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cine Substitution and the Cu Effect in Stille Cross-Coupling Reactions: Mechanistic Perspectives and Synthetic Utility

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cine Substitution arising from slow transmetallation occasionally occurs in classic Pd-catalyzed Stille cross-coupling reactions with sterically hindered vinyltin components. Mechanistic explanations of this "abnormal" cross-coupling mode and the intriguing co-catalytic effects of metallic Cu species in restoring the *ipso* selectivity are summarized. Typical synthetic applications of this unique Cu effect and the advent of Cu-catalyzed Stille-type cross-coupling are also demonstrated.

1. Introduction

The palladium-catalyzed cross-coupling reaction between an organic electrophile and a vinylstannane is known as the Stille reaction,[1] after the late Professor J. K. Stille, who pioneered and subsequently developed this reaction. The Stille reaction remains one of the most widely applied palladium-catalyzed C–C bond-forming reactions, in large part due to its mild conditions, the ease of preparation of wide range of coupling partners, and its tolerance of a wide variety of sensitive functionalities.[2] The many ingenious applications of Stille couplings in total synthesis bear testament to the faith placed in the robustness of this reaction by practitioners of this art.[3]

Mechanistic investigation of the Stille reaction has continued since its discovery.[4] The traditional oxidative addition, transmetallation, and reductive elimination, prevalent in transition-metal-catalyzed C–C bond-forming reactions, has been widely accepted. With sterically hindered vinyltin coupling components, a series of side reactions occur, among which *cine* substitution[5] resulting from slow transmetallation frequently predominates (Scheme 1). This unusual phenomenon also appears in other substitution reactions and has been reviewed recently by Suwiński and coworker.[5]

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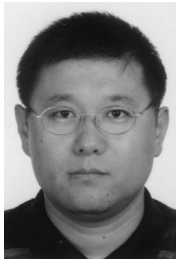

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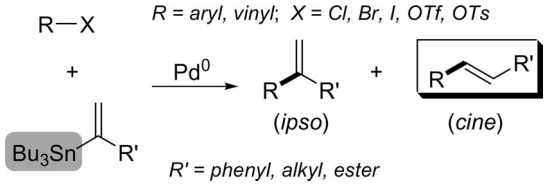


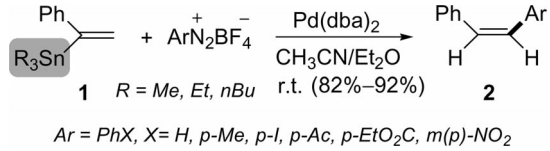
Scheme 1. *ipso* vs. *cine* Substitution in Stille reactions with sterically hindered vinyltins.

In this microreview we focus on mechanistic explanations of *cine* substitution in Stille cross-coupling reactions and the intriguing co-catalytic Cu effect that often suppresses it or even remarkably restores the *ipso* selectivity. The synthetic utility of this dramatic Cu effect in cross-coupling is demonstrated with selected examples.

2. *cine* Substitution in Stille Couplings

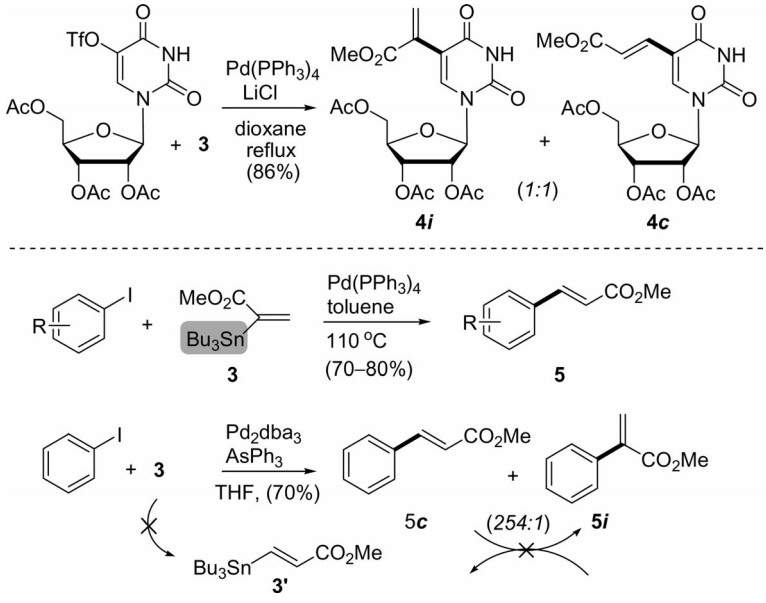
2.1. *cine* Substitution

In 1986, Kikukawa found that the reactions between the trialkyl-(α-styryl)-stannanes **1** and ArN_2BF_4 did not give α-arylated styrenes as expected but selectively produced the (*Z*)-stilbenes **2** in high yields (Scheme 2).[6] This abnormal *cine* substitution occurred in the Stille reactions of sterically hindered stannanes (here the α-substituted vinyltins **1**) and was attributed to slow transmetallation. Bulky substituents on tin give better stereoselectivity. Because excesses of diazonium salts caused considerable isomerization of (*Z*)-**2**, 5–10% excesses of **1** to ArN_2BF_4 should be used. H-Pd species might play a crucial role, because this isomerization does not take place in the absence of the palladium catalyst (see Scheme 10).



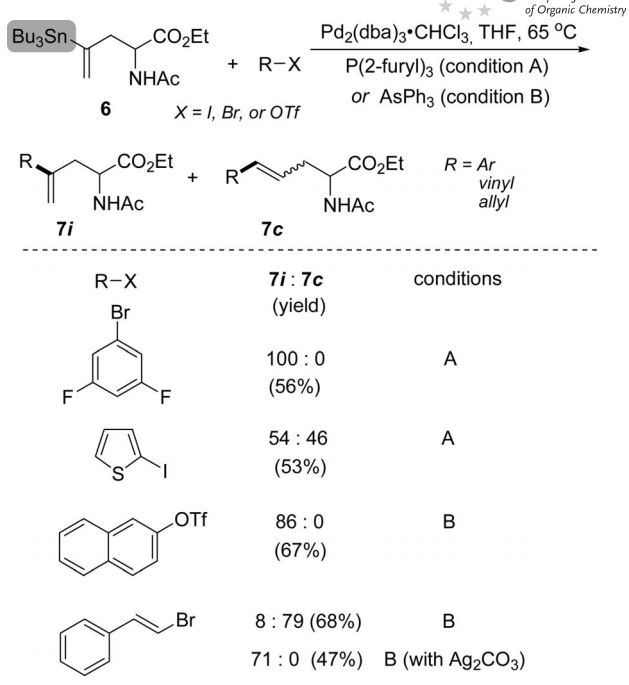
Scheme 2. The first observed *cine* substitution in the Stille reaction.

Flynn et al. developed palladium-catalyzed coupling reactions as a general route to important 5-substituted uridine compounds. Specially, when methyl α-(tributylstannyl)-acrylate (**3**) is utilized for the Stille coupling with triacetate uridine triflate, both the expected product **4*i*** and the *cine* substituted product **4*c*** were obtained in almost 1:1 ratio (Scheme 3).[7a] It is noteworthy that the coupling of 2-(trimethylstannyl)propene, in place of **3**, with triacetate uridine triflate proceeded smoothly and gave a good yield of the desired *ipso*-substituted product. The difference between an electron-withdrawing group (CO_2Me) and an electron-donating group (–Me) attached to the stannane is responsible for the observed regioselectivity. Later, Levin's attempts to couple **3** with substituted aryl iodides under standard Stille conditions resulted exclusively in the formation of the undesired cinnamates **5**,[7b] which was also observed under slightly different conditions [$Pd_2(dba)_3$, $AsPh_3$, THF] by Busacca.[7c] On the basis of the widely accepted Stille mechanism, methyl cinnamate (**5*c***) would be the expected product of coupling of methyl β-(tributylstannyl)acrylate and iodobenzene as shown, so a palladium-catalyzed rearrangement of the α-stannane **3** to the β-isomer **3′** must take place. However, prolonged exposure of **3** to these the reaction conditions does not lead to any rearranged product **3′**. Interconversions of the two products **5*c*** and **5*i*** were also considered by these authors. Treatment of each of the two pure materials under the same conditions, however, led to no isomerization.



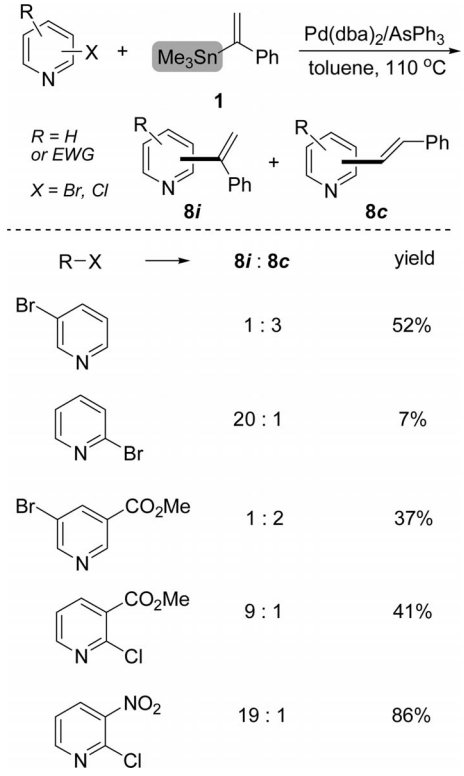
Scheme 3. *cine* Substitution of methyl α-(tributylstannyl)acrylate (**3**).

Treatment of the (tributylstannyl)allylglycine derivative **6** (Scheme 4) with various unsaturated halides or pseudohalides with catalysis by Pd^0 provided an alternative means of access to elaboration of the side chains of non-proteinogenic α-amino acids.[8a] However, after considerable experimentation (variation of Pd^0 source, ligand, additive, and solvents), there were always some *cine* substitution products **7*c*** as *E*/*Z* mixtures together with the desired *ipso* substitution products **7*i***, a situation also encountered in Kazmaier's similar work.[8b] It is interesting to note the effect that the electron densities on the aryl groups have on the *ipso*/*cine* ratios of the Stille reactions. The most electron-deficient – 3,5-difluorobromobenzene – gave no *cine* substitution product, whereas the most electron rich – 2-iodothiophene – gave an almost 1:1 ratio in 53% overall yield. If transmetallation is considered an electrophilic substitution reaction it would be expected to occur more rapidly for more electron-deficient Pd^{II} complexes. Thus, for relatively π-electron-rich Pd^{II} complexes produced by oxidative addition of 2-iodothiophene to Pd^0, transmetallation would occur relatively slowly because of the decreased electrophilicity of Pd^{II} and so a competing *cine* substitution process can become more dominant. The Stille coupling of 2-naphthyl triflate with **6** gave exclusively the *ipso* substitution product only in the absence of LiCl; this is the first example of a Stille reaction of an aryl triflate occurring without the necessity for a halide source. In the case of (*E*)-β-bromostyrene, *cine* substitution took place predominantly under the typical conditions. However, a switch in the regioselectivity can be achieved in the presence of Ag_2CO_3 as a halide abstractor, which is attributed to more electrophilic cationic intermediates and more efficient transmetallation. The above experiments confirm that halide bound to Pd^{II} is an important prerequisite for *cine* substitution.



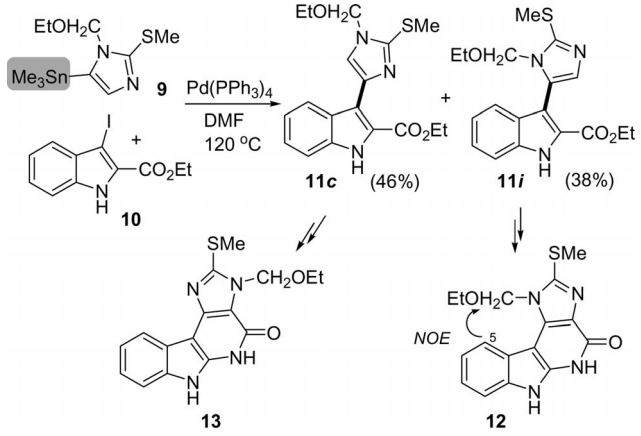
Scheme 4. *cine* Substitution in the elaboration of side chains of α-amino acids.

On studying the Stille vinylation of halopyridines with (α-styryl)trimethyltin (**1**, Scheme 5), Chen found that the product (**8*c*** and **8*i***) ratio (*cine*/*ipso*) varied a lot, mainly depending on the position of the halogen atom and the nature of the substituent R on the pyridine ring.[9a] When a halogen atom was located *ortho* to the nitrogen atom, *ipso* substitution products **8*i*** predominated whether or not additional electron-withdrawing groups (EWGs) were present. Subjection of *m*-halopyridines to identical conditions, however, resulted in *ipso*/*cine* mixtures, with *cine* substitution favored. *ortho* Substituent EWGs and the pyridine ring N atom can thus exert more profound effects than their *meta* substituent counterparts. When 4-bromopyridine was used as the substrate, no cross-coupling product was detected.



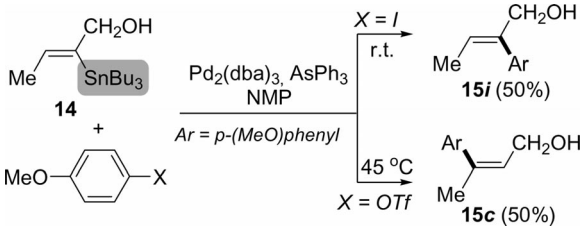
Scheme 5. Influence of the position of the halogen atom and the electronic effects of the R substituent on *ipso*/*cine* ratios.

Another example in a heterocyclic system is the reaction between the 5-trimethylstannylimidazole **9** and the 3-iodoindole **10** (Scheme 6).[9b] During studies directed towards the total synthesis of grossularines, Hibino and co-workers required the 3-imidazoleindole **11*i*** for the synthesis of the key tetracyclic α-carboline framework. However, substantial amounts of the *cine* substitution product **11*c*** were also obtained together with **11*i***, and the two coupling products showed similar spectra data. For the determination of the structures of **11*i*** and **11*c*** they were independently converted into α-carbolines through several steps. In NOE experiments, irradiation of H-5 of **12** caused NOE enhancement (8.0%) of the methylene group, which could not be observed in the case of **13**.



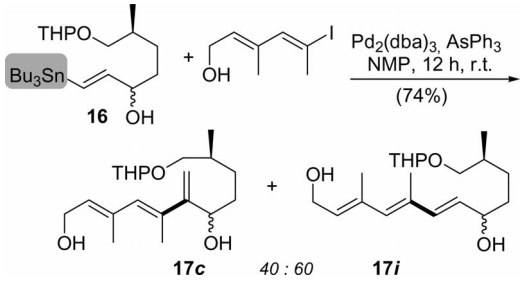
Scheme 6. The first example of *cine* substitution with a heteroarylstannane.

Interestingly, Flohr reported another example of electronic effects influencing the coupling of the sterically hindered stannane **14** (Scheme 7).[10] Control experiments demonstrated that the use of triflates and elevated temperature resulted exclusively in the *cine* substitution product **15*c*** whereas very low ligand-to-palladium ratios (1.5:1), especially with weak ligands and iodides as electrophiles, allowed the *ipso* substitution product **15*i*** to be obtained as the major product.



Scheme 7. Regiodivergent synthesis of (*Z*)-argiobut-2-en-1-ol by tuning of the electronic effects of electrophiles.

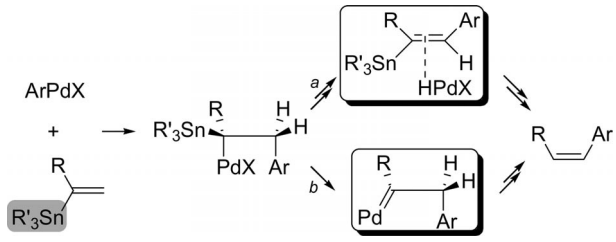
It is noteworthy that not only α-substituted vinyltin species but also β-substituted vinyltin compounds such as **16** could afford an "abnormal" Stille coupling product, as exemplified in Scheme 8.[11] It is interesting to note that the formation of the *cine* substitution product **17*c*** was observed only when $AsPh_3$ was used as ligand. The trienoate **17*i*** can be converted into the decalin system of macrocyclic antibiotics such as kijamicin.



Scheme 8. *cine* Substitution from a β-substituted vinyltin compound.

2.2. Two Mechanisms of *cine* Substitution

Two distinctively different hypotheses for *cine* substitution in Stille cross-coupling reactions have been proposed so far (Scheme 9). The *cine* substitution product can be obtained either through addition/elimination (path a) or through a Pd–carbene intermediate (path b) starting from a common insertion intermediate of arylpalladium across the double bond of α-substituted vinyltin.



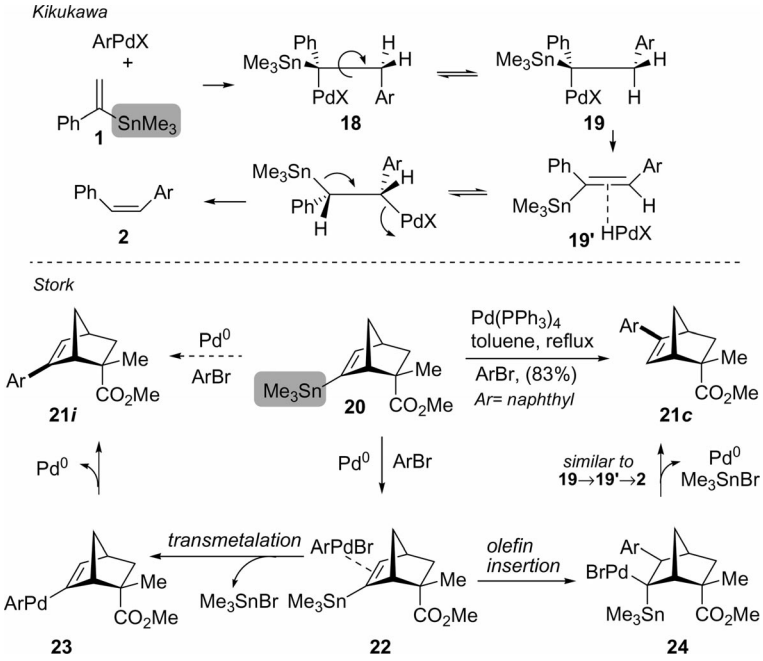
Scheme 9. Addition/elimination vs. Pd–carbene hypotheses.

2.2.1. Addition/Elimination Mechanism

In the first step, a regioselective carbopalladation to afford **18** (Scheme 10, top) would take place, followed by rotation to provide **19**, in which the *syn* orientation needed for a β-elimination of Pd–H is achieved. Readdition of HPdX across the double bond with opposite regiochemistry, followed by an *anti*-elimination of tin halide and Pd^0, would then yield the observed product **2** and regenerate the catalyst. Kikukawa's addition/elimination mechanism[6] lacked evidence in its support, however, and all efforts to detect and identify the uncomplexed vinylstannane **19′** were unsuccessful.

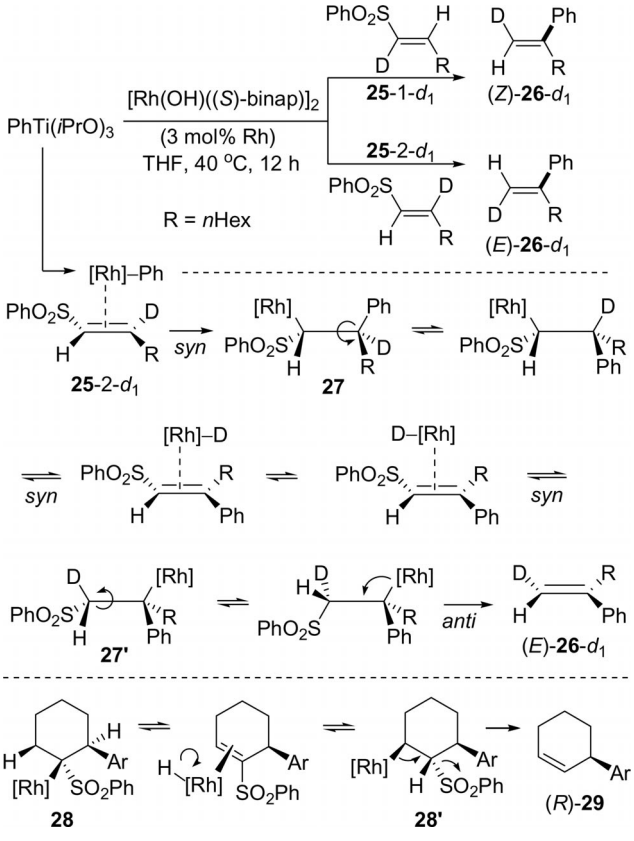
During the course of screening for a general method for the synthesis of 6-arylnorbornenes, Stork and co-worker found that the vinylstannane **20** (Scheme 10, bottom) coupled with 1-bromonaphthalene to give exclusively the *cine* substitution product **21*c*** in 83% yield .[12] Mechanistically, the initial steps are probably oxidative insertion of the catalyst into the aryl bromide to give an Ar–Pd^{II}–Br species, followed by coordination of this species to the vinylstannane **20**. For the "normal" *ipso* substitution to afford **21*i***, transmetallation of the complex **22** to form a vinylpalladium species **23** would have to be the next step, but this is inhibited by what these authors believe to be steric factors. An alternative pathway could be a Heck-type olefin insertion. The resulting intermediate **24** might then undergo the somewhat unusual *trans* β-hydride elimination previously invoked to explain some Heck coupling products. It was also proposed that a Pd–carbene intermediate resulted from α-elimination from **24** could be involved.

Hayashi and co-worker reported novel *cine* substitutions of alkenyl sulfones with aryltitanium reagents catalyzed by rhodium and provided evidence for an addition/elimination mechanism by deuterium labeling experiments. As shown in Scheme 11, the rhodium-catalyzed reaction between (*E*)-**25**–2-d_1 (99% D) and PhTi(*i*OPr)$_3$ gave (*E*)-1-deuterio-2-phenyl-1-octene (**26**-d_1) in which the deuterium content at the *E* position is 97%. Consistently with this deuterium



Scheme 10. Addition/elimination mechanism proposed by Kikukawa[6] and the first example of *cine* substitution in a Stille coupling between a vinylstannane and an aryl halide, reported by Stork.[12]

shift, the reaction of **25**–1-d_1 (99% D) gave (*Z*)-**26**-d_1 with a deuterium content of 97% at the *Z* position. An addition/elimination mechanism similar to Kikukawa's was proposed: the addition of the phenylrhodium species to the alkenyl sulfone in a *syn* fashion generates the alkyl-rhodium **27**, followed by β-deuterium elimination with *syn* stereochemistry. Readdition of the deuterium-rhodium to the double bond with *syn* stereochemistry and opposite regiochemistry forms the new alkyl-rhodium intermediate **27′**. The last step, *anti* elimination of the sulfonyl group and the rhodium from **27′**, should afford the *cine* substitution product (*E*)-**26**-d_1. It is noteworthy that allylarene products resulting from double bond migration could be obtained when cyclic alkenyl sulfones were employed. This interesting observation could be attributed to β-H elimination of *syn* β-H on the other neighboring carbon, because the alkyl-rhodium intermediate **28** formed by the insertion does not have the *syn* β-H on the aryl-substituted carbon. Subsequent *syn* hydro-rhodation and the *anti* elimination from **28′** produce the allylic arenes (*R*)-**29**. Catalytic asymmetric C–C bond formation was thus achieved with high enantioselectivity (>99% *ee*) because the chiral carbon center created at the carbo-rhodation step is retained in the substitution product.

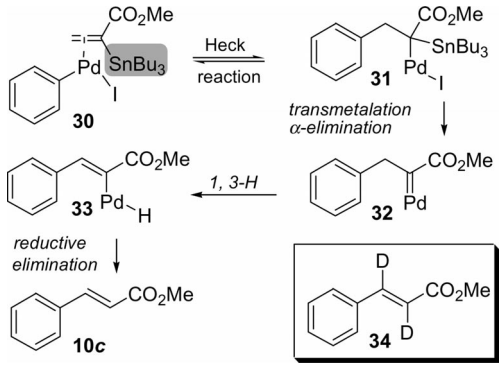


Scheme 11. The related addition–elimination mechanism proposed by Hayashi.[13]

2.2.2. Pd–Carbene Mechanism

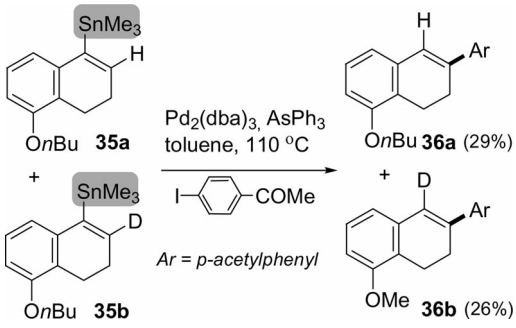
A considerable number of control experiments demonstrated that palladium-catalyzed rearrangement of the starting stannane, rearrangement of either of the two products, protodestannylation, and tin enolate formation were probably not involved, whereas a novel Pd–carbene mechanism[7c] might be responsible for the formation of **10***c*. As shown in Scheme 12, the π complex **30** was reluctant to undergo transmetallation by the normal Stille reaction mechanism due to steric hindrance, and so may be considered as a precursor for the putative Heck adduct **31**, in which a four-

center transmetallation and subsequent α-elimination would lead to the Pd^{II} carbene **32**. In this event, **32** would be expected to undergo a 1,3-H migration to afford the palladium hydride **33**, which could then reductively eliminate and afford the observed *cine* substitution product **10*c***. Their evidence rests mainly on the net retention of deuterium in the 1,3-H migration (as **34**).



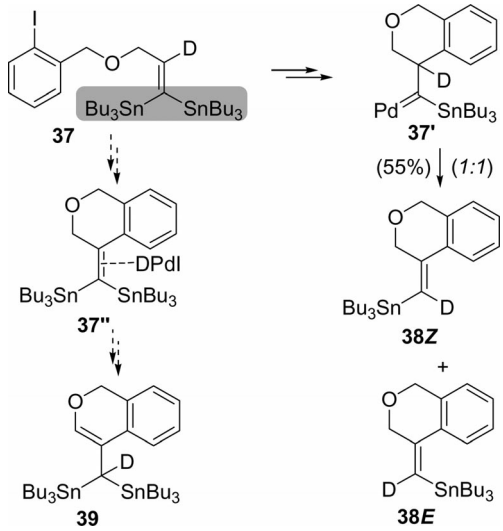
Scheme 12. Pd–carbene mechanism proposed by Busacca.[7c]

Farina designed a labeling and crossover experiment and provided further evidence for the involvement of Pd^0 carbenes in *cine* substitution processes.[14a] As shown in Scheme 13, when an equimolar mixture of the cyclic vinylstannanes **35a** and **35b** was subjected to common Stille coupling conditions with a slight excess of *p*-iodoacetophenone, only the "intramolecular" products were observed. In particular, no loss of *D* (<5%) in **36b** and no *D* incorporation (<2%) in **36a** were detected.



Scheme 13. Farina's crossover experiment.[14a]

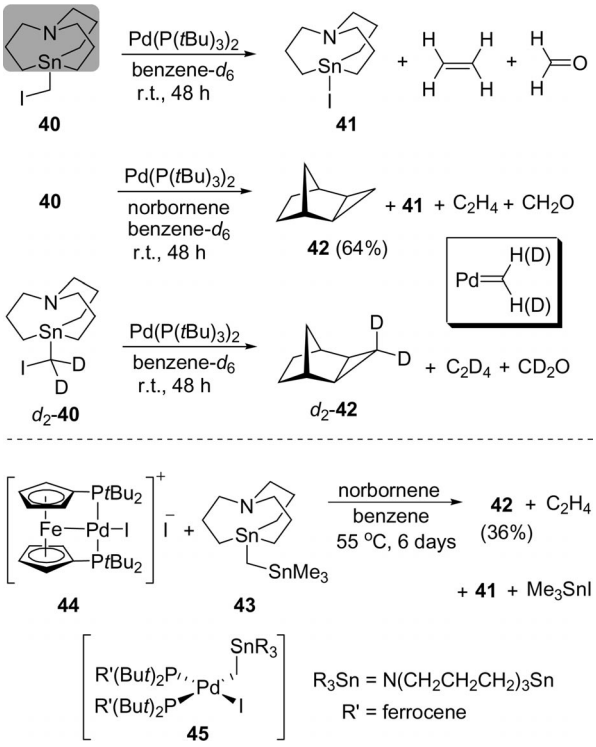
Further evidence was provided in Quayle's deuterium labeling study of intramolecular Stille coupling of the bisstannylethene **37**.[14b] As shown in Scheme 14, **37** (95% D incorporation) was subjected to typical Pd-catalyzed reaction conditions and the *cine* substituted cyclization products **38** were obtained smoothly as an *E*/*Z* mixture. No *ipso*-substituted oxepine product resulting from 7-*endo* cyclization was observed in the crude reaction mixture by ^1H NMR spectroscopy. This fact that 6-*exo* cyclization of **37** proceed without scrambling of the deuterium label and double bond migration (to **39**) is inconsistent with the hydridopalladium readdition process (via **37′′**) proposed by Kikukawa and is more readily accommodated by evoking the Busacca–Farina Pd-carbene mechanism (via **37′**).



Scheme 14. The first observed intramolecular *cine* substitution in the Stille reaction.

Fillion designed *gem*-dimetallic iodopalladio-trialkylstannyl alkane complexes as Pd-carbenoid precursors to probe the *cine* substitution mechanism in the Stille coupling.[14c] The initial efforts were directed at generating sp^3-*gem*-dimetallic iodo-Pd/trialkyl-stannylalkane species by oxidative insertion of Pd^0 catalysts into iodomethyltrialkylstannanes. As shown in Scheme 15, the iodomethyl-stannatrane **40**[15] (δ_H = 1.68 ppm, δ_{Sn} = –29.1 ppm) was allowed to decompose in C_6D_6 in the presence of $Pd[P(tBu)_3]_2$ (25 mol-%) at room temperature for 48 h with monitoring of the reaction progress by ^1H and ^{119}Sn NMR spectroscopy. Interestingly, both ethylene (δ_H = 5.24 ppm, not quantified) and the iodostannatrane **41** (δ_{Sn} = –57.8 ppm) were detected, with competing formation of formaldehyde (δ_H = 8.75 ppm, <1%). More importantly, when the above reaction was run in the presence of an excess of norbornene, *exo*-tricyclo[3.2.1.$0^{2,4}$]octane (**42**) was formed in 64% yield, which indicated the intermediacy of a methylene carbenoid species. Further insights into the Pd-carbene mechanism were gained from the following observations with the deuterium-labeled d_2-**40**, the methylene singlet (δ_D = 1.68 ppm) of which decreased while a set of signals appeared on treatment with $Pd[P(tBu)_3]_2$ and excess norbornene. ^2H NMR established the clean formation of the cyclopropanation product d_2-**42**, CD_2O, and C_2D_4.

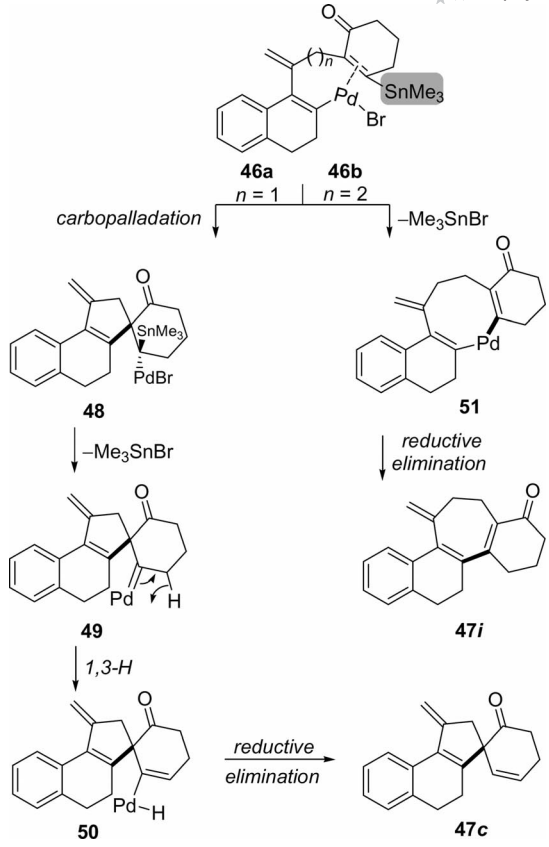
An alternative approach for the generation of halopalladio-trialkylstannylalkane intermediates was also investigated: the stannatrane moiety of $Me_3SnCH_2Sn(CH_2CH_2CH_2)_3N$ (**43**, δ_H = –0.29 ppm) should transmetallate preferentially with the cationic $[Pd^{II}I]^+I^-$ complex **44**, giving the *cis*-$Pd^{II}I(CH_2SnMe_3)$ intermediate **45**, which should dimerize and cyclopropanate alkenes. Indeed, treatment of a C_6D_6 solution of **43** and excess norbornene with **44** (1.05 equiv.) at 55 °C for 6 d provided the tricycle **42** in 36% yield, C_2H_4 (not quantified), the iodostannatrane **41**, and Me_3SnI (δ_H = 0.11 ppm, 59%).



Scheme 15. Fillion's deuterium labeling studies and NMR experiments.[14c]

During an investigation of a synthetic approach to frondosins, Flynn and co-worker found that the intramolecular Stille reaction of **46a** gave the unusual *cine*-substituted nonconjugated product **47*c*** in 81% yield (Scheme 16), whereas the corresponding reaction with the homologous substrate **46b** gave the *ipso*-substituted product **47*i***.[16] On the basis of the Pd-carbene mechanism, they proposed that the common σ,π complexed intermediate **46** should represent the branch point between these two reaction pathways. Presumably, the intermediate **46a** ($n = 1$) prefers to undergo carbopalladation to give **48**, which then loses Me_3SnBr to give the carbenoid **49**. A subsequent 1,3-hydride shift (via **50**) and reductive elimination affords **47*c***. Complex **46b** ($n = 2$), on the other hand, prefers to undergo transmetallation to give the palladacycle **51** and reductive elimination to give **47*i***. This distinctively different chemoselectivity in the fates of **46a** ($n = 1$) and **46b** ($n = 2$) might arise from a better accommodation of the 90° angle in the square-planar eight-membered palladacycle of **51** than in the seven-membered equivalent (not shown), with the additional methylene group allowing a reduction in strain.

From the above discussion, some conclusions are noteworthy. The distributions of (*cine*/*ipso*) coupling products depend on several factors, such as the structure of the substrate, ligand, solvent et al., with sterically hindered α-vinyltins dictating the selectivity and strongly favoring the formation of *cine* substitution products. Generally, electron-rich ligands and nonpolar solvents also play important roles in *cine* substitution. As shown in Scheme 16, the effect of tether length in the intramolecular Stille reaction has also been demonstrated, although this is a rare case.

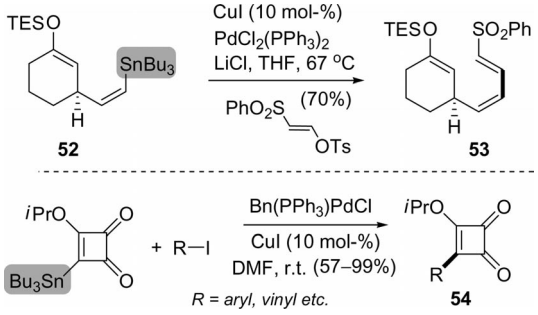


Scheme 16. The effect of tether length on *cine* or *ipso* substitution as reported by Flynn.[16]

3. Copper Effect in Stille Coupling

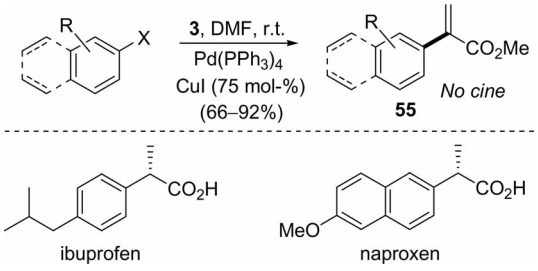
When undesired *cine* substitution and many sluggish or otherwise unsuccessful Stille cross-couplings have been encountered, a lot of factors such as the kind of electrophile, the solvent, ligand, and the addition or not of LiCl have been considered, but only small improvement has been achieved. Because *cine* substitution is the result of slow transmetallation with sterically hindered vinyltins, the acceleration of this rate-limiting step has to be achieved in order to for this unwanted selectivity to be avoided. The following section demonstrates that co-catalysis by Cu^I plays an important role in the restoration of *ipso* selectivity and enhancement of the reaction.

During the stereoselective synthesis of an octahydronaphthalene synthon for dihydrocompactin, Marino first documented the use of a Pd/Cu/LiCl combination (although described in a footnote; Scheme 17).[17a] A Stille coupling between *trans*-2-tosylvinyl phenyl sulfone and the vinyltin compound **52** provided the vinylphenyl sulfone **53** stereospecifically in 70% isolated yield. Pioneeringly, Liebeskind revealed the beneficial effect of catalytic CuI on the Stille reaction for the synthesis of the substituted cyclobutenediones **54** (Scheme 16), valuable precursors of substituted quinones and alkylidenecyclopentenone derivatives.[17b] The practical utility of the "copper effect" was immediately recognized and since then has enhanced numerous C–C bond-forming reactions.[18]



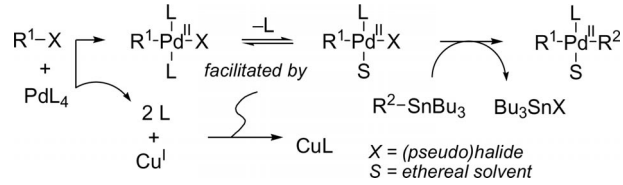
Scheme 17. The Cu effect in Stille couplings: early days.

In 1993, Levin found that aryl iodides can undergo Pd/CuI-catalyzed coupling with methyl α-(tributylstannyl)-acrylate (**3**) to provide the corresponding methyl α-aryl-acrylates **55** (Scheme 18), which are very useful building blocks for non-steroidal anti-inflammatory agents such as ibuprofen and naproxen. *cine* Substitution products as shown in Scheme 3 were completely suppressed by the inclusion of CuI and *ipso* selectivity was restored.[7b]

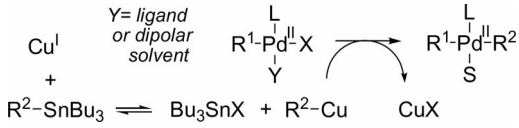


Scheme 18. One-step *ipso*-selective synthesis of methyl α-arylacrylates.

Detailed kinetics studies and quantitative evaluation showed that both mechanistic explanations could be valid for the "copper effect", depending on the reactions conditions (dual mechanism):[19a] 1) in ethereal solvents and in conjunction with highly coordinating ligands (PPh_3), Cu^I acts as an excellent scavenger for free ligands, which are known to inhibit rate-limiting transmetallation and to facilitate formation of the coordinatively unsaturated Pd^{II} intermediate (Scheme 19). Espinet's associative pathway[19b] also shows that the rate-enhancing effect of Cu^I is linked to the autoretardation effect caused by the release of two equivalents of ligand when PdL_4 undergoes oxidative addition to afford $PdRL_2X$. They concluded that Cu^I coordinates to "free" ligand, but does not directly promote the dissociation of ligand from the Pd^{II} species. 2) In highly dipolar solvents such as NMP (DMF or DMSO) and in the presence of "soft" ligands ($AsPh_3$), however, the formation of an organocopper species resulting from preliminary Sn/Cu transmetallation is more likely (Scheme 20). Liebeskind and Farina et al. observed that Stille couplings co-catalyzed by Cu^I displayed second-order kinetics. This is in contrast with the equivalent reaction performed in dioxane, which showed first-order kinetics. Although this change in kinetics could be attributable to catalyst decomposition, it could also be due to a sequence of two transmetallations (Sn/Cu→Cu/Pd). Another observation that could support a Sn/Cu transmetallation mechanism is that addition of CuI affects the group transfer selectivity from the organostannane.

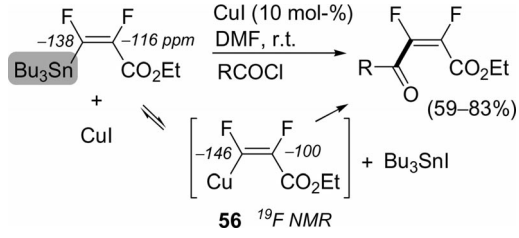


Scheme 19. The mechanistic explanation based on ligand association.



Scheme 20. Sn/Cu preliminary transmetallation.

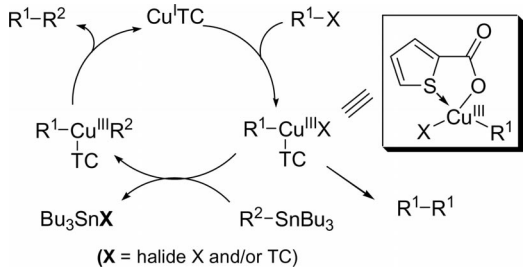
The above Sn/Cu transmetallation is reminiscent of a synthetically powerful process featuring transmetallation from organostannanes to higher-order cuprates developed by Lipshutz and co-workers.[20] Burton et al. also found that reactions between (*E*)-2,3-difluoro-3-stannylacrylic ester and acid chlorides (Scheme 21) under CuI catalysis conditions stereospecifically afforded ethyl (*Z*)-2,3-difluoro-4-substituted but-2-enoates in good yields.[21] More importantly, direct spectroscopic observation of the corresponding organocopper intermediate **56** in Stille coupling reaction of organostannanes was achieved for the first time.



Scheme 21. Direct spectroscopic observation of the organocopper intermediate **56**.

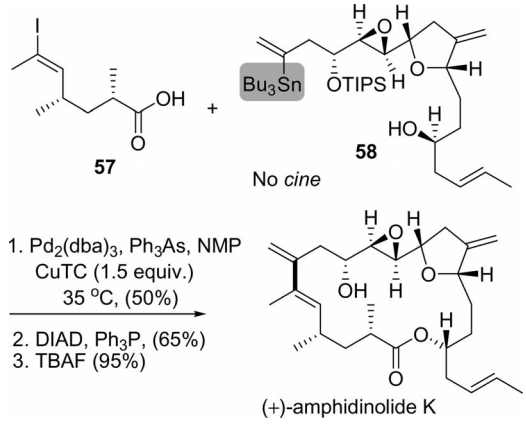
In 1996, Liebeskind developed the more versatile copper mediator copper thiophene-2-carboxylate (CuTC), which by itself made intermolecular cross-coupling proceed at or below room temperature within minutes.[22a] It is noteworthy that the direct oxidative addition of certain Cu^I salts to vinyl(aryl) halides should not be excluded,[23] because symmetrical dienes (biaryls) arising from homocoupling of halides can be obtained in good yields with promotion by CuTC in the absence of organostannanes (Scheme 22).[22b] Other Cu^I carboxylates [CuOCOR: R = Me, Ph, (*E*)-CH=CHPh, 2-pyridyl, 2-furyl] were also screened but were not more effective than CuTC. Internal coordination of sulfur and carboxylate to Cu^{III} can stabilize the oxidative addition intermediate and therefore drive this equilibrium step forward. **X** in Bu_3Sn**X** may arise from halide and thiophene-2-carboxylate (TC). It is noteworthy that excellent re-

tention of stereochemistry in both organostannane and alkenyl iodide was observed, which precludes a radical mechanism and supports a general cross-coupling mechanism consisting of oxidative addition, transmetallation, and reductive elimination steps.



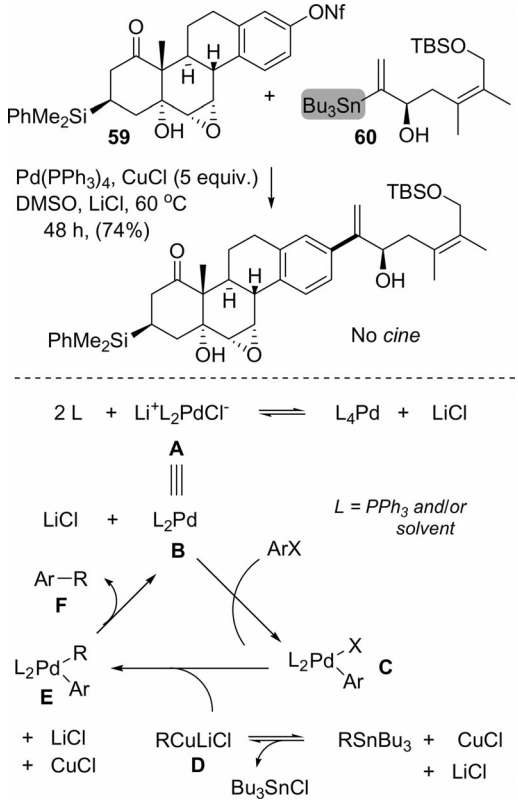
Scheme 22. Direct oxidative addition of $Cu^{I}TC$ to vinyl(aryl) halides proposed by Liebeskind.

In the total synthesis of (+)-amphidinolide K by Williams and co-workers, the formation of butadienes featuring internal (C_2/C_3) dialkyl substitution was a particular challenge. Their studies showed that the vinylstannane **58** (Scheme 23) had a propensity to undergo *cine* substitution rather than the expected *ipso* replacement.[24] Successful coupling of **57** and **58** to give the desired *seco*-acid precursor occurred, however, upon mild heading at 35 °C in the presence of Pd^0 and CuTC. The co-catalyst CuTC produced a dramatic improvement over CuI, and in the absence of CuTC no products were observed. In the absence of Pd^0, only homocoupling product of the stannane **58** was observed.



Scheme 23. Total synthesis of (+)-amphidinolide K.

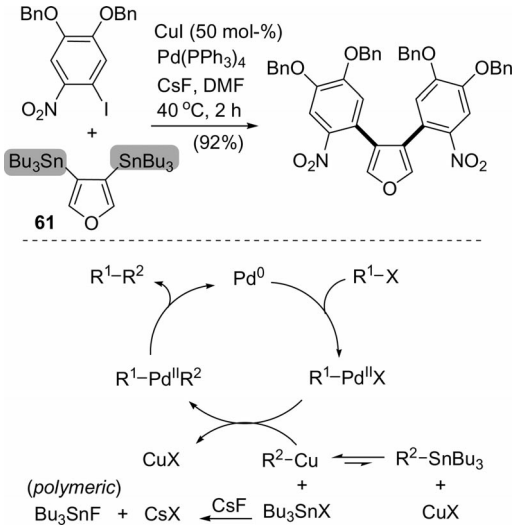
The steroid-derived nicandrenone (NIC) family possess insect repellent and antifeedant properties; Corey and coworkers have recently described the first total syntheses of NIC-1 lactone, NIC-1, and NIC-10, in which the key step was the coupling of the nonaflate **59** (Scheme 24) and the α-substituted vinylstannane **60** under the optimized conditions [$Pd(PPh_3)_4$/CuCl/LiCl/DMSO] developed for such difficult Stille reactions.[25] Initial studies demonstrated that previously successful conditions for overcoming *cine* substitution could not work with the sterically hindered **60**. These authors proposed a similar catalytic cycle based on previous explanations for the "copper effect". The active Pd^0 species is the intermediate **A** or its metenoid equivalent **B**, which reacts with the aromatic substrate ArX to form the intermediate **C**. The function of CuCl is to convert the vinylstannane into the vinylcopper species **D** (or a variant with respect to coordination/aggregation). Here the greater electrophilicity of CuCl relative to CuI was attributed to the greater electronegativity of Cl relative to I and the greater covalency of CuI relative to CuCl. (A metenoid is a metal-centered reactive intermediate that is capable of the same types of reaction as carbenoids; see ref.[25a]) Next the reaction between **D** and **C** forms the key Pd^{II} species **E**, from which the coupling product **F** and the active catalyst(s) **A** and/or **B** are generated by reductive elimination. Previous work by Stille had demonstrated that incorporation of LiCl was necessary to induce coupling of vinyl triflates, which can be interpreted by postulating that initial oxidative addition product is ineffective, whereas ligand substitution with chloride ion leads to more reactive species.[26] In the above coupling reaction, one reason for the beneficial effect of LiCl is suppression of homocoupling of the vinylcopper intermediate **D** to form a substituted 1,3-butadiene.



Scheme 24. The versatile Pd^0/CuCl/LiCl catalytic system developed by Corey et al.[25]

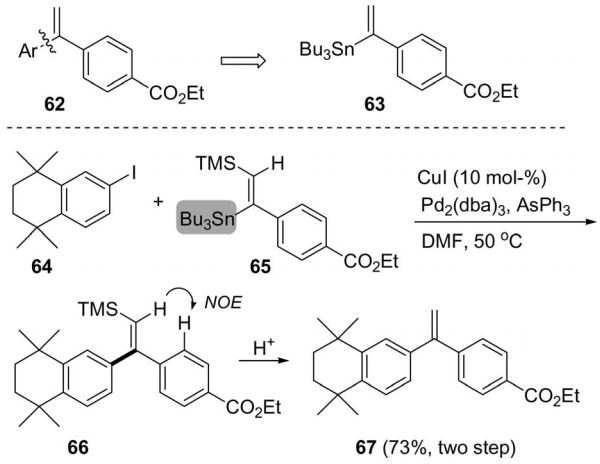
During the total synthesis of a potent antioxidant isolated from the red beetroot, Baldwin and co-workers found that a new catalytic system with CuI and CsF in DMF was most effective for coupling the electronically unfavorable and sterically hindered substrates **61** (Scheme 25), which was attributed to a synergic effect of Cu^{I} and fluoride

ion.[27] When the preliminary transmetallation between the organostannane and CuI was in equilibrium, removal of the Bu_3SnX by-product as insoluble Bu_3SnF should favor the formation of the more reactive organocopper species, resulting in enhancement of the reaction. TBAF seemed comparable to CsF in enhancing the reaction, whereas other fluoride sources (LiF, NaF, KF) were less effective. This trend can be explained by the availability of fluoride in terms of lattice energies. LiF has the highest lattice energy (LiF: 1030 kJ mol^{-1}, NaF: 910 kJ mol^{-1}, KF: 808 kJ mol^{-1}, CsF: 744 kJ mol^{-1}), which would disfavor solubility relative to CsF, so CsF would more easily deliver the fluoride ion.



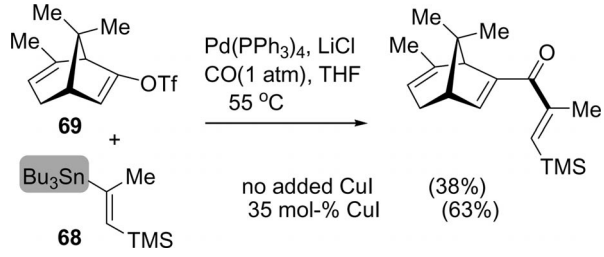
Scheme 25. Synergic effect of Cu^I and fluoride ion proposed by Baldwin.[27]

Scientists at Bristol–Myers Squibb needed to prepare a family of the diarylethylenes **62** (Scheme 26). One logical disconnection is at the aryl–alkene C–C bond, putatively formable from the vinylstannane **63** and an aryl halide or triflate. They did not choose optimization of Stille coupling conditions to minimize the formation of *cine* products and instead elected to explore the applicability of the readily accessible α-stannyl β-silylstyrenes such as **65** in the preparation of the target family of compounds.[28] Addition of the commercially available *n*Bu_3SnTMS across the corresponding alkyne precursor afforded the silylstannane **65** in a high yield. The regio- and stereochemical assignments were confirmed spectroscopically. ^1H NMR revealed Sn/H (vinyl) *J* couplings of 154 and 161 Hz, which are consistent with their *trans* relationship. In a typical reaction, the silylstannane **65** was smoothly coupled with the iodide **64** under palladium catalysis conditions to afford the vinylsilane **66** in a stereospecific fashion. Compound **66** was susceptible to *cis*/*trans* isomerization, however, although this was inconsequential for the next protodesilylation step (to **67**). The above two-step procedure can be extended to a series of aryl iodides with different functional groups and constitutes a practical synthesis of the 1,1-diarylethylenes **62**.



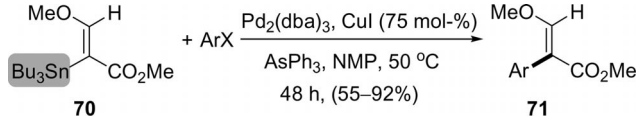
Scheme 26. Combination of a Stille coupling and a protodesilylation reaction with α,β-disubstituted vinyltin compounds.

Stille coupling under standard carbonylative conditions proceeded in poor yield when the hindered alkenylstannane **68** (Scheme 27) and the enol triflate **69** were used. Recently, West reported that inclusion of substoichiometric amounts of CuI or CuBr significantly improved the efficiency of the coupling, providing a variety of complex 1,4-dien-3-ones in good to excellent yields.[29] These are useful synthetic building blocks, especially with regard to their use in the Nazarov reaction.



Scheme 27. Carbonylative Stille coupling of the sterically hindered vinylstannane.

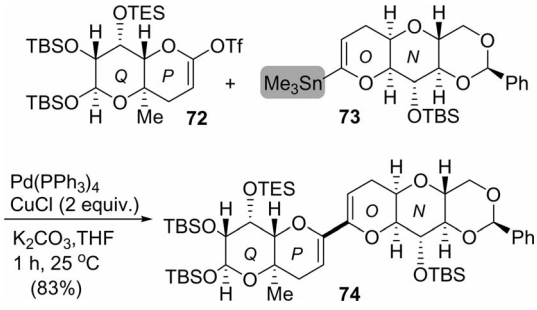
Hodgson also utilized a Pd/Cu/$AsPh_3$ combination to achieve direct introduction of the agrochemically important β-methoxyacrylate toxophore.[30] Previous methods involved stepwise construction through the preparation of ester or α-keto ester precursors. As shown in Scheme 28, (*Z*)-**70** ($^3J_{Sn,H}$ = 72, 69 Hz) was stereospecifically coupled with aryl iodides to afford the diverse α-aryl-β-methoxyacrylates **71** in good yields. Retention of geometry in the acrylate units was observed in compounds **71**: δ_H values for the alkenyl proton were close to 7.5 ppm, which is diagnostic of *E* geometry.



Scheme 28. Stereospecific Stille coupling of methyl (*Z*)-tributylstannyl-3-methoxypropenoate (**70**).

4. Synthetic Uses of the Copper Effect

Nicolaou and co-workers developed a practical and highly efficient method for cross-couplings of enol triflates and stannyl enol ethers to afford complex bisglycals and furthermore demonstrated the applicability of this method in the synthesis of cyclic polyethers, such as a fragment related to the NO–PQ system of maitotoxin.[31] As shown in Scheme 29, the readily accessible building blocks **72** and **73** were coupled smoothly under the optimum $Pd(PPh_3)_4$/ CuCl/ K_2CO_3 conditions to afford the targeted intermediate **74** in 83% yield.



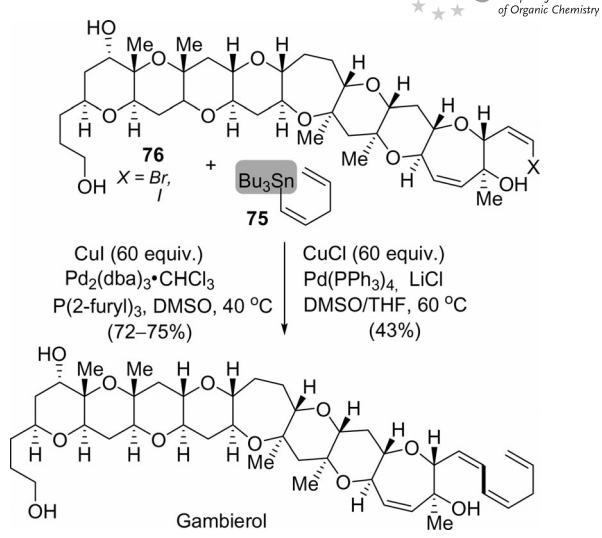
Scheme 29. Synthesis of complex bisglycals for the polyether maitotoxin.

The utility of Cu^I-co-catalyzed Stille coupling is dramatically manifested in the total syntheses of gambierol (Scheme 30) by the Sasaki,[32a] Yamamoto,[32b] and Rainier groups.[32c] The three groups employed Stille reactions in the final steps of their respective syntheses to append the delicate triene-containing side chain **75** onto fully elaborated, protecting-group-free polycyclic ether precursors. Although there were significant differences in the reaction conditions employed, the presence of co-catalytic CuI salts was necessary to facilitate the transmetallation events and hence to allow the reactions to proceed at acceptable rates. The coupling product was formed with the expected retention of the geometry of the alkene, and the overall efficiency of these processes is quite remarkable, given both the steric encumbrance around the coupling sites and the sheer size and complexity of the vinyl halides **76**.

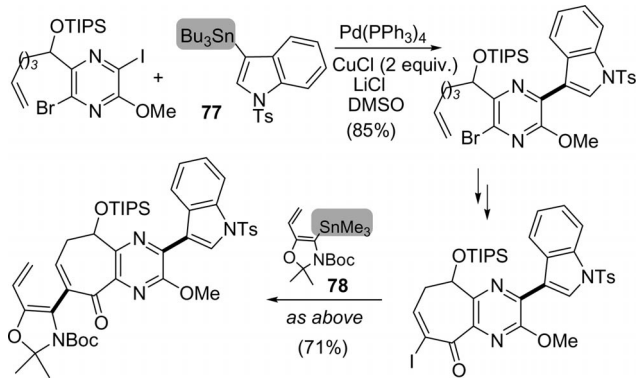
In the elegant approach to the total synthesis of the alkaloid dragmacidine E by Funk et al., Stille cross-couplings at the α-position of a cycloheptenone component and at the β-position of a pyrazine system by Corey's protocol[25a] were utilized (Scheme 31).[33] Both of two key coupling events with the hindered indole derivative **77** and the dienylstannane **78** rely on the copper effect.

The 12-membered B-ring of sesterterpenoid nitiol was efficiently constructed by means of a copper-promoted Stille cross-coupling between **79** and **80** (Scheme 32) by Corey's protocol and a subsequent Nozaki–Hiyama–Kishi (NHK) carbonyl addition reaction.[34]

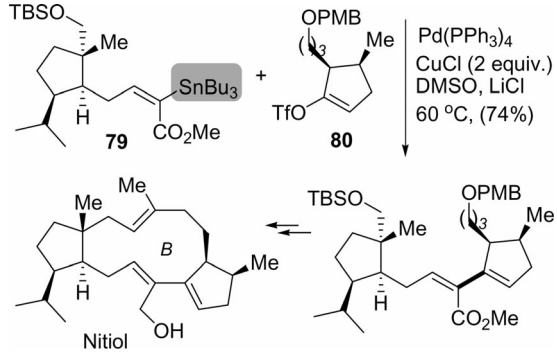
Treatment of a solution of the (*E*)-vinylstannane **81** and the (*E*)-vinyl iodide **82** (Scheme 33) in THF with a catalytic amount of $Pd_2(dba)_3$ in the presence of $AsPh_3$ and CuCl at 50 °C gave crocacin C in 84% yield.[35]



Scheme 30. Appendage of a triene-containing side chain to complete the total synthesis of the polyether gambierol.

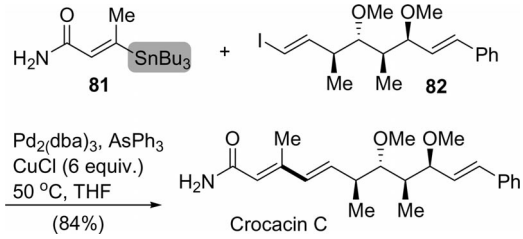


Scheme 31. Construction of the core ring system of dragmacidine E through sequential Stille coupling reactions.



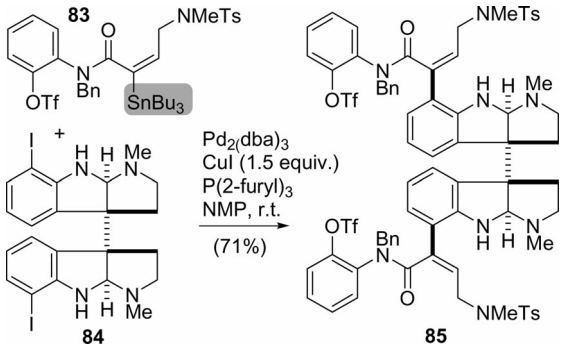
Scheme 32. Construction of the [5–12–5] tricyclic skeleton of nitiol by Stille coupling and NHK reactions.

Quadrigemine C and psycholeine are representatives of higher-order polypyrrolidinoindoline alkaloids. Stimulated by formidable challenges in the construction of contiguous and diaryl stereogenic quaternary carbons, Overman and co-workers described their enantioselective total synthesis. In this context, a chemoselective double Stille cross-coupling of the diiodide **84** with the stannane **83** (Scheme 34)



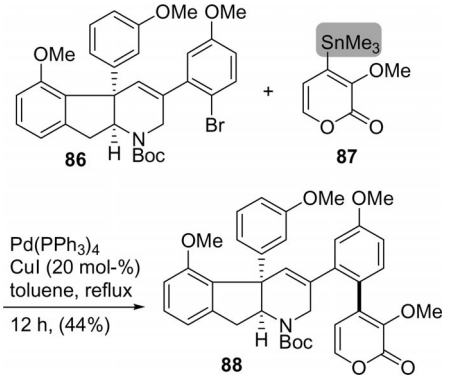
Scheme 33. Total synthesis of crocacin C.

was achieved with a catalyst system derived from $Pd_2(dba)_3{\cdot}CHCl_3$, P(2-furyl)$_3$, and CuI to give the *meso* dibutenanilide **85** in 71% yield.[36]



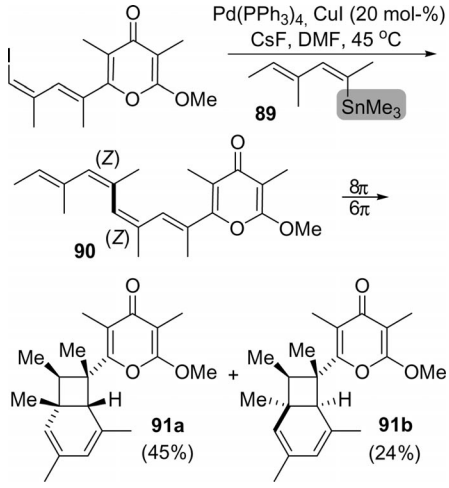
Scheme 34. The key Stille coupling in the enantioselective total syntheses of quadrigemine C and psycholeine.

Baran recently described a short and efficient total synthesis of the structurally unprecedented alkaloid haouamine A, and one of the key steps involved a Stille coupling between the pyrone **87** and the Boc-protected piperidine **86** (Scheme 35), catalyzed by a Pd/Cu combination.[37] In view of the congested environment the modest yield (44%) of the pyrone-piperidine conjugate **88** could be regarded as acceptable, paving the way to subsequent formation of an azaparacyclophane system.



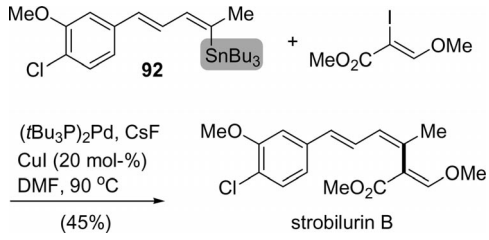
Scheme 35. Construction of the skeleton en route to haouamine A.

Trauner and co-workers reported a diversity-oriented route to polypropionate natural products containing α-methoxy-γ-pyrone units (i.e., cyercene A and placidenes) based on Baldwin's protocol with CsF as additive.[38a] A Stille reaction with **89** (Scheme 36), for example, was used for the synthesis of the (*Z*,*Z*)-tetraene **90**,[38b] which underwent in situ 8π–6π electrocyclization to give the diastereomeric bicyclo[4.2.0]octadienes **91a** and **91b** in 45% and 24% overall yields, respectively.



Scheme 36. Total synthesis of polypropionate pyrones by tandem Stille coupling and electrocyclization reactions.

The key step in the total synthesis of strobilurin B involved a Stille coupling between the vinyl stannane **92** (Scheme 37) and methyl α-iodo-β-methoxyacrylate with tBu_3P[39] as the palladium ligand in the presence of CuI.[40]

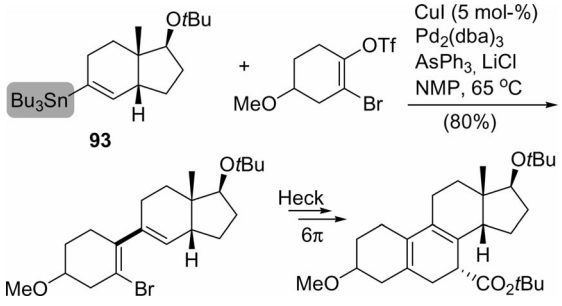


Scheme 37. Total synthesis of strobilurin B.

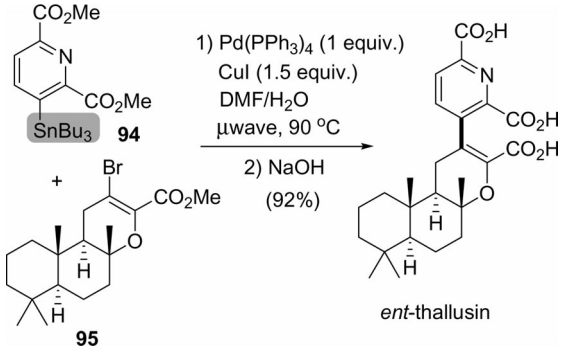
A variety of enantiomerically pure steroidal compounds was synthesized by de Meijere and co-workers, by means of a sequence of Stille and Heck cross-coupling reactions and subsequent thermal 6π-electrocyclizations, constituting a convergent A + CD→ACD→ABCD approach. Among them, a highly chemoselective Stille coupling promoted by CuI between the triflate moiety in 2-bromocyclohex-1-enyl triflate and the bicyclo[4.3.0]nonenylstannane **93** (Scheme 38) furnished the corresponding tricyclic bromobutadiene in good yield.[41]

Snider and co-workers reported a concise synthesis of *ent*-thallusin, with the key transformation involving a microwave-promoted Stille cross-coupling between the bromoester **95** (Scheme 39), obtained from sclareol oxide, and the stannylpyridine **94**.[42] The limitation of this copper-mediated reaction is the requirement for stoichiometric conversion of **95** into a vinyl palladium intermediate prior to the addition of **94** to the reaction mixture.

Stoltz and co-workers developed a diastereoselective tandem Stille oxa-electrocyclization reaction that provided access to the core structure of the caged diterpenoid saudin

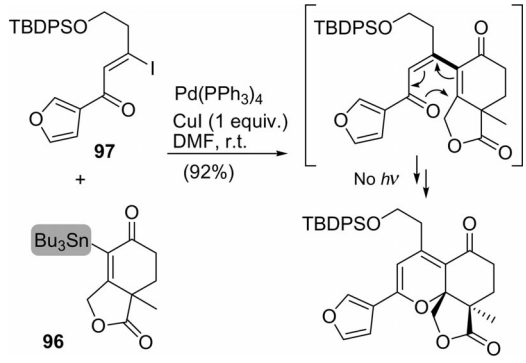


Scheme 38. Construction of steroid B rings through a Stille–Heck coupling and electrocyclization sequence.



Scheme 39. Concise synthesis of *ent*-thallusin.

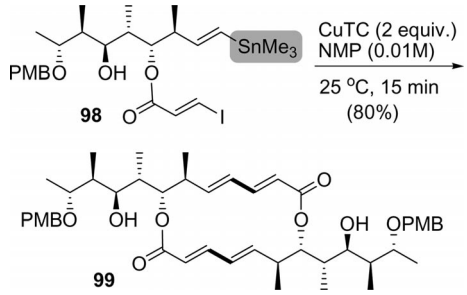
in a rapid and convergent manner (Scheme 40).[43] The presence of CuI and the absence of light were both essential for the success coupling of the α-stannyl enone **96** and the (*Z*)-vinyl iodide **97**.



Scheme 40. Convergent synthesis of the polycyclic pyran core of saudin through a tandem Stille oxa-electrocyclization reaction.

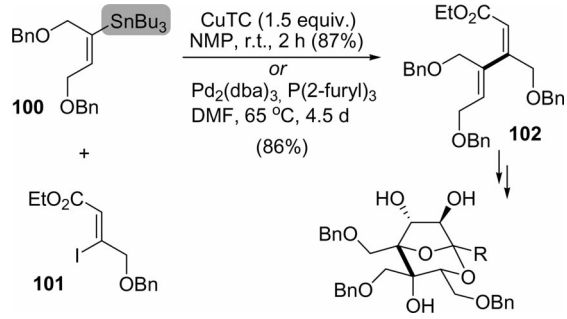
In particular, Cu^I salts alone can promote Stille-type cross-coupling reactions, indicating that facile transmetallation from the organostannane to the copper species has taken place. Cu-only cross-coupling reactions of this type are generally much faster and cleaner than the conventional Pd^0-catalyzed processes.

Elaiolide, a 16-membered macrodiolide possessing antimicrobial and anthelmintic activity, has been prepared by Paterson and co-workers. The key step was a CuTC-promoted cyclodimerization of the vinyl stannane **98** (Scheme 41) to give the C_2-symmetric macrocycle **99** in 80% yield without the isolation of open-chain intermediates, which suggests the occurrence of a rapid CuTC-mediated cyclization without competing oligomerization.[44]



Scheme 41. Total synthesis of elaiolide by cyclodimerization.

Armstrong and co-workers found that Stille coupling between the trisubstituted vinyltin compound **100** (Scheme 42) and the vinyl iodide **101** can be effected in good yield at room temperature with use of stoichiometric CuTC rather than conventional Pd catalysis.[45] The resulting diene product **102** can easily be converted into the 2,8-dioxabicyclo[3.2.1]octane core of (+)-zaragozic acid C, which is an efficient inhibitor for cholesterol biosynthesis.

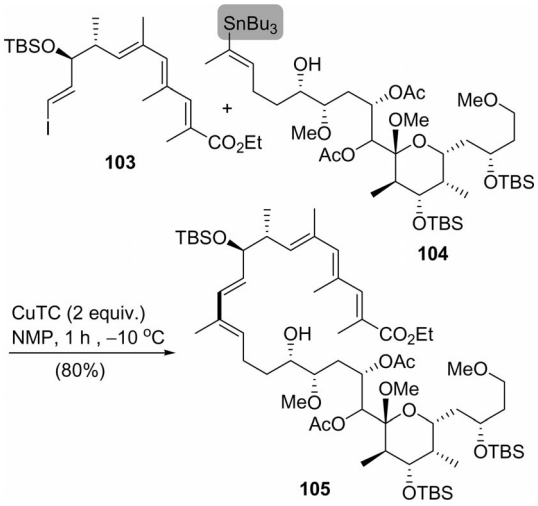


Scheme 42. The synthesis of the bicyclo[3.2.1]octane core of (+)-zaragozic acid C.

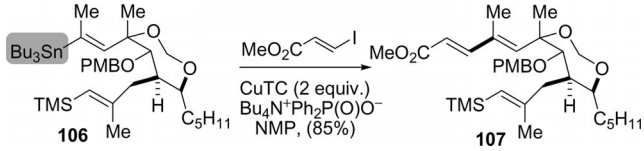
Koert et al. reported the synthesis of the aglycon of the 20-membered macrolide apoptolidin. Initial attempts at Pd^0-catalyzed Stille coupling between **103** and **104** (Scheme 43) were disappointing (<30% yields at prolonged reaction times and 60 °C). In contrast, the use of two equivalents of CuTC gave **105** in 80% yield under very mild conditions (–10 °C, 1 h).[46]

CuTC-promoted cross-coupling of the vinyl stannane **106** (Scheme 44) and methyl (*E*)-β-iodoacrylate on a multigram scale furnished the acetal **107**, an intermediate in the synthesis of formamicinone by Roush and coworkers.[47] They also showed that homocoupling of the (*E*)-β-iodoacrylate was a competing background reaction, which could be minimized by syringe pump addition of this vinyl iodide into a mixture of **106** and CuTC. It is noteworthy that the trialkyltin halide scavenger tetrabutylammonium diphenylphosphinate [$Bu_4N^+Ph_2P(O)O^-$] eventually proved to be a particularly effective additive.[48]

As shown in Scheme 45, the α- and β-stannylated trifluorobutenoates **108** reacted smoothly in the presence of a catalytic amount of CuI with a range of allylic bromides,

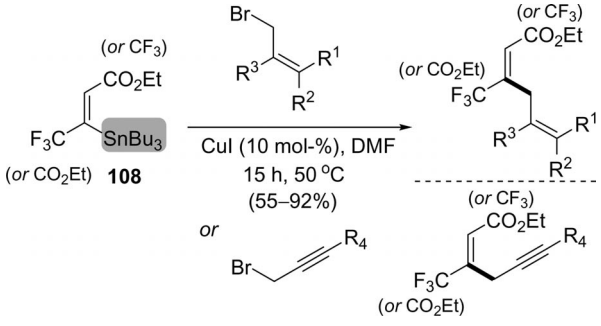


Scheme 43. CuTC-mediated coupling of the "southern" and "northern" halves of apoptolidinone.



Scheme 44. Synthesis of the diene fragment for formamicinone.

leading to the expected allylation and propargylation products with excellent yields and stereospecificities.[49] Interestingly, the use of a stoichiometric amount of copper salt led only to moderate yields of coupling products (<60%), although no homocoupling products (dienes) and allenic products were observed under the conditions employed. Specially, the cross-coupling of **108** and crotyl bromide provided the corresponding product without allylic transposition. The above results indicate that the presumed intermediate copper reagent formed after catalytic transmetallation of **108** with CuI is configurationally stable and reacted stereoselectively with the bromides. No coupling reaction was observed under Pd^0 catalyst conditions.



Scheme 45. Allylation and propargylation reactions catalyzed by CuI alone.

5. Summary and Outlook

The Stille cross-coupling reaction is one of the most widely applied palladium-catalyzed C–C bond-forming reactions and has today become a popular tool in practical organic synthesis. The general efficiency of this coupling reaction is highly dependent on the substrate structures of the two partners. The not-so-infrequently encountered *cine* substitution represents a general regioselectivity issue on occasions in which sterically hindered vinyltins are employed as coupling components. Fortunately, the often anticipated *ipso* selectivity of the Stille coupling can frequently be restored by adjusting the metallic catalyst system in combination with optimization of practical reaction conditions. The powerful Cu effect was observed and interpreted in terms of the acceleration of the speed-limiting transmetallation step of the conventional coupling cascade. The advent of the Cu-only catalytic system for Stille-type cross-couplings implies the probably underestimated unique catalytic reactivity power of this transition metal, as evidenced in some recent examples of efficient Pd/Cu-cocatalyzed Ullmann-type cross-coupling reactions.[50] We believe that future development in this field will welcome the rationally designed combined metallic catalytic systems for effective C–C cross-coupling processes. The previous work from Liebeskind's, Farina's, and Espinet's research groups has already demonstrated that ligand association and Sn/Cu preliminary transmetallation are probably responsible for the powerful copper effect, as has been ascertained by application in the total synthesis of complex natural products with various functional groups.

The past few years have seen the development of couplings of nucleophiles and electrophiles in which sp^3–sp^3 C–C bonds are formed.[51] This is particularly challenging in view of the reluctance of alkyl electrophiles to undergo oxidative addition and their tendency towards β-elimination. We believe that application of the copper effect will also be demonstrated in cross-coupling reactions with this class of substrates.

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