Stille coupling reaction.[49] The reaction of vinyl iodide **137** and vinyl stannane **138** under the MLB conditions delivered triene **139** in 83% yield, with the silyl protecting group remained intact in the coupling reaction. The authors reported that when the coupling reaction was carried out with Pd(0) catalyst alone, partial isomerisation of the triene was observed. Compound **139** was converted to Oxazolomycin A (**140**) through a multi-steps sequence. (Scheme 25)



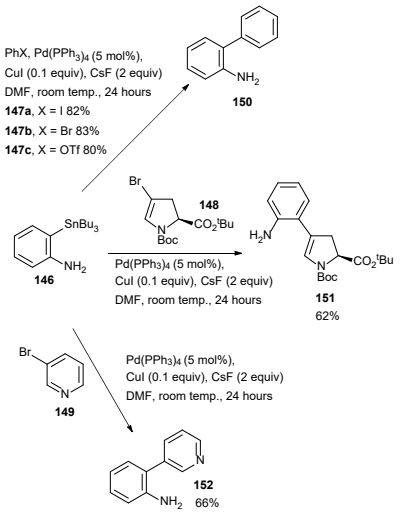
Scheme 25 Synthesis of Oxazolomycin A (**140**).

A stereoselective synthesis of the *cis*-hydroxydecalin core of Crotonins (**141a-d**), a group of 19-*nor*-Clerodanes, was completed by Williams *et al*.[50] In this investigation, vinyl stannane **142** was coupled to vinyl triflate **143**, under the MLB conditions, to deliver triene **144** in 92%. This compound was converted to *cis*-hydroxydecalin **145** in a few steps. (Scheme 26)



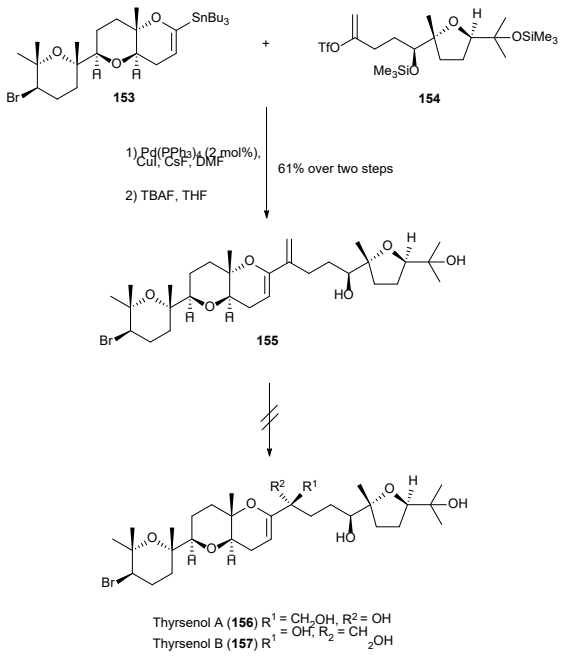
Scheme 26 Synthesis of Crotinons *cis*-hydroxydecalin core **145**.

Izgu and Hoye prepared *o*-(tributylstannyl)aniline **146** as a 2-aminophenyl synthon and examined some of its coupling reactions with various halides.[51] It was observed under the MLB conditions, stannane **146** coupled to halides **147a-c**, **148** and **149** to delivered **150**, **151** and **152** as products respectively in satisfactory yields. (Scheme 27)



Scheme 27 Coupling reactions of *o*-(tributylstannyl)aniline **146**.

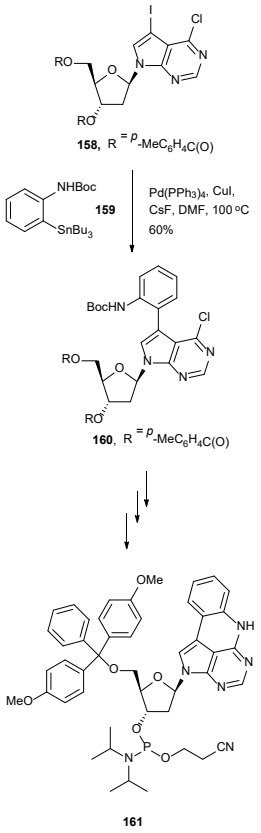
Thyrsenols A (**156**) and B (**157**) are cytotoxic marine polyether triterpenes isolated from the red alga *Laurencia viridis*. The synthesis of 15, 28-dideoxy-15, 28-didehydrothyrsenol (**155**) was achieved in 61% yield by Smart and McDonald. In a two steps process, stannane **153** was coupled to vinyl triflate **154** under the MLB protocol, followed by TBAF deprotection of the trimethylsilyl protecting groups.[52] It was observed that the use of the MLB protocol is crucial as this minimised the homodimerisation of stannane **153**. Unfortunately, attempts to convert **155** into the natural products Thysenols A (**156**) and B (**157**) were unsuccessful. (Scheme 28)



Scheme 28 Synthesis of 15, 28-dideoxy-15, 28-didehydrothyrsenol (**155**).

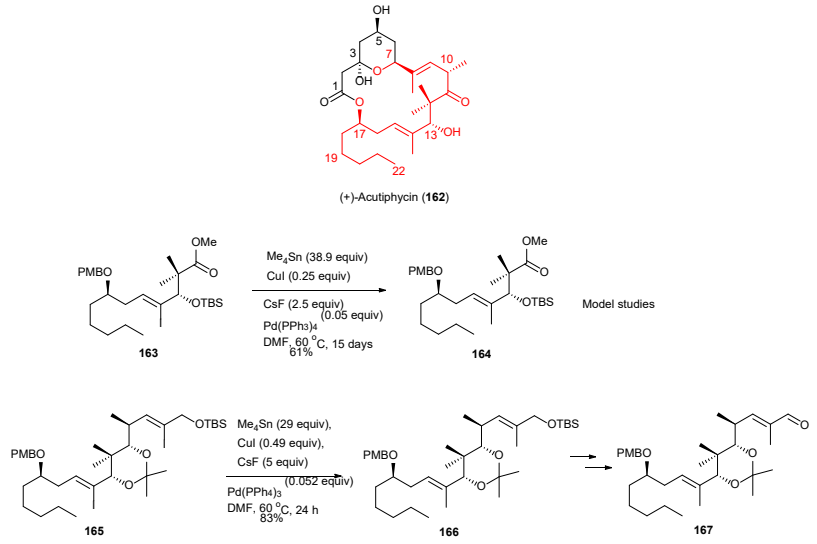
Wilhelmsson *et al.* investigated the synthesis of a non-perturbing fluorescent quadracyclic adenine analogue **161** for detailed studies of nucleic acid-containing systems.[53] This was achieved by the reaction of iodide **158** and arylstannane **159**, under the MLB conditions, to give compound **160** as

product in 60% yield. Compound **160** was transformed to quadracyclic adenosine phosphoramidite monomer **161**. (Scheme 29)



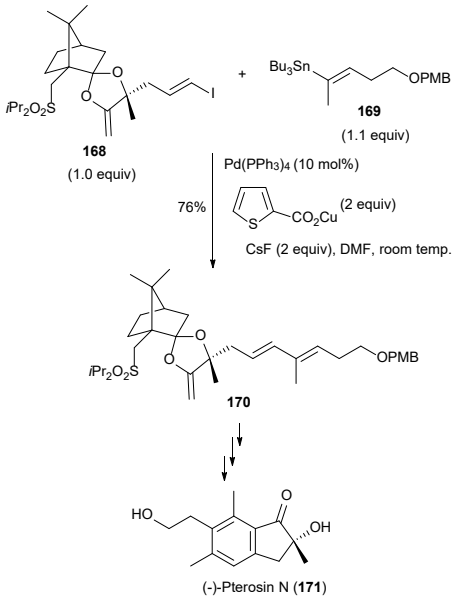
Scheme 29 Synthewsis of a quadracyclic adenosine phosphoramidiate monomer **161**.

(+)-Acutiphycin (**162**) is a pyranylated macrolide, with antitumour activities, first isolated from the blue green alga *Oscillatoria acutissima*. A novel application of the MLB protocol is found in the synthesis of the C(7)-C(22) sector of this natural product.[54] One structural feature of **162** is the presence of two trisubstituted *E*-olefins at C(7)-C(10) and C(13)-C(16). Initially, a model study was conducted by Hale *et al.* in which vinyl iodide **163** was reacted with a large excess of Me_4Sn under the MLB conditions to give tri-substituted olefin **164** in 61% yield. Application of the same reaction conditions to the coupling *bis*-vinyl iodide **165** and excess Me_4Sn gave **166** in 83% yield. Compound **166** was converted to **167**, the C(7)-C(22) sector of (+)-Acutiphycin (**162**). (Scheme 30)



Scheme 30 Synthesis compound **167**, the C(7)-C(22) sector of (+)-Acutiphycin (**162**).

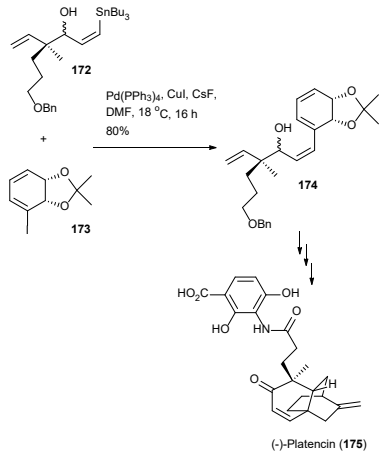
In the asymmetric synthesis of (-)-Petrosin N (**171**), a sesquiterpene found in the bracken fern *Pteridium aquilinum*, Uang *et al.* performed the coupling of vinyl iodide **168** to vinyl stannane **169** under a modified MLB conditions.[55] Interesting they observed that the use of an excess of copper thiophene-2-carboxylate as the Cu(I) additive benefited the coupling reaction, and the desired product **170** was formed in 76% yield. Compound **170** was converted to (-)-Petrosin N (**171**) in a few steps. (Scheme 31)



Scheme 31 Asymmetric synthesis of (-)-Petrosin N (**171**).

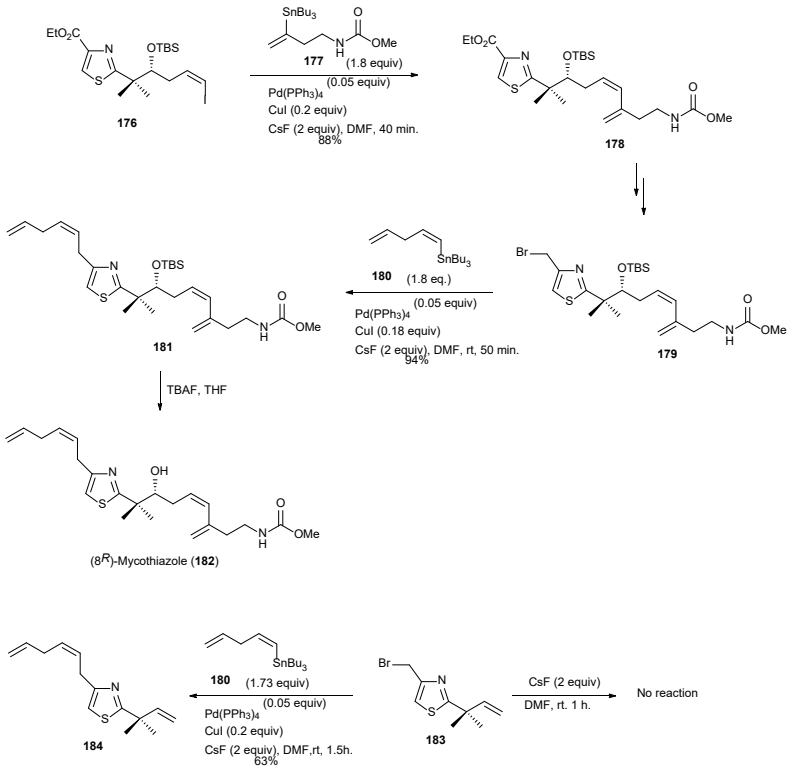
(-)-Platencin (**175**) is an antibacterial natural product isolated from various strains of *Streptomyces platensis*. In Banwell's synthesis of (-)-Platencin (**175**), the coupling of vinylstannane **172** to iodide **173** was achieved using the MLB protocol to give the desired product **174** in 80% yield.[56] It should be noted that this reaction was conducted at 18 °C as the authors were cautious with the possible fragile

nature of compound **174**. Compound **174** was transformed into (-)-Platencin (**175**) in a multi-steps sequence. (Scheme 32)



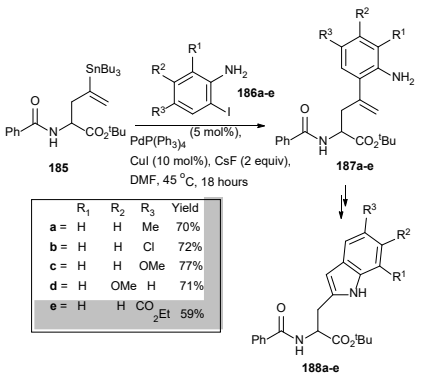
Scheme 32 Synthesis of (-)-Platencin (**175**).

The synthesis of the marine sponge natural product (8*R*)-Mycothiazole (**182**) was completed by Wang and Hale in 2015.[57] This work featured the use of two separate Stille coupling reactions. In the first Stille coupling reaction, vinyl iodide **176** was coupled to vinylstannane **177**, under the MLB conditions, to give diene **178** as the desired product in 88% yield. Compound **178** was transformed into organobromide **179** in two steps. Bromide **179** was then reacted with vinylstannane **180**, again under the MLB conditions to afford compound **181** in 94% yield. The interesting aspect of this second Stille coupling is the formation of sp^2-sp^3 C-C bond. Deprotection of compound **181** with TBAF delivered (8*R*)-Mycothiazole (**182**) as product. Initially, Wang and Hale were concerned that the use of CsF in the coupling of **179** to **180** might be detrimental to the reaction, as the reactive C-Br bond in **179** could possibly suffer a S_N2 attack by fluoride ion. This potential problem was investigated through a model coupling reaction between bromide **183** and vinylstanne **180**, under the MLB conditions to give **184** in 63% yield. Interesting when **183** was treated with CsF alone in DMF at room temperature for one hour, no reaction was observed and compound **183** was recovered unchanged. This showed that CsF was not reactive towards **183** and this model studies alleviated Wang and Hale's concern. (Scheme 33)



Scheme 33 Synthesis of (8*R*)-Mycothiazole (**182**).

The coupling of amino acid derived vinylstananne **185** to various aromatic 1-amino-2-iodoaryls **186a-e** gave the **187a-e** respectively in satisfactory yields.[58] These compounds were converted to the corresponding tryptophan derivatives **188a-e**. However, it should be noted that if the nitrogen protecting group in the stannane was changed from benzoyl to trifluoroacetyl group, the coupling reactions proceeded with diminished yields when the MLB protocol was utilised. (Scheme 34)

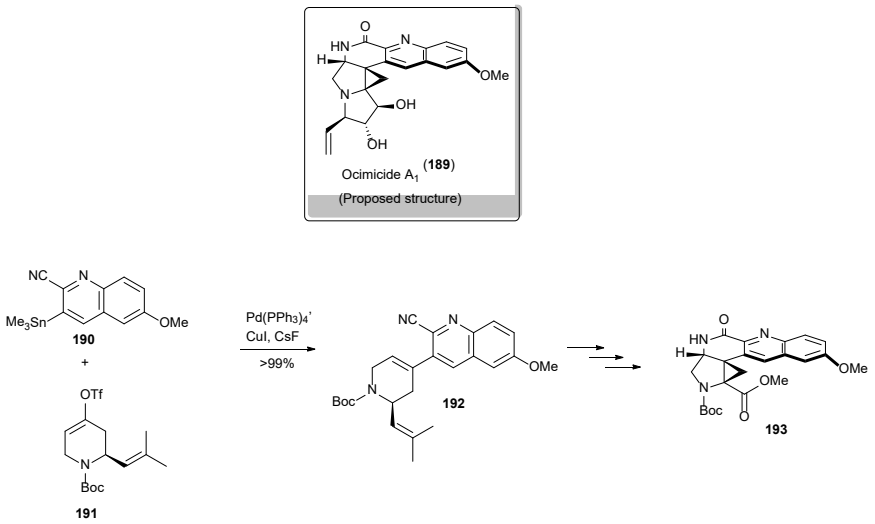


	R_1	R_2	R_3	Yield
a =	H	H	Me	70%
b =	H	H	Cl	72%
c =	H	H	OMe	77%
d =	H	OMe	H	71%
e =	H	H	CO_2Et	59%

Scheme 34 Synthesis of tryptophan derivatives **188a-e**.

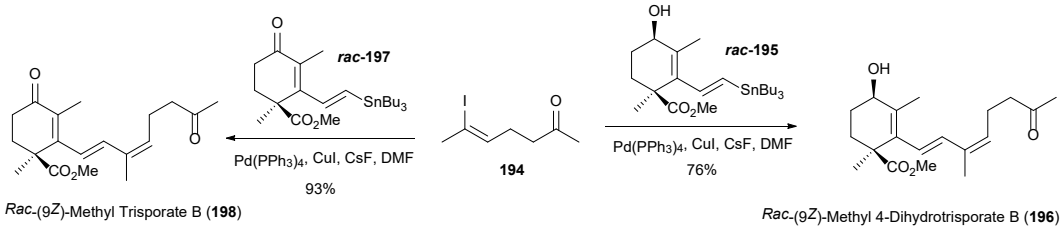
In the synthetic studies towards the antimalarial alkaloid Ocimicide A_1 (**189**), Herzon *et al.* coupled heterocyclic stannane **190** with vinyl triflate **191** to afford **192** in almost quantitative yield. Compound **192** was converted to **193**, supposedly an advanced *N*-acylated pentacyclic precursor to Ocimicide A_1 (**189**). The authors observed that the *tert*-butoxycarbonyl group in **193** could be removed by trifluoroacetic acid but attempts to neutralise the salt to obtain the free amine was unsuccessful. This

prompted them to conducted DET calculations on the ^{13}C chemical shifts on Ocimicide A_1 (**189**) and concluded that the proposed structure of **189** was incorrect. [59] (Scheme 35)



Scheme 35 Synthetic studies of Ocimicide A_1 (**189**).

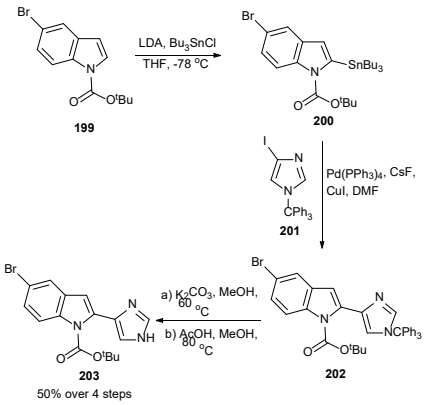
(9*Z*)-Methyl 4-Dihydrotrisporate B (**196**) and (9*Z*)-Methyl Triporate B (**198**) are morphogenetic factors isolated from the Zydomycetes fungi. The protecting-group-free synthesis of *rac*-**196** and *rac*-**198** was reported by Boland *et al.*[60] Vinyl iodide **194** was coupled to *rac*-stannane **195** under the MLB conditions to delivered *rac*-(9*Z*)-Methyl 4-Dihydrotrisporate B (**196**) in 76% yield. Similarly, the coupling of **194** and *rac*-stannane **197** under the same conditions gave *rac*-(9*Z*)-Methyl Triporate B (**198**) in 93% yield. (Scheme 36)



Scheme 36 Synthesis of rac-(9*Z*)-Methyl 4-Dihydrotrisporate B (**196**) and *rac*-(9*Z*)-Methyl Trisporate B (**198**).

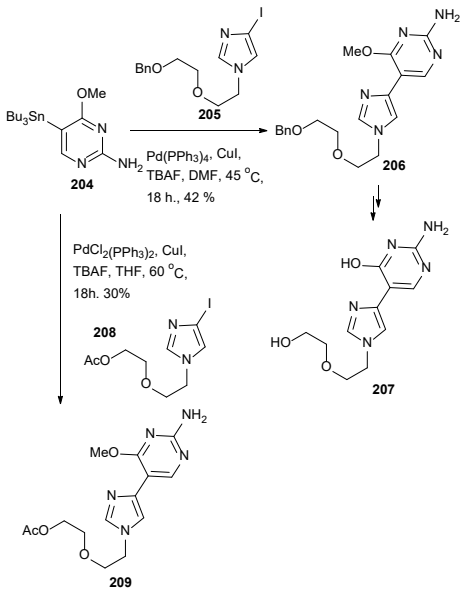
A strategy for cancer treatment is through the inhibition of indoleamine 2,3-dioxygenamine 1 (IDO1). Weaver *et al.* designed compound **203** as a possible IDO1 inhibitor, based on the results of molecular modelling.[61] The synthesis of **203** began with the lithiation of protected indole **199** followed by quenching the corresponding anion with Bu_3SnCl to give stannane **200**. Stannane **200** was coupled to 4-iodo-1-triylimidazole **201** using the MLB protocol to afford compound **202**. Compound **202** was treated sequentially with K_2CO_3 in methanol followed by acetic acid in methanol to deliver compound **203** in an overall yield of 50% over four steps. Remarkably, the first three reactions of this four steps synthetic sequence, including the Stille coupling reaction, were performed on crude reaction products.

It is also interesting to note that bifunctional compound **200** underwent the MLB modified Stille reaction selectively without polymerisation. (Scheme 37)



Scheme 37 Synthesis of indoleamine 2,3-dioxygenamine 1 inhibitor **203**.

The synthesis of acyclic flexmier nucleotide analogues, having anti-coronavirus activity, is reported in a patent by Radtke *et al*. In this work the common synthetic intermediate stannane **204** was coupled to iodide **205**, under the MLB conditions, to give compound **206** in 42% yield. Compound **206** was transformed to **207** in a few steps. Similarly, the coupling of stannane **204** with iodide **208** deliver compound **209** in 30% yield. In this work TBAF was used as the fluoride source and $PdCl_2(PPh_3)_2$ was utilised as the palladium catalyst in the second coupling reaction. [62, 63] (Scheme 38)



Scheme 38 Synthesis of acylic nucleotides analogues **207** and **209**.

The (3*R*)-Inthomycin C conundrum.

The MLB protocol is usually utilised in synthesising sp^2-sp^2 C-C bonds and it is rather surprising this reaction was embroiled in an "absolute configuration dispute" in natural product synthesis.

Inthomycins are a group of bioactive natural products isolated from *Streptomyces*. In 2008, Taylor *et al.* reported the synthesis of *rac*-Inthomycin A (***Rac*-216**), (+)-Inthomycin B (**213**) and 3*R*-Inthomycin C (**220**) through a unified approach.[64] A common oxazole vinyl iodide intermediate **210** was coupled to various stereodefinied stannyl-diene units. For the synthesis of (3*R*)-Inthomycin B (**213**), different conditions were examined for the coupling of iodide **210** to *Z*,*E*-stannane **211**. The use of $Pd(MeCN)_2Cl_2$ as catalyst resulted in various degree of isomerisation of the triene unit. (Table 1) It was found that the MLB protocol gave quantitative yield of triene **212** in short reaction time at 45°C with only traces of isomerisation observed. This compound was eventually transformed into (3*R*)-Inthomycin B (**213**). (Scheme 39)

Table 1

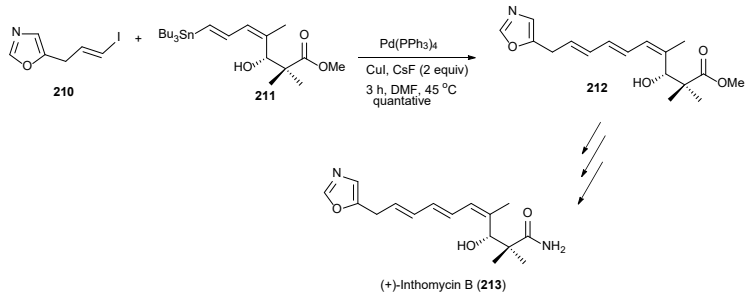
Catalyst	mol %[a]	Time	Temp (°C)	Yield %	Isomerisation %
$Pd(CH_3CN)_2Cl_2$	7	4.5 h	rt	55	30
$Pd(CH_3CN)_2Cl_2$	1	24 h	rt	37[b]	Trace
$Pd(CH_3CN)_2Cl_2$	1	14 h	80	72	20
$Pd(CH_3CN)_2Cl_2$	1	7 h[c]	50	22[b]	15
$Pd(CH_3CN)_2Cl_2$	1	5 d[d]	50	Quant.	Trace
$Pd(PPh_3)_4$, CuI, CsF (2 equiv)	**1**	**3 h**	**45**	**Quant.**	**Trace**

[a] Reaction concentration 0.12 M in degassed DMF.

[b] Mainly recovered coupling partners.

[c] Reaction performed in CEM microwave.

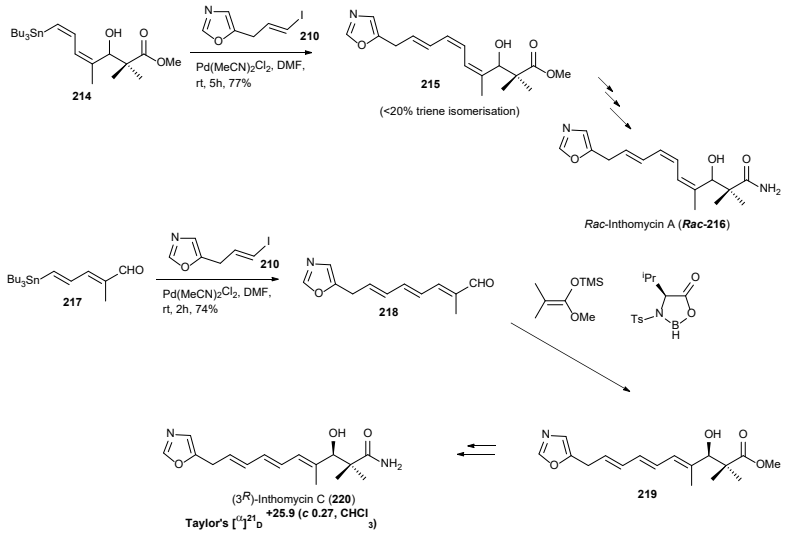
[d] If stopped after 24 h, product was isolated in 43% yield.



Scheme 39 Taylor's Synthesis of (+)-Inthomycin B (**213**).

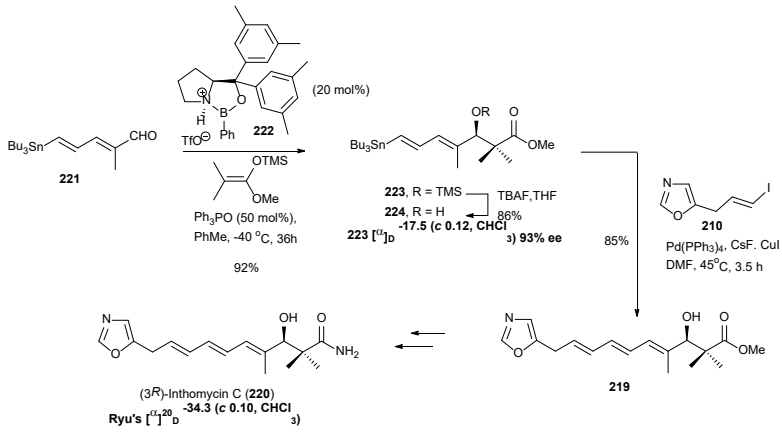
The same Stille coupling strategy was used in the synthesis of *rac*-Inthomycin A (***Rac*-216**). Strangely, $Pd(MeCN)_2Cl_2$ was used as the catalyst for the coupling reaction of stannane **214** and iodide **210**. The corresponding triene **215** was formed in 77% and with less than 20% triene isomerisation. Compound **215** was converted to *rac*-Inthomycin A (***Rac*-216**). It is not explained in the publication that why, after establishing the MLB protocol performed admirably in the coupling reaction, the Taylor group would choose to use $Pd(MeCN)_2Cl_2$ instead, which was shown to cause isomerisation in the (+)-Inthomycin B (**213**) synthesis. For the synthesis of (3*R*)-Ithnomycin C (**220**), vinyl iodide **210** was coupled to vinylstannane **217** using $Pd(MeCN)_2Cl_2$ to give aldehyde **218**. Interestingly, it was observed the use of

MLB conditions for this coupling reaction gave no product. This aldehyde was reacted with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane, under the modified Kiyooka conditions,[65-68] to afford **219** as product with 3*R*- as the absolute configuration. Compound **219** was converted to (3*R*)-Ithnomycin C (**220**) in two steps. Taylor *et al*. reported the specific rotation of this compound as $[\alpha]^{21}_{D}$ +25.9 (*c* 0.27, $CHCl_3$). (Scheme 40)



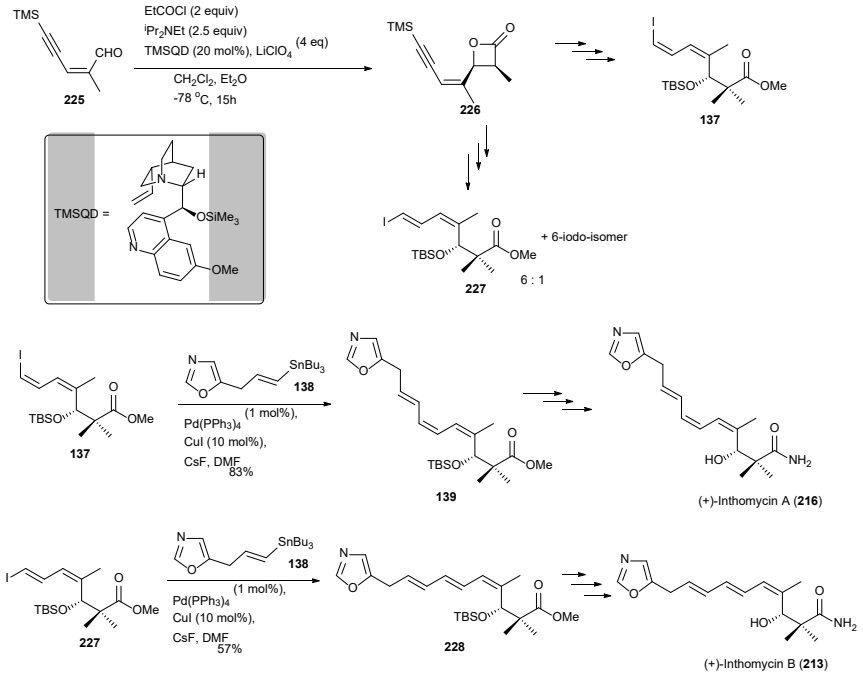
Scheme 40 Taylor's synthesis of *Rac*-Inthomycin A (***Rac*- 216**), (3*R*)-Inthomycin C (**220**).

In 2010 another asymmetric synthesis of (3*R*)-Inthomycin C (**220**) was disclosed by Ryu *et al.*[69] In this work chiral stannane **224** was prepared by a catalytic enantioselective Mukaiyama Aldol reaction. Using oxazaborolidinium salt **222** as catalyst with triphenylphosphine oxide as additive, aldehyde **221** reacted with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane afforded compound **223**, which was deprotected to give stannane **224**. Stille coupling of stannane **224** to vinyl iodide **210** under the MLB conditions gave **219** in 85% yield. This compound was subsequently converted into (3*R*)-Inthomycin C (**220**). (Scheme 41) The observed specific rotation of Ryu's synthetic (3*R*)-Inthomycin C (**220**) was $[\alpha]^{21}_{D}$ -34.3 (*c* 0.10, $CHCl_3$), which was opposite in sign to that reported by Taylor *et al.* ($[\alpha]^{21}_{D}$ +25.9 (*c* 0.27, $CHCl_3$). At this stage, both the Taylor group and the Ryu group had apparently synthesised (3*R*)-Inthomycin C (**220**), as depicted in their publications. Yet the Taylor's and Ryu's specific rotation values are opposite in signs!



Scheme 41 Ryu's synthesis of (3*R*)-Inthomycin C (**220**).

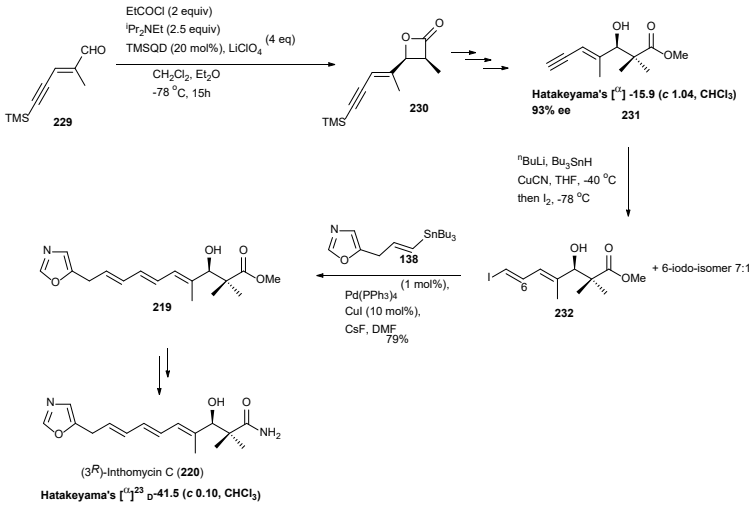
The asymmetric synthesis of Inthomycins A (**216**), B (**213**) and C (**220**), also using a unified strategy, was reported by Hatakeyama *et. al.* in 2012.[70] Thus, chiral β-lactone **226** was synthesised from aldehyde **225** and propionyl chloride using Nelson's method.[71-73] This compound was transformed to vinyl iodides **137** and **227** separately. Vinyl iodide **137** was coupled to stannane **138** to afford **139**, using the MLB protocol, this coupling reaction was previously reported in Hatakeyama's synthesis of Oxazolomycin (**140**). Compound **139** was subsequently transformed to (+)-Inthomycin A (**216**). Similarly, coupling of stannane **138** to vinyl iodide **227** gave **228**, which was converted into (+)-Inthomycin B (**213**). (Scheme 42)



Scheme 42 Hatakayama's synthesis of (+)-Inthomycin A (**216**) and (+)-Inthomycin B (**213**).

For the synthesis of (3*R*)-Inthomycin C (**220**), Hatakeyama *et al*. performed the Nelson reaction on aldehyde **229** to form β-lactone **230**, which was converted to terminal acetylene **231** in a few steps.[70] This compound was subjected to a stannylation/iodination sequence to give vinyl iodide **232** as a

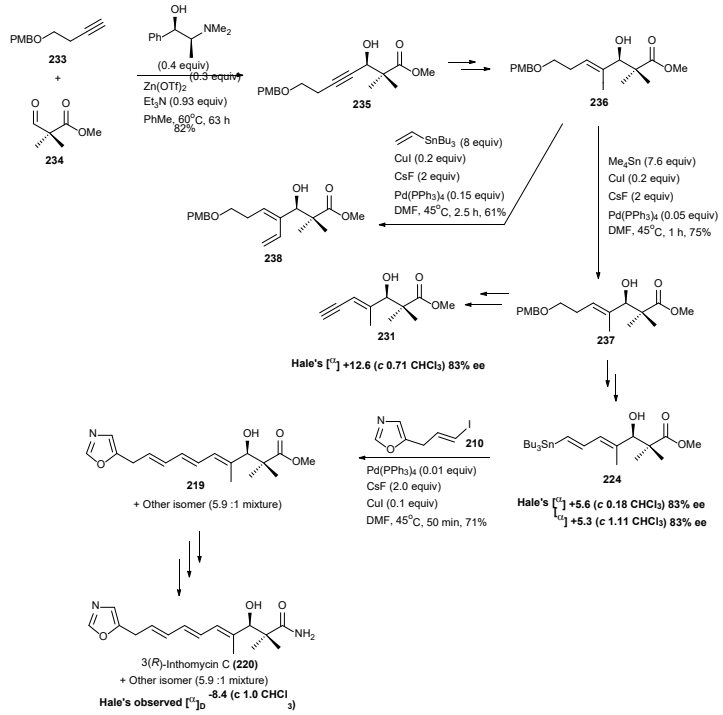
mixture of 7:1 mixture. Compound **232** was coupled to stannane **138** under the MLB condition to give triene **219** in 79% yield. This compound was transformed to 3(*R*)-Inthomycin C (**220**) in a four-step sequence. (Scheme 43)



Scheme 43 Hatakeyama/s synthesis of (3*R*)-Inthomycin C (**220**).

The difference in Hatakeyama's approach is the polarity reversal of the Stille coupling components relative to that of Taylor's and Ryu's. Hatakeyama *et al.* reported the specific rotation of their synthetic (3*R*)-Inthomycin C (**220**) as $[\alpha]^{23}_{D}$-41.5 (*c* 0.10, $CHCl_3$). At this stage it appeared that both Japanese groups were in good agreement with respect to their synthetic (3*R*)-Inthomycin C (**220**)'s specific rotation values. The work of Ryun and Hatakeyama on (3*R*)-Inthomycin C (**220**) synthesis contradicted and seemingly casted doubt on the absolute configuration assignment made by Taylor *et al*.

However, Ryun's and Hatakeyama's results were disputed by Hale *et al.* in 2014.[74] The Hale synthetic route to (3*R*)-Inthomycin C (**220**) was designed to intercept Ryu's intermediate **224** but also branch out to synthesise Hatakeyama's intermediate **231**. The single stereocentre of (3*R*)-Inthomycin C (**220**) was established by reaction of terminal acetylene **233** with aldehyde **234** using Carreira's method[75-77] to give **235** as product. Compound **235** was transformed into vinyl iodide **236** in a few steps. Vinyl iodide **236** was coupled to tetramethyltin using the MLB conditions to afford trisubstituted olefin **237**. From compound **237**, Hale *et al*. prepared the Hatakeyama intermediate **231**, and found that its specific rotation value had similar magnitude but opposite to that reported by Hatakeyama (see Scheme 43). Compound **237** was also converted to the Ryu intermediate **224**. Interestingly, Hale *et al.* observed that the specific rotation value of this compound was opposite in sign and different in magnitude to that of Ryu. The Hale group also repeated the Ryu coupling reaction between **224** and **210** under the MLB conditions and observed isomerisation of the triene occurred during the reaction. The coupled product **219** was obtained as a 5.9:1 mixture favouring **219**. (3*R*)-Inthomycin C (**220**), also as a 5.9:1 mixture, was prepared from **219** through a three-steps sequence. The observed specific rotation value of Hale's (3*R*)-Inthomycin C (**220**) was found to be [α]-8.4 (*c* 1.0, $CHCl_3$). Hale *et al.* suggested that the low negative specific rotation value of their compound **220** was due to the presence of unidentified triene isomer and concluded that Taylor's structure of **220** should be reinstated. The Hale group also demonstrated their trisubstituted olefin synthesis methodology by conducting the coupling of vinyl iodide **236** to tributyl(vinyl)tin to afford **238** in 61% yield. (Scheme 44)



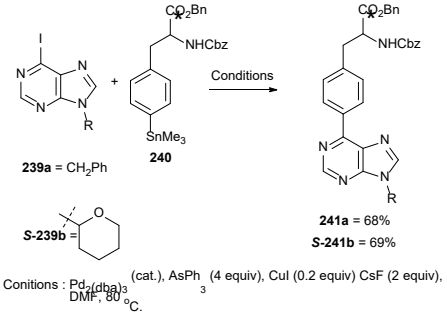
Scheme 44 Hale's synthesis of intermediates **231**, **224** and 3(*R*)-Inthomycin C (**220**).

Subsequent collaboration between the Hale and Hatakeyama groups established that both groups had in fact, synthesised (-)-(3*R*)-Inthomycin C (**220**).[78] The discrepancy between the specific rotation values of synthetic (3*R*)-Inthomycin C observed by Hale, Hatakeyama and others was resolved in this work. The detail of this investigation is beyond the scope of this article and readers who are interested in this specific investigation should refer to reference 78. The Hale and Hataketama groups also commented that the Taylor group had also synthesised (3*R*)-Inthomycin C (**220**) and the positive specific rotation value reported in Taylor's paper was the result of a 20% tetramethylurea contamination in the sample. In addition, both the Hale and Hataketayma groups believed that the Ryu group had indeed synthesised (-)-(3*R*)-Inthomycin C (**220**), despite the specific rotation value reported the Ryu group is a large negative value. The conclusion of Hale and Hatakeyama's collaborative work was further supported by the reported synthesis of (-)-(3*R*)-Inthomycin C (**220**) by the Donohoe group,[79] where they obtained a similar specific rotation value to that of Hale/Hatakeyama's.

Just a few slightly less successful examples.

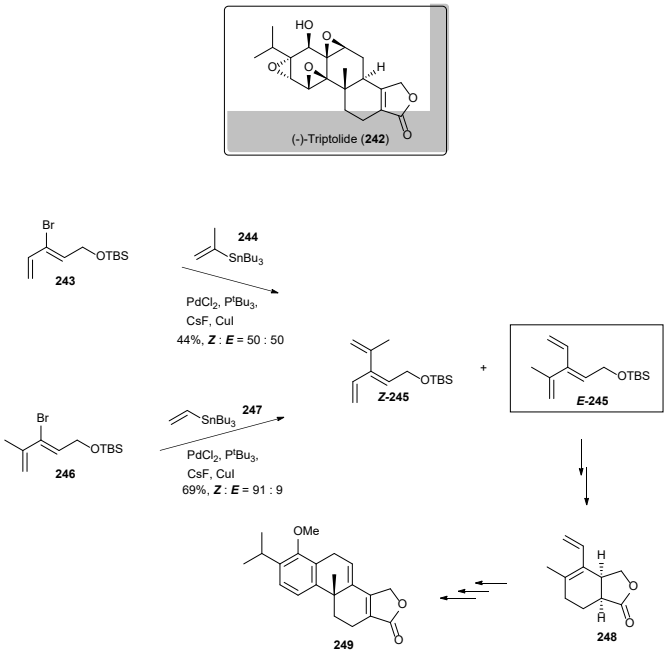
No synthetic method is infallible and here are a few examples in which the modified Stille reactions were found to be "underperforming", relative to other palladium catalysed coupling methods. Nonetheless, these "underperforming" reactions did deliver the desired products. Hoeck *et al*. investigated the synthesis of purin-6-ylphenylalanines and their nucleosides using palladium catalysed coupling reactions.[80] Initially the authors had some success in using the Suzuki-Miyaura coupling reactions, but partial racemisation of the coupled products were observed. The authors then examined the use of the Stille reaction. It was observed that the coupling reaction between aryliodide **239a** and arylstanne **240** was sluggish, when a combination $Pd_2(dba)_3/AsPh_3$ was used as catalyst and ligand. However, the inclusion of two equivalents of CsF and 0.2 equivalent of CuI greatly accelerated

and enhanced the reactions and gave **241a** in 68% yield. Similarly, the coupling of ***S*-239b** and **240** under the same conditions gave ***S*-241b** in 69% yield. However, when ***S*-241b** was deprotected and treated with Marfey's reagent, the product obtained was showed to have 63% de. This partial racemisation of ***S*-241b** was likely due to the presence of basic CsF in the Stille coupling reaction. (Scheme 45)



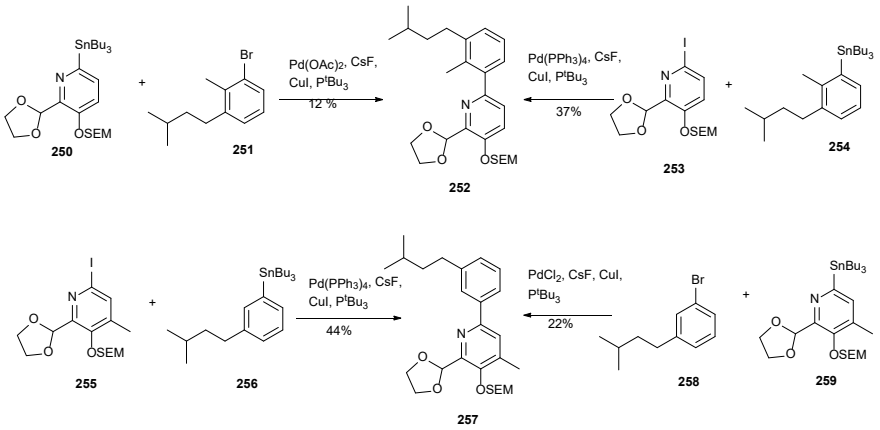
Scheme 45 Synthesis of protected 4-(purin-6-yl)phenylananines **241a** and **241b**.

In the formal total synthesis of the natural product Triptolide (**242**), Sherburn *et al*. investigated the preparation of the synthetic intermediate ***E*-245** using the Stille coupling reactions.[81] It was observed that the coupling reaction of vinyl bromide **243** to vinylstanne **244** under the MLB conditions developed for organobromide gave a mixture of ***Z*-** and ***E*-245** in a ratio of 50 : 50. Alternatively, when vinyl bromide **246** was coupled to vinylstannane **247** under the same conditions, ***Z*-** and ***E*-245** were formed as a 91: 9 mixture. ***E*-245** was converted to **248** in two steps. However, the authors eventually opted for an alternative approach to compound **248** due to the unfavourable stereocontrol in the Stille reaction. Compound **248** was transformed into compound **249**, which constituted a formal total synthesis of Triptolide.



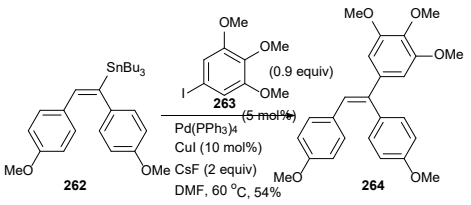
Scheme 46 Formal total synthesis of Triptolide (**242**).

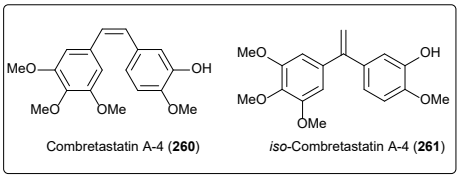
The synthesis of phenylpyridal scaffolds as helical peptide mimetics were reported by Marshall *et al*.[82] Initially the Bourne group examined the use of the Stille reaction under MLB conditions for the synthesis of phenylpyridal skeletons **252** and **257**. The coupling stannane **250** and arylbromide **251**, under the MLB conditions developed for bromide, gave compound **252** in poor yield (12%). If the polarity of the reactants were reversed by using iodide **253** and stannane **254** and as coupling partners, compound **252** could be obtained 37% yield. However, the authors found the Suzuki reaction of iodide **253** with corresponding organoboronate delivered compound **252** in excellent yield. The authors also synthesised compound **257** in two ways. The Stille coupling of iodide **255** to stannane **256** afford compound **257** in 44% yield while reaction between bromide **258** and stannane **259** gave inferior result. It is unclear in the publication that why the authors utilised P^tBu_3 as ligand for the coupling reactions of iodides **253** and **255**, which is usually unnecessary. Only compound **252** was transformed to various scaffoldings. (Scheme 47)



Scheme 47 Synthesis of Phenylpyridal Scaffold.

Alami *et al.* investigated the synthesis of triarylolefins as hybrid analogues of the antitumour natural products Combretastatin A-4 (**260**) and *iso*-Combretastatin A-4 (**261**).[83] In their initial investigation, stannane **262** was coupled to aryliodide **263**, under the MLB conditions, to give trisubstituted olefin **264** in 54% yield. However, the authors later found that the yield of **264** could be improved by using a longer synthetic route in-cooperated with the Negishi coupling reaction instead.

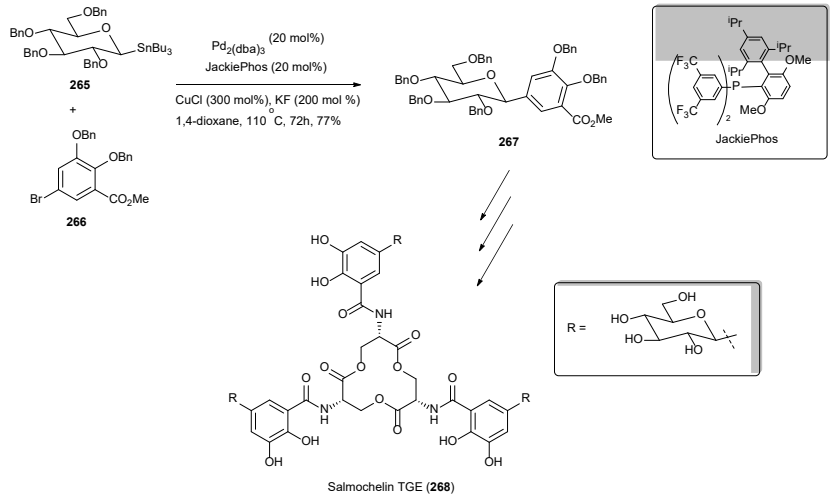




Scheme 48 Synthesis of trisubstituted olefin **264**.

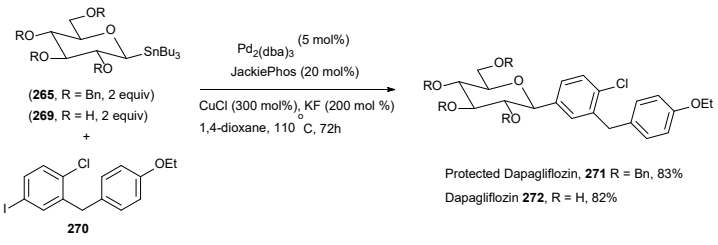
Synthesis of C-aryl glycosides using Cu(I) salt and Fluoride mediated Stille reactions.

The synthesis of C-aryl glycosides through stereospecific Stille cross-coupling reactions of anomeric stannanes was recently reported by Walczak *et al*.[84-86] The authors observed that by using $Pd_2(dba)_3$ and JackiePhos as the catalyst/ ligand combination, anomeric stannanes could be coupled to various aryl halides, with the retention of the stereochemistry at the anomeric centre. These coupling reactions were conducted using KF (200 mol%) and CuCl (300 mol%) as additives at high temperature. This methodology was utilised in the synthesis of TGE (**268**) and Dapagliflozin **272** and its protected form **271**.[85] TGE (**268**) is a triply glycosylated salmochelin and a siderophore produced by the *Salmonella* species. In the synthesis of this natural product, stannane **265** was coupled to arylbromide **266** under Walczak's conditions, to give **267** in 77% yield. This compound was converted to TGE **268** in a few steps. (Scheme 49)



Scheme 49 Synthesis of Salmochelin TGE (**268**).

Dapagliflozin **272** is a drug used in the treatment of diabetes mellitus type 2. The synthesis of protected Dapagliflozin **271** was achieved by the coupling of stannane **265** with aryliodide **270**. Similarly, Dapagliflozin **272** was synthesised in one step from stannane **269** and aryliodide **270**. (Scheme 50)



Scheme 50 Synthesis of protected Dapagliflozin (**271**) and Dapagliflozin (**272**).

Conclusions

The inclusion of Cu(I) salt and fluoride is shown to accelerate and improve the performance of the Stille coupling reactions. This highly versatile method has been adopted in complex natural product synthesis and can be strategically integrated as part of the cascade ring formation processes. The elegant work of Trauner[87], Padwa[32, 33] and Lebel[34] competently demonstrated the power of the Stille coupling/cascade strategy. Another attractive feature of the MLB protocol is its functional group tolerance, which makes this methodology suitable for the synthesis of complex natural products. The work of López,[35] Lebel,[34] Hatakeyama,[49, 70] and Hale[54, 57] shows that silylated substrates can undergo Stille coupling reactions under the MLB conditions, with no detrimental effect to the silyl protecting groups. Hopefully these observations will provide assurance to those who are unsure about the compatibility of silylated substrates with fluoride in the MLB conditions.

The MLB protocol is originally developed for the synthesis of sp^2C-sp^2C bond and has subsequently been modified for sp^2C-sp^3C bond formation.[54, 57, 84-86] It is possible that this modification can be further developed into a general methodology. In fact, Fairlamb *et al.* showed that it is possible to coupled allylic and benzyl bromides to vinyl and aryl stannanes, using phosphine-free dinuclear anionic palladacyclopentadienyl catalysts possessing (*N*,*O*)-imidate ligands under the MLB conditions.[88] However, this methodology has not been utilised in natural product synthesis so far.

Naturally no method is prefect and there are a few cases which the MLB protocol was found to be less efficient than other coupling conditions or methods. Gratifyingly, the number of successful cases far outweighed the less successful ones. Since Cushman *et al.* observed the beneficial effect of utilising excess CuI in their coupling reactions,[37] it is possible that this modification can be considered for more challenging coupling reactions. Alternatively, copper thiophene-2-carboxylate can be examined as a CuI substitute for underperforming reactions.[55] It is hope that this review will serve as a platform to encourage more synthetic organic chemists to utilise this simple coupling protocol in natural product synthesis.

Conflicts of interest

There are no conflicts of interest to declare.

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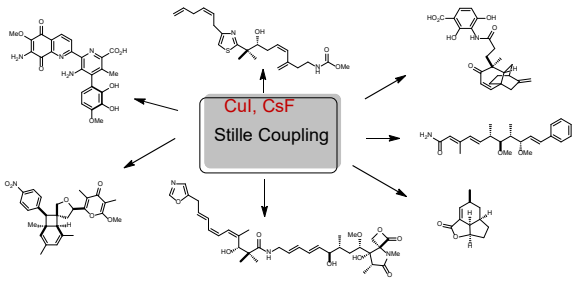
Graphical Abstract


CuI, CsF
Stille Coupling