The intramolecular Stille reaction

Matthew A. J. Duncton and Gerald Pattenden

School of Chemistry, The University of Nottingham, Nottingham, UK NG7 2RD

Received (in Cambridge) 29th January 1999

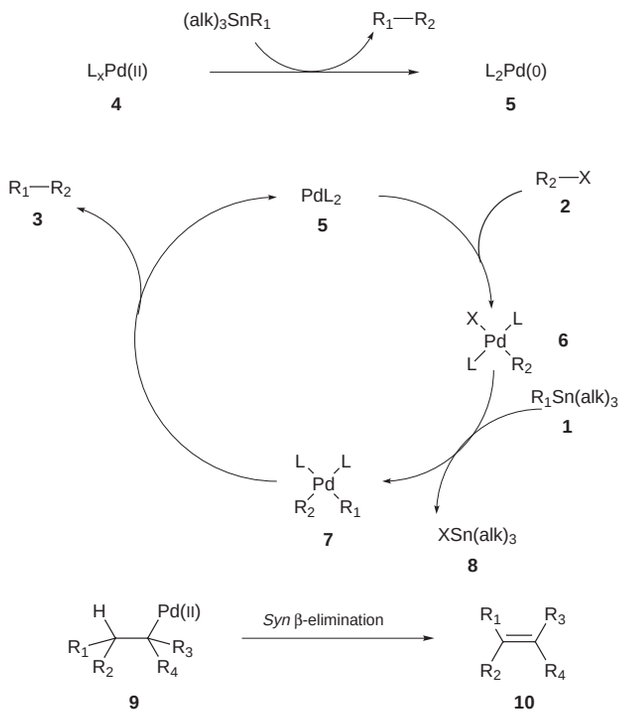
Covering: up to December 1998

1 Introduction

The palladium(0)-catalysed coupling reaction between an organotin reagent (also referred to as an organostannane) **1** and an organic electrophile **2** to form a new carbon-to-carbon sigma bond, *e.g.* **3** (Scheme 1), is a process widely referred to as the Stille coupling reaction, after the late John K. Stille, who discovered the reaction in the late 1970s[1] and pioneered its use in synthetic organic chemistry in the early 1980s.[2,3] At the time of its discovery the Stille reaction provided one of only a few known examples of a transition metal-catalysed coupling-reaction between an organometallic reagent and an organic electrophile.[4] Over the past decade, however, the area of transition metal-catalysed cross-coupling reactions has received intense interest from the research community, and the Stille reaction is now recognised as just one illustration of many such similar processes.[5]

Scheme 1

The generally accepted catalytic cycle for the Stille coupling reaction was proposed in the 1970s, although the detailed mechanism of the reaction is still a matter of some debate.[6] The active catalyst is believed to be a 14-electron palladium(0) complex **5** which can be generated from a suitable palladium(0) precursor, such as $Pd(PPh_3)_4$. Alternatively, the active palladium(0) catalyst can be formed by reduction of a suitable palladium(II) precursor **4** such as $(Ph_2P)_2PdCl_2$, where the organometallic coupling partner **1** normally serves as an adequate reducing agent (Scheme 2). Palladium(0) complexes are nucleophilic and they react readily with organic electrophiles in an oxidative addition reaction to produce a 16-electron palladium(II) intermediate **6**. The electrophilic component R_2–X in the reaction is frequently an organohalide or organotriflate compound. A limitation of the Stille reaction is that electrophiles that contain an alkyl group (other than methyl) cannot be used in the cross-coupling process. This is because a facile β-elimination (dehydropalladation) takes place in the alkyl palladium(II) complex **6**, *cf*. **9** leading to **10** (Scheme 2), before any further steps in the catalytic cycle can take place.



Scheme 2

The next step to occur in the catalytic cycle in the Stille reaction is a transmetallation reaction. In the transmetallation step one group from the organotin reagent **1** transfers to the palladium(II) intermediate **6** whilst the halide or triflate group becomes associated with the tin of the organostannane. Fortunately, from a synthetic point of view, different types of group attached to the tin of the organostannane coupling partner transmetallate to the palladium(II) intermediate at different rates. The order of migration of groups is: alkynyl > vinyl > aryl > allyl ~ benzyl ⋙ alkyl. Since alkyl groups migrate from tin to palladium at the slowest rate, mixed organostannanes that contain three spectator methyl or butyl groups can be used, so that exclusive transfer of a more chemically complex group such as a vinyl or aryl moiety can occur. The transmetallation step **6/1→7/8** is the rate-determining step in the catalytic cycle. Over the last few years much research has been devoted to increasing the rate of this transmetallation reaction by designing new palladium catalysts for use in the Stille coupling reaction.[6] In the final step of the catalytic cycle the cross-coupled product **3** is expelled from the palladium(II) intermediate **7** and the active palladium(0) catalyst **5** is regenerated.

2 Scope of the reaction

The emergence of the Stille coupling reaction as a powerful method for the formation of carbon–carbon bonds is largely due to the overall mildness of the technique. The Stille reaction conditions are compatible with many types of functional group such as carboxylic acid, ester, amide, nitro, ether, amine,

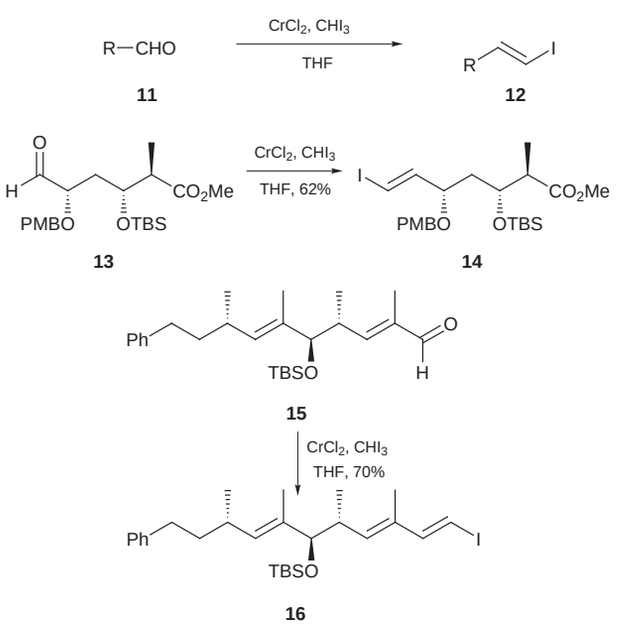
hydroxy ketone and even aldehyde groups. Since the reaction conditions are very mild, a high degree of stereochemical complexity can be tolerated in either of the coupling partners **1** and **2**. In addition, since the oxidative addition and transmetallation steps **2**→**6** and **6**→**7** occur with retention of configuration, vinyl–vinyl couplings proceed with retention of stereochemical integrity in the coupling partners. These facets of the Stille coupling reaction combine to make the process particularly useful in natural product synthesis, where sensitive functionality and stereochemical detail need to be accommodated in the strategy.

Although the Stille coupling reaction is just one member of a whole host of transition metal-catalysed cross-coupling reactions,[5] it is perhaps the most versatile and the most selective of these processes. The reason for this is two-fold. First, as already mentioned, the reaction is a particularly mild process which tolerates a wide variety of functionality and stereochemical detail in the coupling partners. Secondly, there are a number of methods for the formation of organostannanes, and the organometallic reagents themselves are isolable and easily handled compounds since they are relatively insensitive to moisture and oxygen. Related palladium(0) cross-coupling reactions such as those that employ organolithium, magnesium, copper, zinc, or silicon reagents, suffer from either low conversions to the cross-coupled product, poor tolerance of functionality and stereochemical detail in the coupling partners, or difficulty in the preparation of the organometallic reagent. The palladium(0)-catalysed vinylation or arylation of alkenes (Heck reaction)[7] does not enjoy the same scope as the Stille coupling reaction, and the process can lead to regio- and stereoisomeric products depending upon the particular reaction conditions. One of the major side reactions associated with the Stille coupling reaction is an oxidative homocoupling of the organostannane reagent **1**. However, this homocoupling is encountered only in special circumstances and can usually be overcome by optimisation of the reaction conditions.

Since there are a large number of different methods available for the synthesis of the organostannane and electrophilic components in the Stille reaction it would be prudent to briefly survey the most useful methods for making these two classes of compound.

3 The coupling partners

The synthetic utility of the Stille reaction owes a great deal to the ease with which the organostannane **1** and organic electrophile **2** coupling partners can be synthesised, compared with related coupling reactions. Here we briefly focus on the main methods of making alk-1-enyl halides and alk-1-enylstannanes in a regio- and stereoselective fashion.



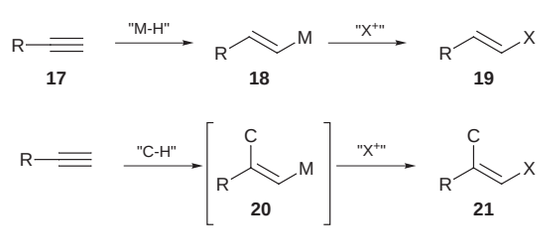
Scheme 3

3.1 (*E*)- and (*Z*)-Alkenyl halides

(*E*)-Alk-1-enyl halides are probably the most widely used organic electrophiles in the Stille coupling reaction. There are many methods for making this type of compound, but very few of them are mild enough to be used with highly functionalised substrates. In addition, some of the procedures give unfavourable ratios of *Z*/*E* geometric isomers.

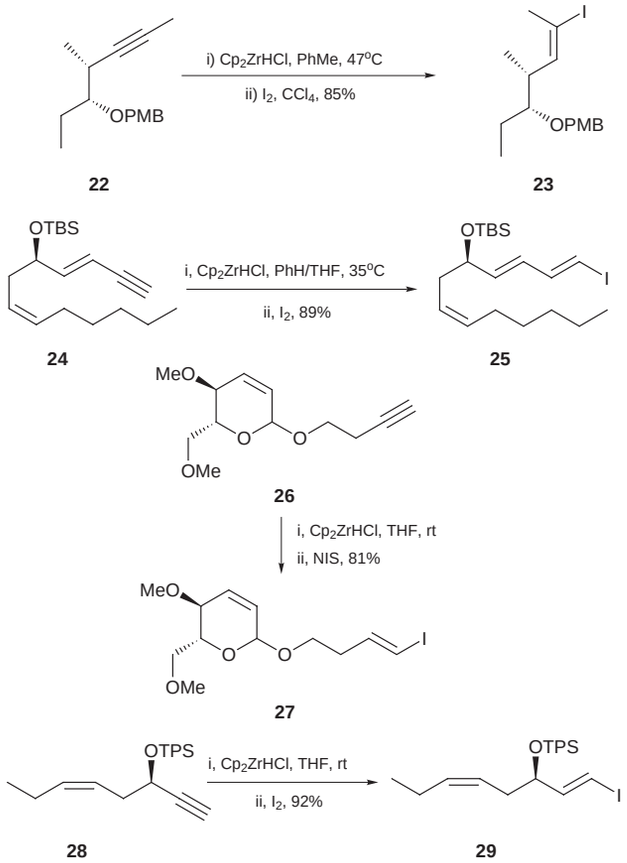
One of the mildest and most selective methods for preparing alk-1-enyl halides uses the reaction between an aldehyde and the active *gem*-dichromium organometallic reagent derived from chromium(II) chloride and iodoform, *viz*. **11**→**12** (Scheme 3).[8] The reaction is easy to perform, with the aldehyde starting material and iodoform simply being added to a suspension of anhydrous chromium(II) chloride in tetrahydrofuran, or a tetrahydrofuran–dioxane mixture. The yield of the alk-1-enyl iodide **12** is very satisfactory (*ca*. 50–70%) and the (*E*) selectivity is normally very high (>95%). The reaction has been used to make alk-1-enyl iodides from some complex and sensitive aldehyde precursors. Thus in their synthesis of lankacidin C, Kende *et al.* [9] used this chromium-mediated reaction to prepare the (*E*)-vinyl iodide **14** from the aldehyde **13**, and in a synthesis of stipiamide the vinyl iodide **16** was prepared in a good yield and with excellent stereoselectivity from the aldehyde **15**.[10]

Another highly predictable and much favoured method for the synthesis of vinyl iodides involves the formal addition of hydrogen iodide across an alkyne precursor. Normally such reactions are performed by hydrometallation or carbometallation of the alkyne **17**, followed by quenching with an electrophilic source of halide *i.e.* **17**→**19** *via* **18** and **17**→**21** *via* **20** (Scheme 4).[11] Of the several hydrometallation procedures now available, reactions based on hydrozirconation appear to be the most synthetically useful, since the most commonly used hydrozirconating agent, Schwartz's reagent (Cp_2ZrHCl), is easily prepared and is found to hydrozirconate alkyne precursors very readily at room temperature.[12] The reaction is conveniently performed using a Lewis base as solvent (*e.g.* THF) as this increases the rate of hydrozirconation. The two step hydrozirconation–halide quenching reaction has been used to synthesise several geometrically pure alk-1-enyl halides from some relatively complex substrates, as illustrated by the examples **22**→**23**,[13] **24**→**25**,[14] **26**→**27**,[15] and **28**→**29**[16] (Scheme 5).

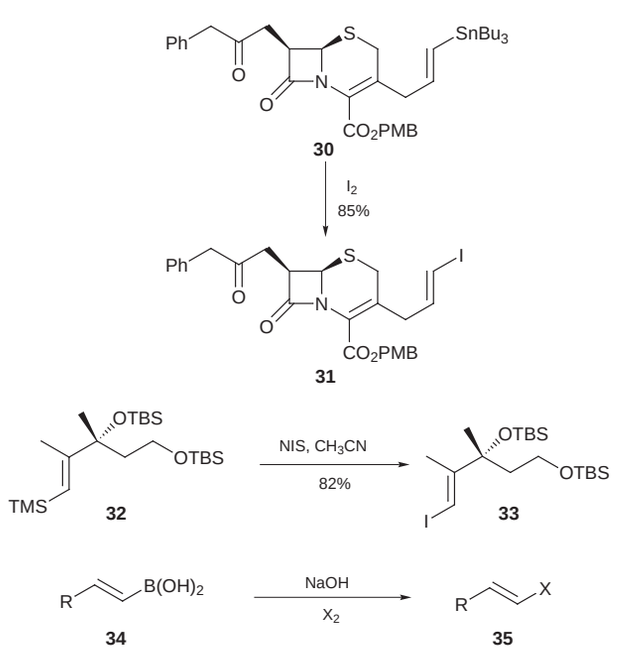


Scheme 4

A further useful method for the synthesis of geometrically defined vinyl halides involves the halogenation of a vinylstannane or vinylsilane precursor with an electrophilic source of halide (*e.g.* NIS, I_2, NBS). The reaction proceeds with retention of stereochemistry of the double bond and has been used to make alk-1-enyl halides in several complex systems. For example, Farina *et al.* have used this reaction to transform the (*E*)-vinylstannane **30** into the (*E*)-vinyl iodide **31** (Scheme 6), which is an intermediate in their synthesis of cephem,[17] and our own research group has used an analogous reaction to convert



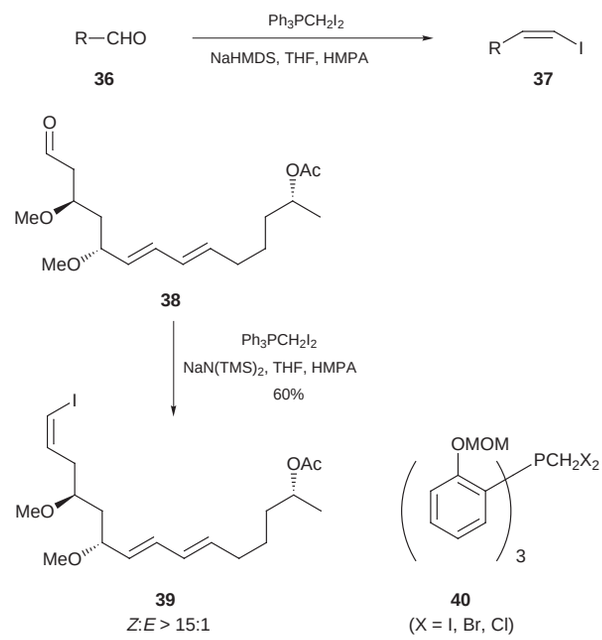
Scheme 5



Scheme 6

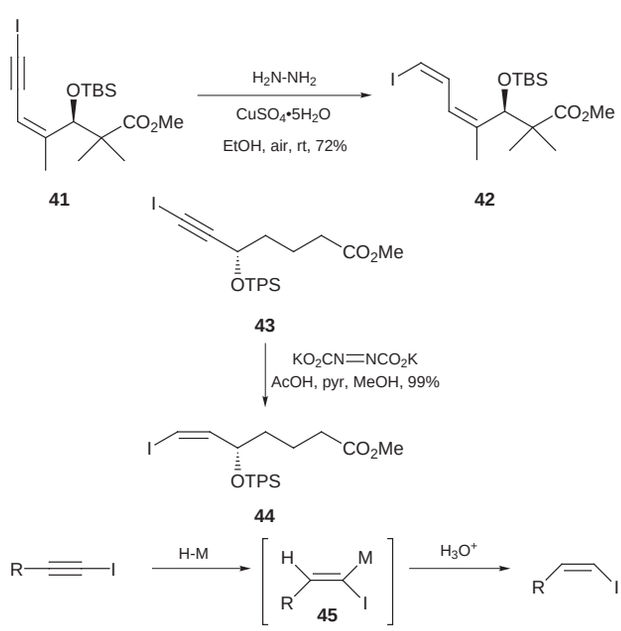
the vinylsilane **32** into the vinyl iodide **33**.[18] Vinylboronic acids **34**, which are smoothly prepared by hydrolysing the product from the hydroboration of an alkyne with catecholborane, are also useful sources of (*E*)-vinyl halides **35** following treatment with NaOH and then molecular halogen X_2.[19]

There are fewer synthetic methods available for the formation of (*Z*)-alk-1-enyl halides than there are for their *E*-counterparts. However, the reactions used to form (*Z*)-alk-1-enyl halides are quite well known processes. Thus, aldehydes are converted into (*Z*)-alk-1-enyl iodides with good stereoselectivity by use of a 'salt free' Wittig reaction, *viz.* **36**→**37** (Scheme 7).[20] Our own research group, for example, has used this procedure to make the (*Z*)-vinyl iodide **39** from the aldehyde **38** with good control of stereoselectivity, and Schlosser and Zhang have dramatically increased the scope of the reaction by using the Wittig reagent **40** which leads to the (*Z*)-alk-1-enyl halides (X = I, Br, Cl) with excellent stereoselectivity.[21]



Scheme 7

(*Z*)-Alk-1-enyl halides can also be synthesised from l-haloalkynes by reduction with diimide. This strategy has been used by Kende *et al.*[22] in their approach towards a total synthesis of neoxazolomycin and by Nicolaou *et al.*[23] during their synthesis of an isomer of lipoxin B_4 *i.e.* **41**→**42** and **43**→**44** (Scheme 8). A less exploited approach to (*Z*)-alk-1-enyl halides involves the hydrometallation of l-haloalkynes followed by protonation of the resulting vinyl organometallic intermediate **45**.[24]

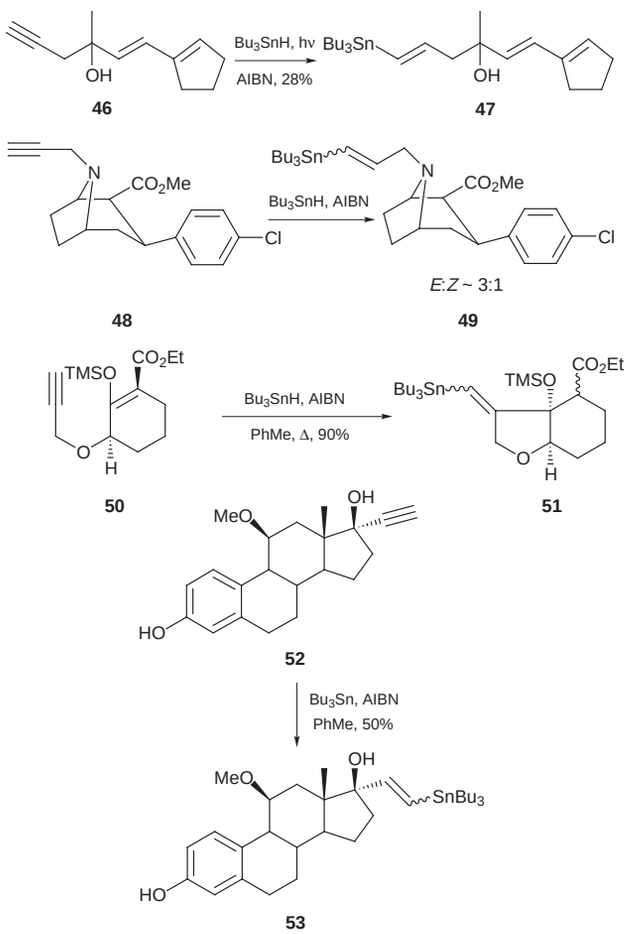


Scheme 8

3.2 (*E*)- and (*Z*)-Alkenylstannanes

(*E*)-Alk-1-enylstannanes are most frequently prepared *via* the hydrostannylations of alk-1-yne precursors. In most cases the reactions are performed using a radical initiator such as 2,2-azobis(isobutyronitrile) (AIBN) in benzene. As radical species

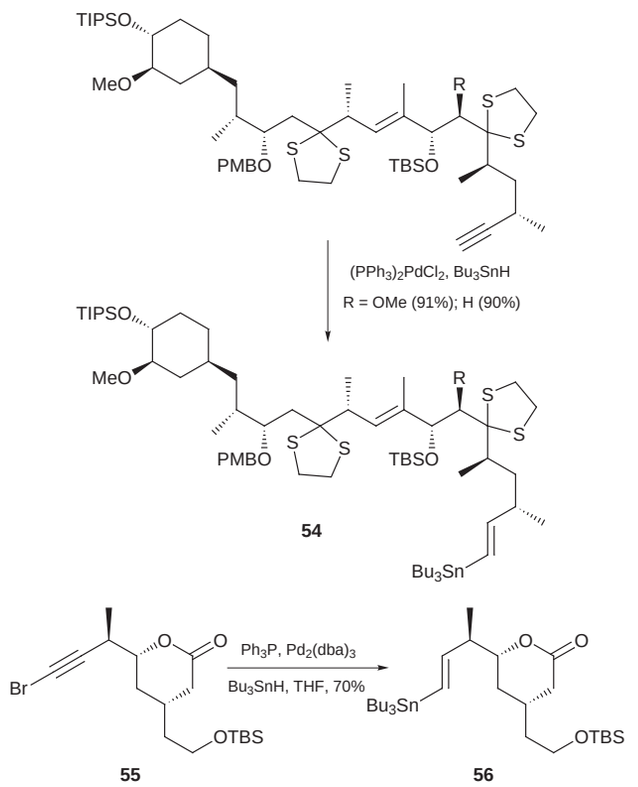
are involved in these transformations, the protection of hydroxy and amino functional groups are not normally required. Unfortunately, the reactions tend to generate a mixture of geometrical isomers, although the (*E*)-vinylstannane product usually predominates. This radical-based method for making (*E*)-vinylstannanes has found extensive use in synthesis, as evidenced by the examples **46**→**47**,[25] **48**→**49**,[26] **50**→**51**[27] and **52**→**53** (Scheme 9).[28]



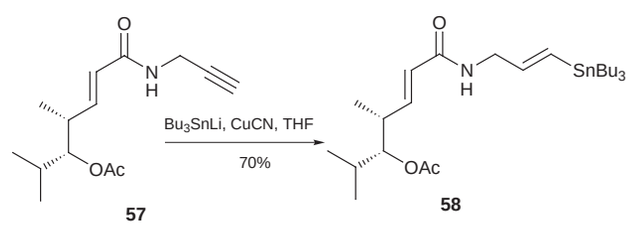
Scheme 9

Hydrostannylations of alk-1-ynes are also promoted by palladium-catalysis.[29] These reactions are more stereoselective than the aforementioned radical-initiated hydrostannylation approach, especially if a l-bromoalkyne is used instead of the free alkyne.[29,30] The reaction has been used to great effect in the preparation of some highly functionalised precursors for use in total synthesis. For example Smith *et al.*[31] have used the reaction to prepare the (*E*)-vinylstannane **54**, an advanced intermediate in their synthesis of rapamycin, and our own research group has used the reaction to convert the l-bromoalkyne **55** into the (*E*)-vinylstannane **56** (Scheme 10).[30]

The procedure of stannyl-metallation of alkynes has been shown to be a highly predictable and stereoselective method for the synthesis of vinylstannanes.[32] By appropriate choice of the stannyl-metallating agent, both (*E*)- and (*Z*)-alk-1-enylstannanes *and* alk-2-enylstannanes may be synthesised selectively by this method. An example of this reaction, to make alk-1-enylstannanes, can be found in our own studies towards a total synthesis of the virginiamycins, *i.e.* **57**→**58** (Scheme 11).[33] The combination of hydrozirconation of alkynes followed by transmetallation with Bu_3SnOEt can also be used to make (*E*)-alk-1-enyl stannanes from alk-1-ynes.[34] However the reaction has so far found little use in the synthesis of complex substrates, even though the method can be adapted to prepare allylstannanes.



Scheme 10

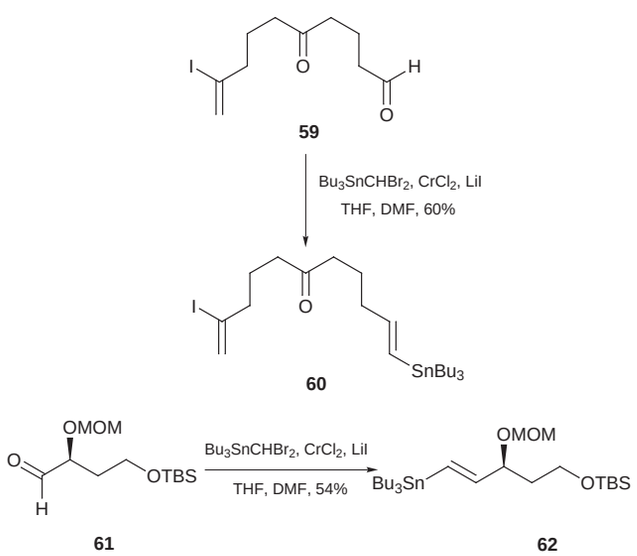


Scheme 11

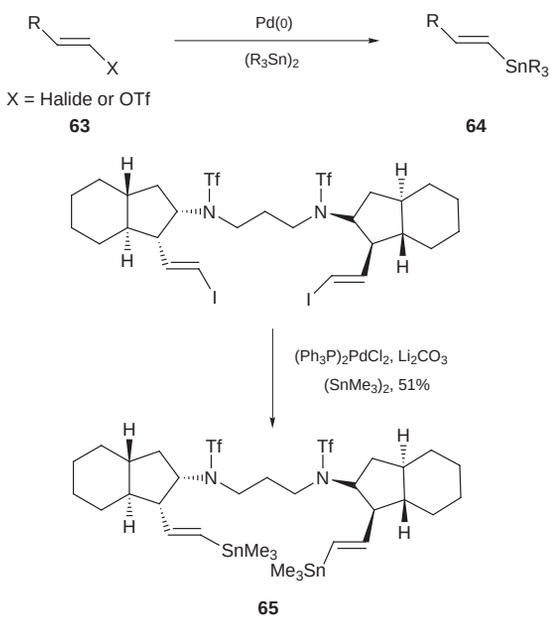
Hodgson *et al.* have reported a very mild and stereoselective method for the synthesis of alk-1-enylstannanes which is based on a modified Takai reaction between an aldehyde and $Bu_3SnCHBr_2$ in the presence of chromium(II) chloride.[35,36] The reaction tolerates ester, nitrile, ketone, ketal and ether functional groups amongst others, and the procedure has been used to good effect in natural product synthesis. For example, Hodgson *et al.*[37] have used the reaction to synthesise the precursor **60** from **59** in their approach to the germacrane carbon skeleton, and our own research group has used this procedure to produce the C_1 to C_9 fragment **62** of the polyene macrolide macrolactin A from **61** (Scheme 12).[38] The method can also be adapted to make the corresponding trimethylstannylalkenes.[39]

A very reliable method for the synthesis of (*E*)-alk-1-enylstannanes involves a Stille reaction between an appropriate precursor (such as a vinyl halide or vinyl triflate) and hexabutylditin or hexamethylditin *i.e.* **63**→**64** (Scheme 13).[40] This method has found numerous applications *en route* to naturally occurring substances. For example, Barrett *et al.*[41] used this reaction to prepare the advanced intermediate **65** in their synthesis of (+)-papuamine.

Similar to the case for (*Z*)-alk-1-enyl halides, there are fewer methods for making (*Z*)-alk-1-enylstannanes than their (*E*)-counterparts. However, the methods available for making (*Z*)-alk-1-enylstannanes are reliable and powerful processes. Thus, Corey *et al.*[42] have used the directed metal hydride reduction of a propargylic alcohol (prop-2-ynylic alcohol) followed by a transmetallation process to gain access to (*Z*)-vinylstannanes,



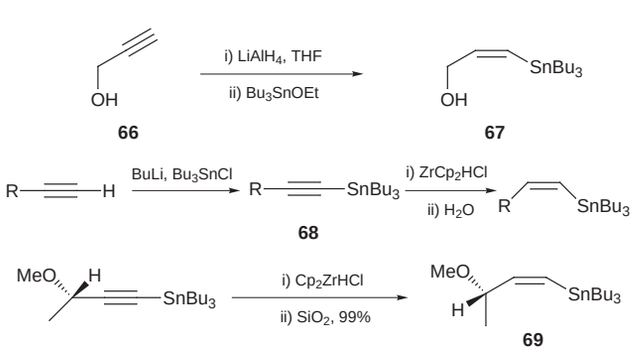
Scheme 12



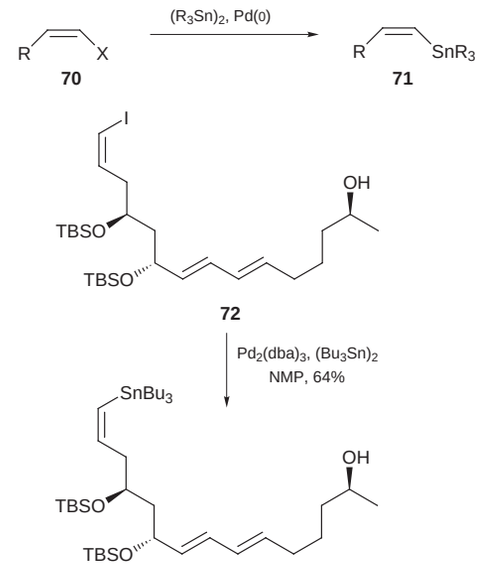
Scheme 13

viz. **66**→**67** (Scheme 14), and Lipshutz *et al.*[43] have disclosed a general synthesis involving the hydrometallation–protonation of a stannyl alkyne intermediate **68**, which is readily available from a terminal alkyne.[44] The latter procedure has been used to prepare the (*Z*)-vinylstannane **69**, as an intermediate in a projected synthesis of tetronasin.

Perhaps the most useful method for the synthesis of (*Z*)-alk-1-enylstannanes, however, uses the Stille coupling approach to transform an appropriate electrophile **70** into a vinylstannane **71** in the presence of hexabutylditin or hexamethylditin; an analogous approach can be used on some highly functionalised substrates (Scheme 15). For example, in their synthesis of (−)-macrolactin Smith *et al.*[45] have used this approach to prepare the (*Z*)-vinylstannane **73** from the (*Z*)-vinyl iodide **72**.



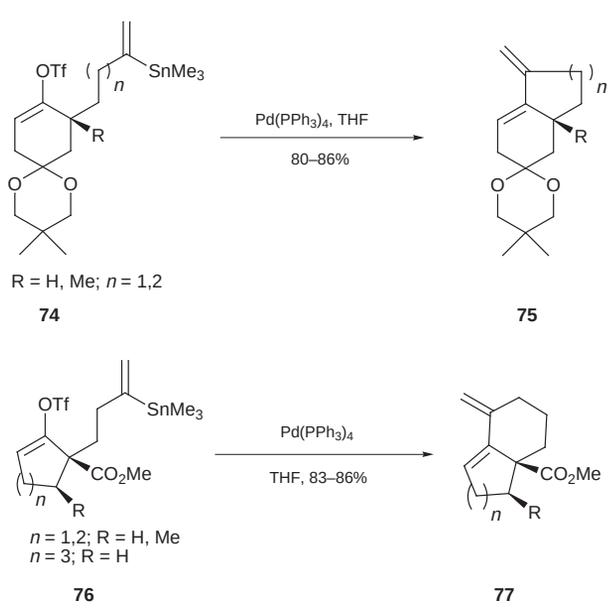
Scheme 14



Scheme 15

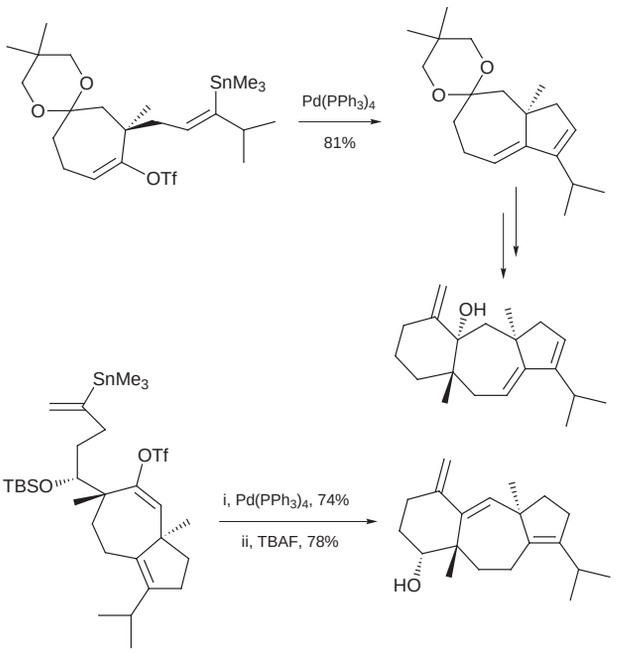
4 Synthesis of macrocarbocycles

Piers and co-workers described the first example of an intramolecular Stille reaction in 1985. In this initial report Piers *et al.*[46] described the use of an sp^2–sp^2 annulation strategy to synthesise diene-containing bicyclic systems from monocyclic precursors, *i.e.* **74**→**75**, **76**→**77** (Scheme 16). The excellent yields observed in these pioneering studies (*ca.* 70–90%) gave an early indication that the intramolecular Stille process could be exploited to prepare more structurally challenging substrates.[47,48] Thus, Piers and his co-workers extended their contributions in this area by using the intramolecular sp^2–sp^2 coupling reaction as a key step in a synthesis of the diterpenoids (+)-(5*S*,12*R*,14*S*)-dolasta-l(15),7,9-trien-14-ol [49] and



Scheme 16

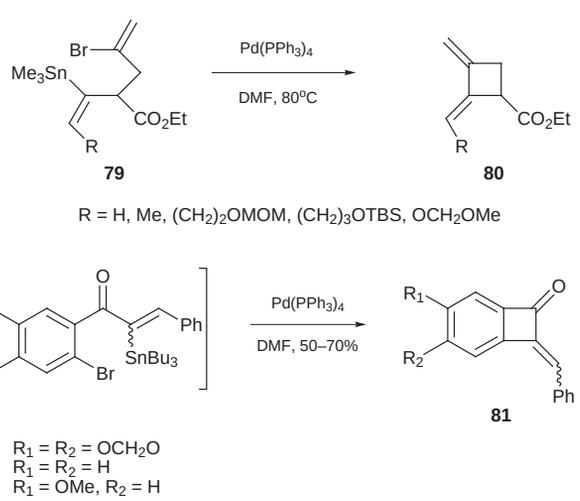
(±)-amijitrienol **78**.[50] The synthesis of (±)-amijitrienol was of particular note as two sp^2–sp^2 annulation sequences were utilised during the total synthesis (Scheme 17).



78

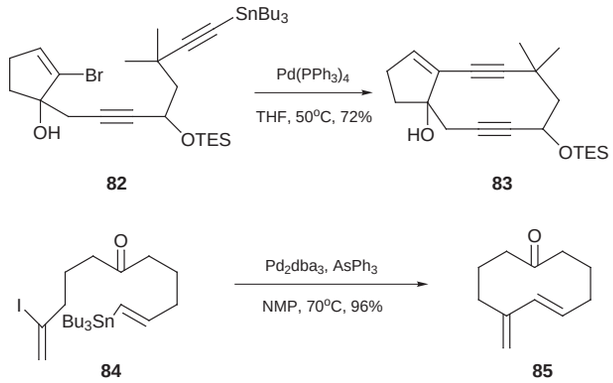
Scheme 17

Carbocycles that would be expected to contain a degree of ring-strain are also accessible by a Stille annulation technique. For example, Piers and Lu[51] have described a general method for the preparation of 2-alkylidene-3-methylenecyclobutanecarboxylates *via* an sp^2–sp^2 cyclisation, *e.g.* **79**→**80** (Scheme 18), and Bradley and Durst [52] have extended this method to prepare 2-benzylidenebenzocyclobutenones **81**.



Scheme 18

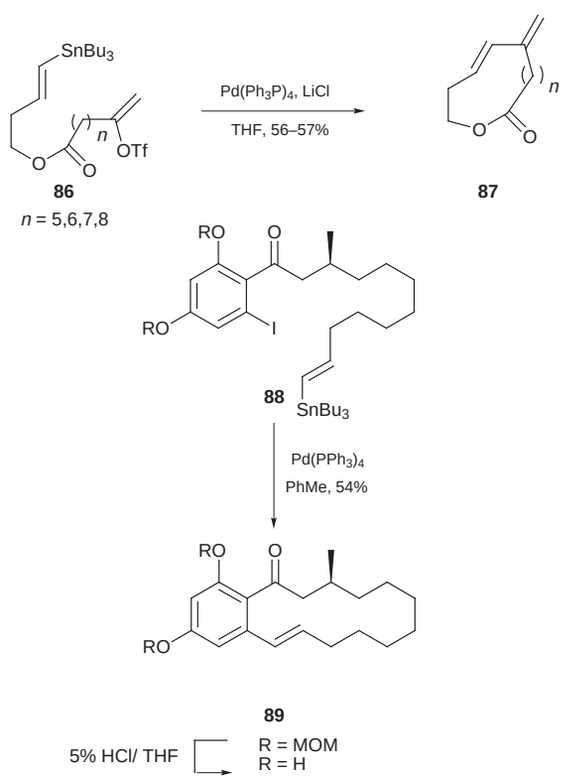
During their investigations towards the synthesis of novel 10-membered ring analogues of the neocarzinostatin chromophore, Hirama *et al.*[53] described the use of an sp–sp^2 intramolecular Stille coupling as a key step *en route* to a number of target enediyne structures, *e.g.* **82**→**83** (Scheme 19). More recently the intramolecular Stille reaction has been used to generate the carbon skeleton of the germacrane family of diterpenes, *i.e.* **84**→**85**.[37] The stunning yield obtained in this latter cyclisation was attributed to a templating effect of the palladium and a reduction in non-bonding transannular interactions arising from the presence of the ketone and alkene groups in the cyclisation precursor **84**.



Scheme 19

5 Macrolactones and macrolactams

New strategies for the construction of macrolactones and macrolactams are always of interest to complement the conventional methods based on straightforward macrolactonisation or macrolactamisation procedures. Since the Stille reaction is a very mild chemical process it appears to be an ideal method for use as a macrocyclisation technique. Fittingly, it was studies initiated by Stille *et al.* that first demonstrated the potential of this reaction for making macrolactones. Thus, the cyclisations of a number of esters containing both a vinyl triflate and a vinylstannane under palladium(0) catalysis and using a high dilution technique gave good yields of the corresponding macrolactone products, **86**→**87** (Scheme 20).[54] Of particular interest in these early studies was the observation that the chemical yield was insensitive to the ring-size of the macrolactone product **87**, even in the 12-membered example, which is a notoriously difficult ring size to prepare. In the aforementioned study Stille *et al.* postulated that the palladium catalyst could act as a template to bring the reacting termini in close proximity, thereby facilitating the macrocyclisation process. When cofunctionality is also present to aid this pre-organisation a very favourable arrangement for cyclisation could be created. Building upon their findings Stille *et al.* utilised this cyclisation as a

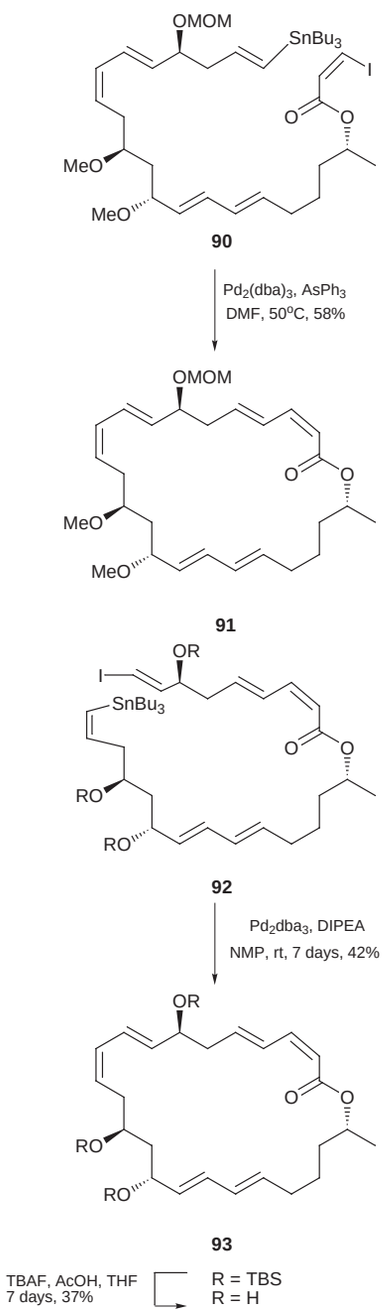


Scheme 20

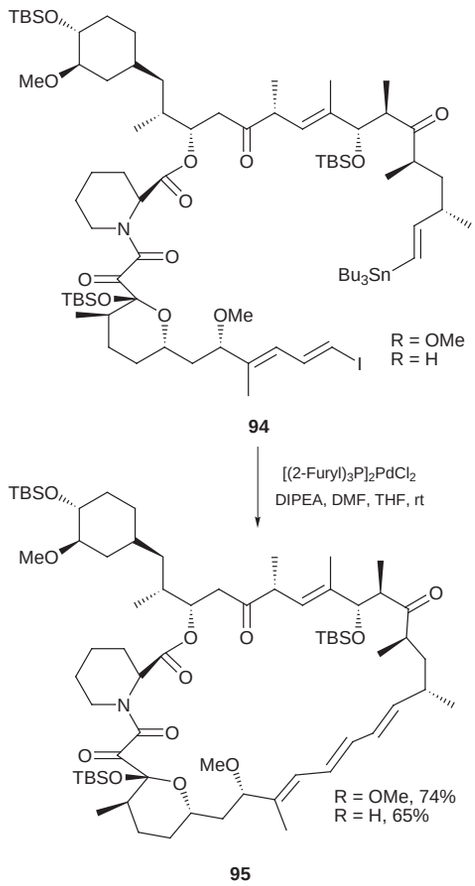
pivotal reaction in their synthesis of the important β-resorcylic macrolide, (*S*)-zearalenone **89** from **88**;[55] interestingly the best yield for this macrocyclisation step was obtained when the catalyst was introduced on a solid support.

Other studies have demonstrated the scope for the intramolecular sp^2–sp^2 Stille coupling reaction in the area of macrolide and macrolactam synthesis. For example, three approaches employing Stille coupling reactions have been used towards the antiviral macrolide macrolactin A. Our own research group was the first to describe an unprecedented series of sp^2–sp^2 palladium-catalysed coupling reactions culminating in the intramolecular sp^2–sp^2 Stille macrocyclisation **90**→**91** (Scheme 21) to generate the 24-membered ring of macrolactin A,[38] and in a complementary approach Smith *et al.*[56] described the corresponding sp^2–sp^2 macrocyclisation **92**→**93**; a similar approach to the synthesis of (−)-macrolactin A was later reported by Carreira *et al.*[57]

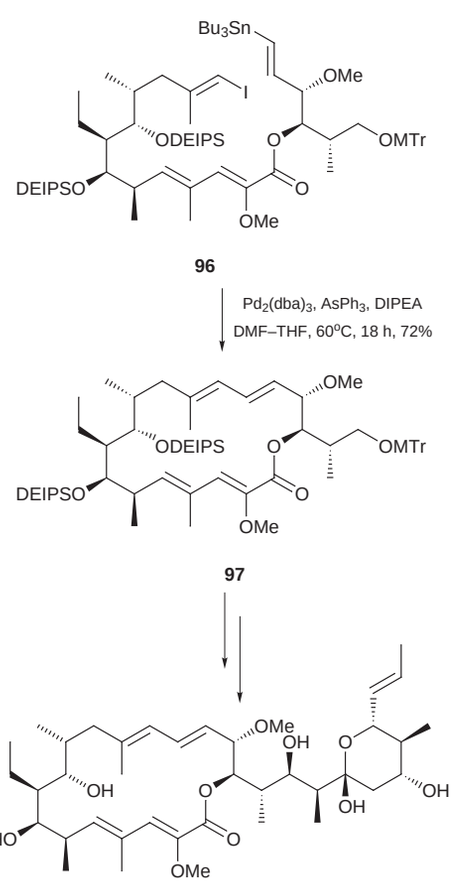
Smith *et al.*[58] have also used an sp^2–sp^2 Stille macrocyclisation approach to construct the 31-membered macrocycle of the immunosuppressants rapamycin and demethoxyrapamycin.



Scheme 21



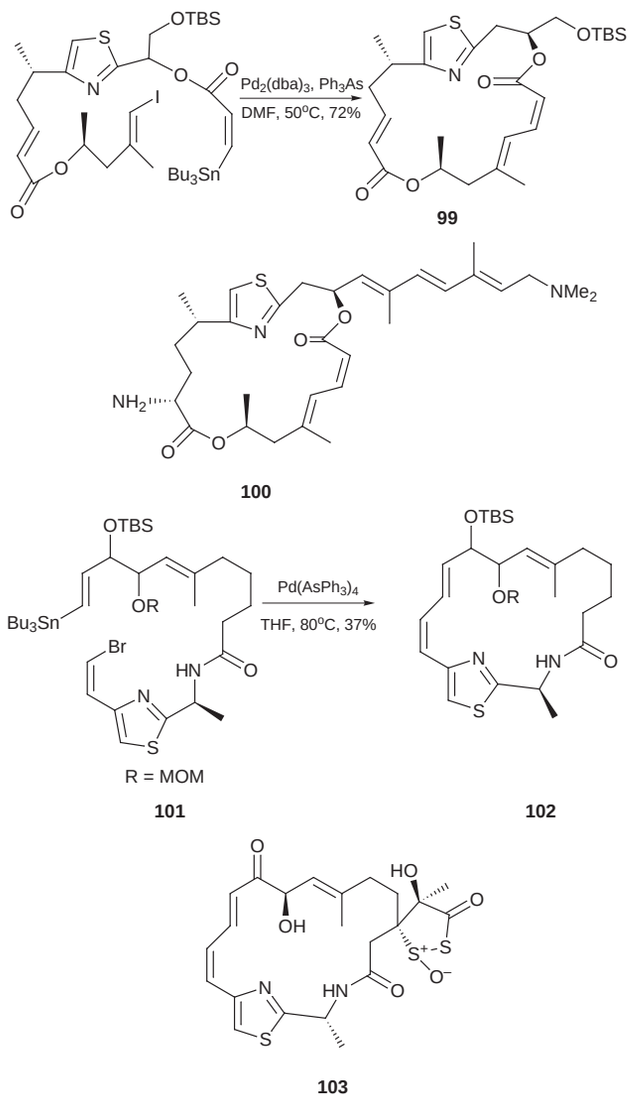
Scheme 22



Scheme 23

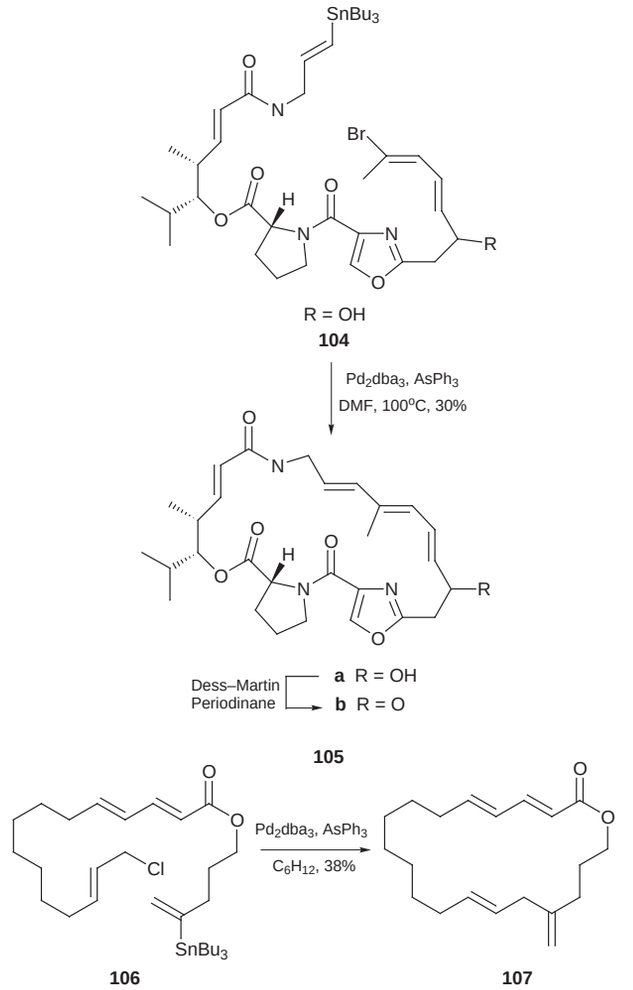
The yields obtained in these macrocyclisations, *e.g.* **94→95** (Scheme 22), are impressive considering the dense array of functionality present and the documented instability of rapamycin itself. In an equally impressive illustration of the use of the intramolecular Stille reaction in the synthesis of densely oxygen-functionalised macrolides, Toshima *et al.*[59] have described the cyclisation **96→97** in their total synthesis of concanolide A **98** (Scheme 23).

Our own research group has described other examples which demonstrate the scope for the intramolecular sp^2–sp^2 Stille reaction in synthesis. For example, we employed a Stille macrocyclisation to make the 19-membered bis-lactone core **99**, related to pateamine **100**, an antifungal agent isolated from the marine sponge *Mycale* sp,[60] and during our studies towards leinamycin **103**, we reported one of the earliest examples of a Stille macrocyclisation to make a model compound of this novel antitumour antibiotic (Scheme 24).[61] Of particular note in this latter study was the use of the catalytic system introduced by Farina *et al.*[17] to bring about the cyclisation of **101→102**; the more traditional catalytic system employing Ph_3P as a ligand for palladium failed to yield any of the desired macrocycle **102** in this instance.



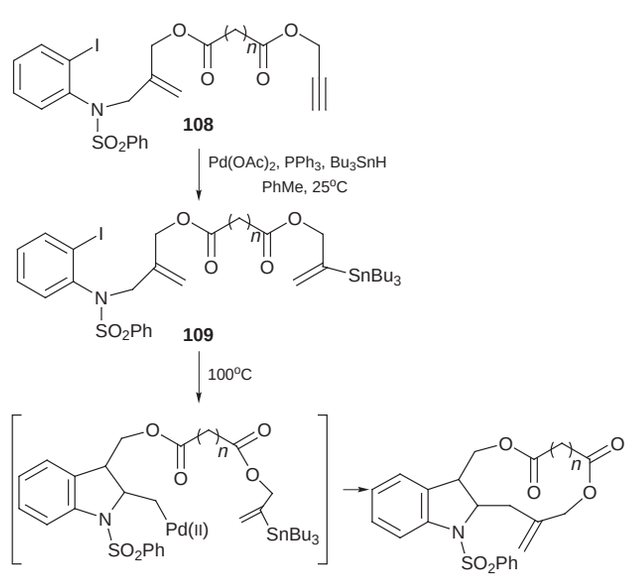
Scheme 24

A significant demonstration of the synthetic prowess of the intramolecular Stille coupling approach to polyenes was provided in our synthesis of 14,15-anhydropristinamycin II_B **105b** (Scheme 25) a member of the virginiamycin family of antibiotics. The twenty three membered ring system in these oxazole-containing macrolactams is notoriously difficult to construct. However, an intramolecular sp^2–sp^2 Stille coupling procedure, *viz.* **104→105** provided a novel entry into this important family of macrolactam.[33,62]



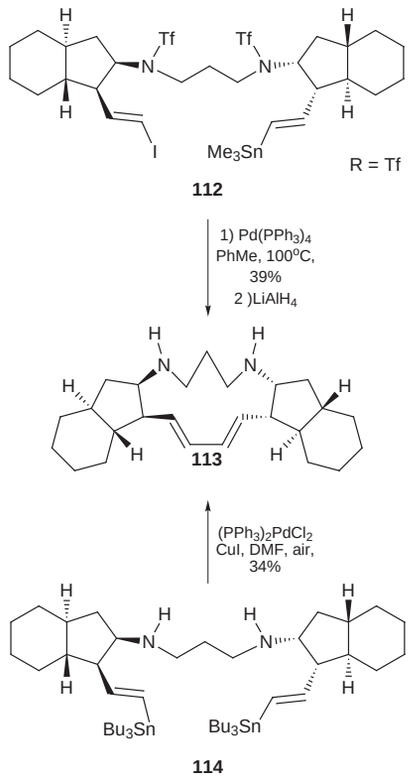
Scheme 25

Our research group has also extended the scope of the intramolecular Stille reaction to encompass cyclisations that utilise an sp^2–allylic sp^3 coupling reaction to form macrocyclic struc-



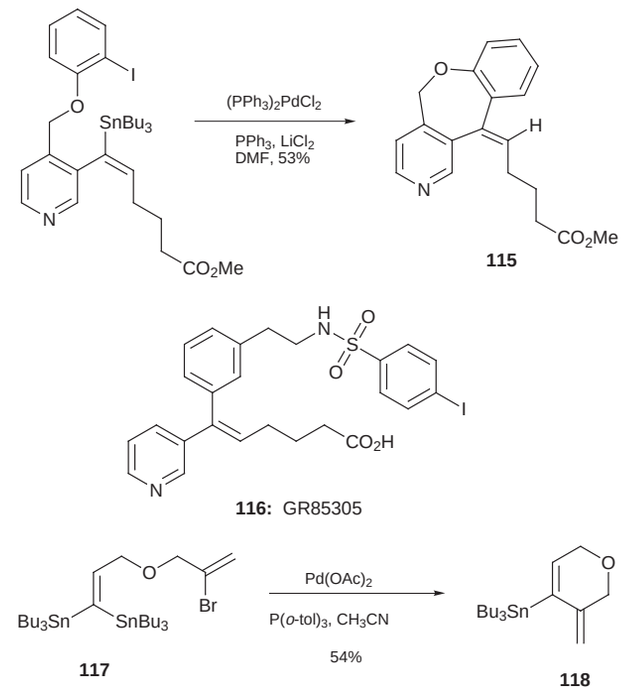
Scheme 26

tures incorporating a 1,4-diene subunit. Thus, we have used such an approach to prepare a model system of the unique polyene macrolide amphidinolide A, *i.e.* **106→107**.[63]

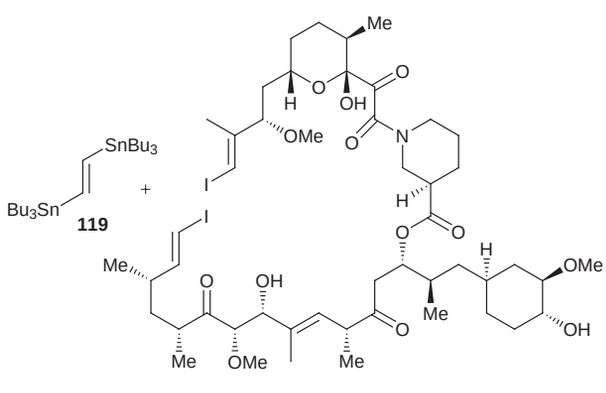


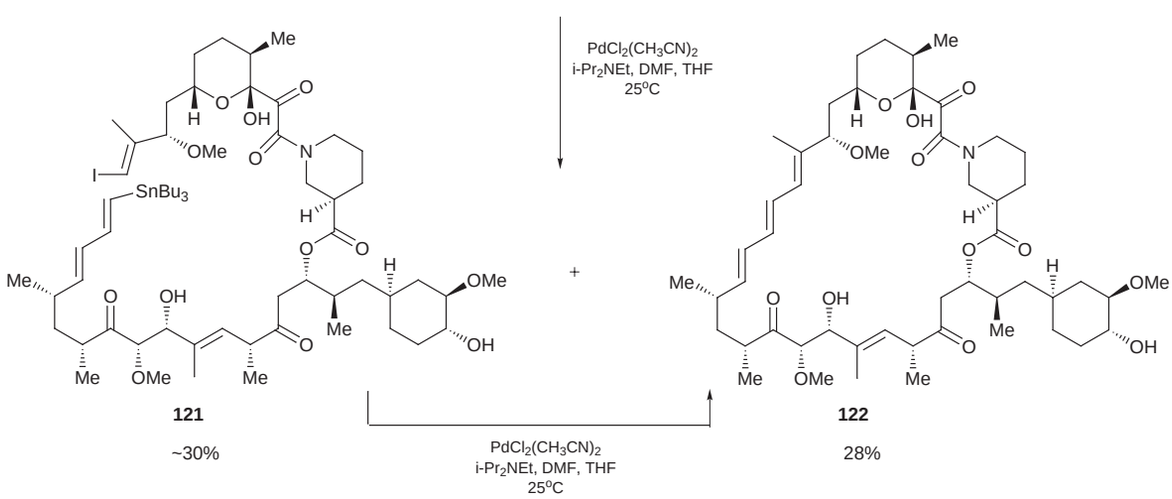
Scheme 27

Grigg *et al.*[64] have also described a variant of the intramolecular sp^2–sp^3 Stille coupling reaction to make macrocyclic species, whereby a vinylstannane acts as an internal nucleophile to terminate a palladium-catalysed cascade cyclisation–anion capture sequence; a representative example is shown by **108→109→110→111** (Scheme 26).



Scheme 28





Scheme 29

6 Macrocyclic amines and ethers

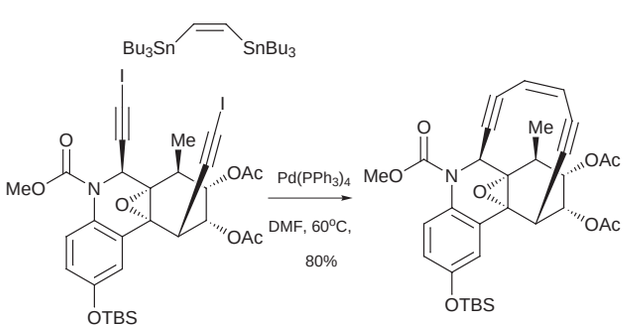
A strategy based on the intramolecular Stille reaction has been a fruitful approach *en route* to a number of natural and non-naturally occurring macrocyclic amines and ethers. Thus, Barrett *et al.*[41] have utilised an intramolecular sp^2–sp^2 Stille coupling in a synthesis of the C_2-symmetric antifungal agent (+)-papuamine **113** from **112** (Scheme 27), and an identical strategy has been used by Taber *et al.*[65] in their synthesis of (−)-haliclonadiamine, an unsymmetrical epimer of papuamine. As highlighted earlier, a side reaction sometimes encountered in the Stille coupling reaction is dimerisation (*i.e.* homo-coupling) of the organostannane coupling partner. An ingenious exploitation of this 'side reaction' has been described by Heathcock and co-workers[66] in their synthesis of (−)-papuamine and (−)-haliclonadiamine whereby treatment of the bis(vinylstannane) **114** with Pd(II) led to **113** in 34% yield; the modest yield of this cyclisation probably reflects the inherent strain present in the thirteen-membered diamine ring of **113**.

An intramolecular Stille reaction pathway has also been used to produce conformationally restrained analogues, *viz*. **115** (Scheme 28), of the thromboxane antagonist/synthase inhibitor GR85305 **116**,[67] and in a study of the reactivity of 1,1-bis-(trialkylstannyl) ethers, *i.e.* **117**→**118**.[68]

7 "Stitching" cyclisations

During their synthetic investigations towards the immunosuppressants rapamycin **122**, Nicolaou *et al.*[69] introduced the concept of the "stitching" cyclisation as a tool for making polyene macrocyclic structures. The basic idea behind a "stitching" cyclisation is that a (normally) short bifunctional reagent can be inserted in both an inter- and intramolecular fashion into an appropriately functionalised seco-precursor to produce a cyclic structure. The landmark studies reported by Nicolaou *et al.* used the ene distannane unit **119** as the bifunctional reagent in a breathtakingly bold stitching cyclisation reaction with the fully functionalised rapamycin precursor **120** (Scheme 29). The intermediate iodo-stannane **121** that was also produced along with rapamycin **122** under the reaction conditions could be isolated and converted into the desired natural product by subjection to the original reaction conditions.

Since the introduction of the "stitching" cyclisation concept, further descriptions of this approach towards the total syntheses of natural products have appeared. Thus, Danishefsky and co-workers[70] have described the formation of the 10-membered cyclic enediyne **123** (Scheme 30) which served as an advanced intermediate in a total synthesis of dynemicin A by an sp–sp^2 "stitching" annulation technique,[71] and Panek *et al.*[72] have disclosed a synthesis of (+)-mycotrienol and (+)-mycotrienin I **124** (Scheme 31) based on this general concept.

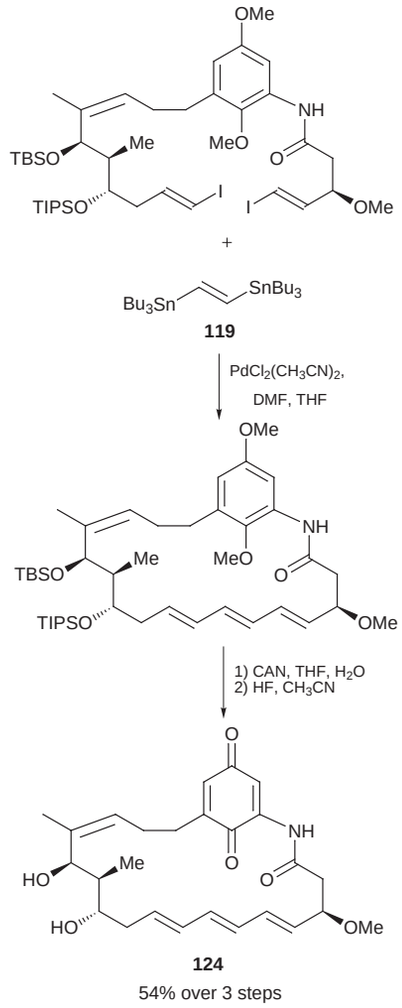


123

Scheme 30

8 Macrocyclisation with carbonyl insertion

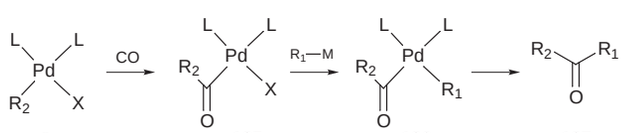
An important facet of palladium chemistry is the ability of an



Scheme 31

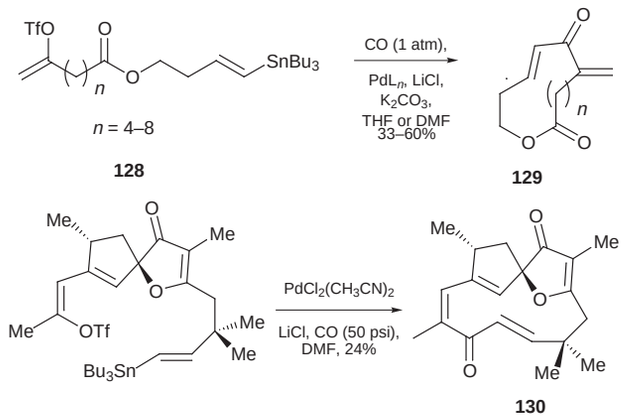
organopalladium(II) species, *e.g.* **6**, to undergo a carbonyl insertion reaction with carbon monoxide to give an acyl palladium(II) intermediate **125** (Scheme 32). Under a moderate pressure of carbon monoxide (1–3 atm) the equilibrium in this reaction lies heavily to the right. The acylpalladium(II) intermediate **125** shows the normal behaviour expected of palladium(II) compounds and reacts with organometallic compounds by the usual route of transmetallation and reductive elimination to give cross-coupled products, *i.e.* **126**. Since carbonyl insertion into palladium(II) compounds such as **125** is faster than any competing transmetallation process, a cross-coupling reaction performed under an atmosphere of carbon monoxide will yield a ketone **126** as the product. This observation has found extensive use in contemporary organic synthesis, and the reaction has also been utilised in an intramolecular fashion. Thus, Stille, Hegedus and co-workers[73] have used such a process to synthesise 12–16-membered cyclic keto-lactones, *i.e.* **128**→**129** (Scheme 33). Stille and Hegedus also utilised a cross-coupling reaction incorporating a carbonyl insertion in their total synthesis of (±)-jatrophone **130**, a macrocyclic diterpene which exhibits *in vivo* activity against various carcinomas.[74]

A complementary approach using an intramolecular Stille coupling to synthesise ketone-containing cyclic structures has



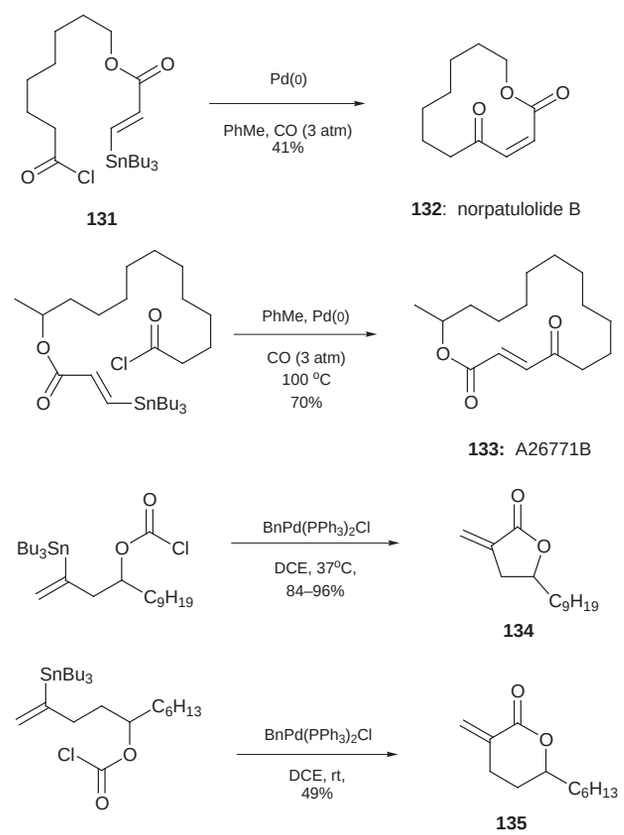
6 **125** **126** **127**

Scheme 32



Scheme 33

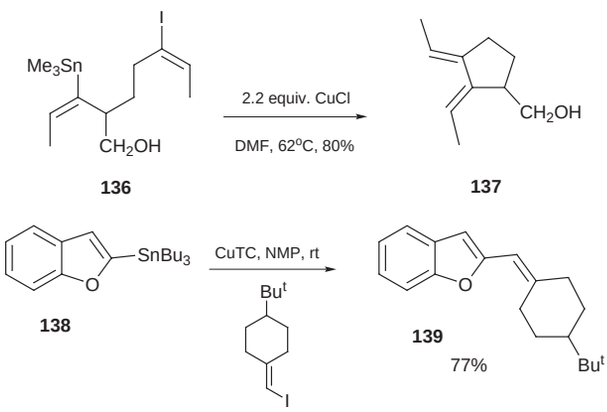
also been reported by Baldwin *et al.*[75] In this approach an acid chloride **131** is used as a precursor to an acylpalladium(II) intermediate (Scheme 34) which is then trapped by an internal organometallic nucleophile (this is an intramolecular version of the original palladium(0)-mediated cross-coupling reaction reported by Stille *et al*). Baldwin and co-workers have used this approach to prepare macrocyclic ketones, including those found in the antibiotic A26771B **133** and norpatulolide B **132**[76] and in the synthesis of small ring α-methylene lactones, *e.g.* **134** and **135**.[77]



Scheme 34

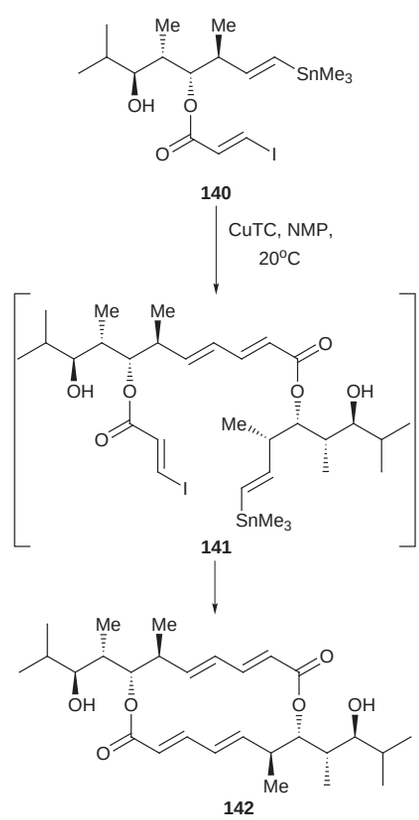
9 Future developments

Since its discovery the Stille coupling reaction has attracted considerable interest from the research community. This interest has resulted in new palladium catalysts being developed for the coupling reaction that can bring about carbon–carbon bond formation under even milder conditions than those originally reported by Stille and co-workers.[6] In addition, a number of inorganic additives have been found to increase the rate of Stille coupling reactions. Of particular note is the use of copper(I) salts.[6] The study of copper-promoted Stille reactions has resulted in a number of significant new developments in the field of cross-coupling reactions. One of the most important discoveries, reported by Piers and Wong,[78] has described the use of copper(I) chloride to effect an intramolecular cyclisation of a precursor, *e.g.* **136**→**137**, in the *absence* of any palladium catalyst (Scheme 35). This discovery has led to the rapid introduction of other copper(I) salts, such as copper(I) thiophene-2-carboxylate (CuTC) which can promote intermolecular Stille-type coupling reactions between a vinylstannane and vinyl halide in the absence of a palladium catalyst, *e.g.* **138**→**139**.[79]



Scheme 35

The potential for these new discoveries in the area of total synthesis has been recognised by Paterson and Man[80] who have reported a copper(I)-mediated cyclodimerisation process to make the model ring system **142** of elaiophylin (Scheme 36). Thus, exposure of the precursor **140** to ten equivalents of CuTC at room temperature gave an excellent yield (70%) of the dimer **142** *via* the intermediate **141**. These copper(I)-promoted



Scheme 36

Stille-type reactions appear to tolerate the same range of functionality as the more traditional palladium variant. In addition, the rapid nature and mild reaction conditions may mean that particularly sensitive structures may be more amenable to this newly developed reaction.

10 References

1 D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1978, **100**, 3636.
2 D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1979, **101**, 4992.
3 For a review see J. K. Stille, *Angew Chem., Int. Ed. Engl.*, 1986, **25**, 508. See also V. Farina, V. Krishnamurphy and W. J. Scott, *Organic Reactions*, **50**, 1997, John Wiley & Sons, New York, and references therein.
4 For other contemporaneous metal-catalysed coupling reactions see: E. Negishi, A. O. King and N. Okukado, *J. Org Chem.*, 1977, **42**, 1821 and references cited therein.
5 *Metal-catalysed Cross-coupling Reactions*, ed. F. Diederich and P. J. Stang, Wiley-VCH, 1998. For organomagnesium coupling see M. Kumada, *Pure Appl. Chem.*, 1980, **52**, 669. For organozinc coupling see E. Erdik, *Tetrahedron*, 1992, **48**, 9577. For organoborane coupling (Suzuki reaction) see N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457 and references cited therein. For organosilane coupling see Y. Hatanaka and T. Hiyama, *Synlett*, 1991, 845.
6 For an excellent discussion of *New perspectives in the cross-coupling reactions of organostannanes*, see V. Farina, *Pure Appl. Chem.*, 1996, **68**, 73, and references therein.
7 For reviews of the Heck reaction see: A. de Meijere and F. E. Meyer, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **33**, 2379; S. E. Gibson and R. J. Middleton, *Contemp. Org. Synth.*, 1996, **3**, 447 and references therein.
8 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.
9 A. S. Kende, K. Koch, G. Dorey, I. Kaldor and K. Liu*, J. Am. Chem. Soc.*, 1993, **115**, 9842.
10 M. B. Andrus, S. D. Lepore and T. M. Turner, *J. Am. Chem. Soc.*, 1997, **119**, 12159.
11 For carbometallation/halide quench see: T. Jyojima, M. Katohno, N. Miyamoto, M. Nakata, S. Matsumara and K. Toshimo, *Tetrahedron Lett.*, 1993, **39**, 6003, and references cited therein.
12 J. Schwartz and J. A. Labinger, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 333. For the *in situ* generation of Schwartz's reagent see B. H. Lipshutz, R. Keil and E. L. Ellsworth, *Tetrahedron Lett.*, 1990, **31**, 7257.
13 K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty and N. Minowa*, J. Chem. Soc.*, *Chem. Commun.*, 1993, 619.
14 M. Treilhou, A. Fauve, J.-R. Pougny, J.-C. Promé and H. Veschambre, *J. Org. Chem.*, 1992, **57**, 3203.
15 D. J. Critcher, S. Connolly and M. Wills, *Tetrahedron Lett.*, 1995, **36**, 3763.
16 B. H. Lipshutz, C. Lindsley and A. Bhandari, *Tetrahedron Lett.*, 1994, **35**, 4669.
17 V. Farina, S. R. Baker, D. A. Benigni, S. I. Hauck and C. Sapino, *J. Org. Chem.*, 1990, **55**, 5833.
18 M. Belén Cid and G. Pattenden, *Synlett*, 1998, 540.
19 S. K. Steward and A. Whiting, *Tetrahedron Lett.*, 1995, **36**, 3929.
20 G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 2173.
21 X. Zhang, and M. Schlosser, *Tetrahedron Lett.*, 1993, **34**, 1925.
22 A. S. Kende, K. Kawamura and R. J. DeVita, *J. Am. Chem. Soc.*, 1990, **112**, 4070.
23 K. C. Nicolaou, B. E. Marron, C. A. Veale, S. E. Webber and C. N. Serhan, *J. Org. Chem.*, 1989, **54**, 5527.
24 Y. Masuda, M. Hoshi and A. Arase, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 3294.
25 P. W. Collins, A. F. Gasiecki, W. E. Perkins, G. W. Gullikson, R. G. Bianchi, S. W. Kramer, J. S. Ng, E. E. Yonan, L. Swenton, P. H. Jones and R. F. Bauer *J. Med. Chem.*, 1990, **33**, 2784.
26 M. M. Goodman, M.-P. Kung, G. W. Kabalka, H. F. Kung and R. Switzer, *J. Med. Chem.*, 1994, **37**, 1535.
27 J. P. Férézou, M. Julia, Y. Li, L. W. Liu and A. Pancrazi, *Synlett*, 1991, 53.
28 H. Ali, J. Rousseau, M. A. Ghaffari and J. E. van Lier, *J. Med. Chem.*, 1991, **34**, 854.
29 H. X. Zhang, F. Guibé and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857.
30 C. D. J. Boden, G. Pattenden and T. Ye, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2417.
31 A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy and R. E. Maleczka, *J. Am. Chem. Soc.*, 1995, **117**, 5407.
32 S. Sharma and A. C. Oehlschlager, *J. Org. Chem.*, 1989, **54**, 5064 and references cited therein.
33 D. A. Entwistle, S. I. Jordan, J. Montgomery and G. Pattenden, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1315.
34 S. Kim and K. H. Kim, *Tetrahedron Lett.*, 1995, **36**, 3725.
35 D. M. Hodgson, *Tetrahedron Lett.*, 1992, **33**, 5603.
36 D. M. Hodgson, L. T. Boulton and G. N. Maw, *Tetrahedron Lett.*, 1994, **35**, 2231.
37 D. M. Hodgson, L. T. Boulton and G. N. Maw, *Synlett*, 1995, 267.
38 R. J. Boyce and G. Pattenden, *Tetrahedron Lett.*, 1996, **37**, 3501.
39 M. D. Cliff and S. G. Pyne, *Tetrahedron Lett.*, 1995, **36**, 763.
40 W. D. Wulff, G. A. Peterson, W. E. Bauta, K.-S. Chan, K. L. Faron, S. R. Gilbertson, R. W. Kaesler, D. C. Yang and C. K. Murray, *J. Org. Chem.*, 1986, **51**, 277.
41 A. G. M. Barrett, M. L. Boys and T. L. Boehm, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 1881.
42 E. J. Corey and T. M. Eckrich, *Tetrahedron Lett.*, 1984, **25**, 2419.
43 B. H. Lipshutz and R. Keil, *Inorg. Chim. Acta*, 1994, **220**, 41.
44 B. H. Lipshutz, R. Keil and J. C. Barton, *Tetrahedron Lett.*, 1992, **33**, 5861.
45 A. B. Smith, and G. R. Ott, *J. Am. Chem. Soc.*, 1996, **118**, 13095.
46 E. Piers, R. W. Friesen and B. A. Keay, *J. Chem. Soc.*, *Chem. Commun.*, 1985, 809.
47 E. Piers, R. W. Friesen and B. A. Keay, *Tetrahedron*, 1991, **47**, 4555.
48 E. Piers, R. W. Friesen and S. J. Rettig, *Can. J. Chem.*, 1992, **70**, 1385.
49 E. Piers and R. W. Friesen, *J. Org. Chem.*, 1986, **51**, 3405.
50 E. Piers and R. W. Friesen, *Can. J. Chem.*, 1992, **70**, 1204.
51 E. Piers and Y.-F. Lu, *J. Org. Chem.*, 1988, **53**, 926.
52 J. C. Bradley and T. Durst, *J. Org. Chem.*, 1991, **56**, 5459.
53 M. Hirama, K. Fujiwara, K. Shigematu and Y. Fukazawa, *J. Am. Chem. Soc.*, 1989, **111**, 4120.
54 J. K. Stille and M. Tanaka, *J. Am. Chem. Soc.*, 1987, **109**, 3785.
55 A. Kalivretenos, J. K. Stille and L. S. Hegedus, *J. Org. Chem.*, 1991, **56**, 2883.
56 A. B. Smith III and G. R. Ott, *J. Am. Chem. Soc.*, 1998, **120**, 3935.
57 Y. Kim, R. A. Singer and E. M. Carreira, *Angew. Chem. Int. Ed.*, 1998, **37**, 1261.
58 A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy and R. E. Maleczka, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 5407.
59 T. Jyojima, N. Miyamoto, M. Katohno, M. Nakata, S. Matsumura, K. Toshima, *Tetrahedron Lett.*, 1998, **39**, 6007.
60 D. J. Critcher and G. Pattenden, *Tetrahedron Lett.*, 1996, **37**, 9107.
61 G. Pattenden and S. M. Thom, *Synlett*, 1993, 215.
62 D. A. Entwistle, S. I. Jordan, J. Montgomery and G. Pattenden, *Synthesis*, 1998, 603.
63 C. Boden and G. Pattenden, *Synlett*, 1994, 181.
64 A. Casaschi, R. Grigg, J. M. Sansano, D. Wilson and J. Redpath, *Tetrahedron Lett.*, 1996, **37**, 4413.
65 D. F. Taber and Y. Wang, *J. Am. Chem. Soc.*, 1997, **119**, 22.
66 T. S. McDermott, A. A. Mortlock and C. H. Heathcock, *J. Org. Chem.*, 1996, **61**, 700.
67 H. Finch, N. A. Pegg and B. Evans, *Tetrahedron Lett.*, 1993, **34**, 8353.
68 P. Quayle, J. Wang and J. Xu, *Tetrahedron Lett.*, 1998, **39**, 485.
69 K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa and P. Bertinato, *J. Am. Chem. Soc.*, 1993, **115**, 4419.
70 M. D. Shair, T. Yoon and S. J. Danishefsky, *J. Org. Chem.*, 1994, **59**, 3755; M. D. Shair, T. Yoon, and S. J. Danishefsky, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 1721.
71 For a similar approach to the 9-membered enediyne unit in neocarzinostatin chromophore see: H. Tanaka, H. Yamada, A. Matsuda and T. Takahashi, *Synlett*, 1997, 381.
72 J. S. Panek and C. E. Masse, *J. Org. Chem.*, 1997, **62**, 8290; C. E. Masse, M. Yang, J. Solomon and J. S. Panek, *J. Am. Chem. Soc.*, 1998, **120**, 4123.
73 J. K. Stille, H. Su, D. H. Hill, P. Schneider, M. Tanaka, D. L. Morrison and L. S. Hegedus, *Organometallics*, 1991, **10**, 1993.
74 A. C. Gyorkos, J. K. Stille and L. S. Hegedus, *J. Am. Chem. Soc.*, 1990, **112**, 8465.
75 J. E. Baldwin, R. M. Adlington and S. H. Ramcharitar, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 940.
76 J. E. Baldwin, R. M. Adlington and S. H. Ramcharitar, *Tetrahedron Lett.*, 1992, **48**, 2957.
77 R. M. Adlington, J. E. Baldwin, A. Gansäuer, W. McCoull and A. T. Russell, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 1697.
78 E. Piers and T. Wong, *J. Org. Chem.*, 1993, **58**, 3609.
79 G. D. Allred and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1996, **118**, 2748.
80 I. Paterson and J. Man, *Tetrahedron Lett.*, 1997, **38**, 695; *cf*. B. W. Dymock, P. J. Kocienski and J.-M. Pons, *Synthesis*, 1998, 1655.

Review 8/08261H