# The Stille Reaction, 38 Years Later

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ABSTRACT: The first now-named Stille reaction was published 38 years ago, and the last comprehensive revision of this catalysis was in 2004. Since then, the knowledge of the different steps of the three possible (and sometimes competing) reaction pathways (cyclic, open, and ionic) has been almost completed by synergistic experimental and theoretical studies: the Stille reaction is perhaps the best characterized catalytic process if we consider the number of intermediates that have been detected. This review concentrates on the mechanistic new knowledge and on important aspects such as the revolution with the use of bulky phosphines, the bimetallic alternative of the Stille reaction, the enantioselectivity in Stille and palladium-free Stille processes, the meaning of copper effect, or the possible approaches to make Stille coupling a greener process.

KEYWORDS: *Stille cross-coupling, reaction mechanism, transmetalation, palladium, tin*
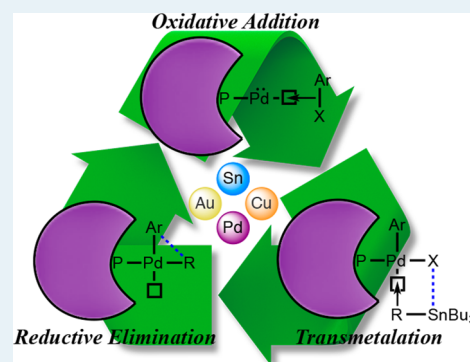
1. INTRODUCTION

The cross-coupling reaction of organic electrophiles with organostannanes (eq 1) is traditionally known as the Stille reaction. The first examples of the coupling, published by the groups of Eaborn[1] and Kosugi-Migita,[2] preceded the first report on the topic by Milstein and Stille,[3] but the synthetic works of Stille since 1978, and his amazingly modern mechanistic studies on the different steps involved in the catalytic cycle, merit that the reaction is identified with his name. Were it not for his premature death at the age of 59 in an airplane crash,[4] John Kenneth Stille would have likely shared the 2010 Nobel Prize in Chemistry for "work on palladium-catalyzed cross-coupling reactions".[5]

$$R^1-X + R^2-SnR_3 \xrightarrow{[Pd]} R^1-R^2 + SnR_3-X \qquad (1)$$
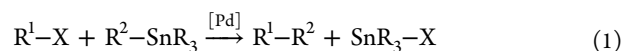
The understanding of the mechanism, which shares common steps with other palladium-catalyzed cross-coupling reactions, progressed fast in the hands of Stille, and the review he published in 1986 presented and discussed a four-step cycle including sequential oxidative addition, transmetalation, isomerization, and reductive elimination processes[6] as well as the proposal that transmetalation of chiral fragments occurred with inversion of configuration. In 2004, Espinet and Echavarren published a major critical actualization of the Stille reaction mechanisms, in which each step was considered and discussed.[7] The mechanism had gained complexity as a result of the proposal of two transmetalation pathways (open and cyclic), to account for the observation of inversion and retention, respectively, of configuration in the transmetalation step.[8] An additional third pathway accounting for transmetalations via cationic species was also considered.[9,10] The change of paradigm considering several mechanisms rather than only one is still the major mechanistic change from the early proposals and remains a useful map of the territory nowadays.

In the time elapsed since our review in 2004, several others have appeared, usually included in a more general cross-coupling context. These are given in the references.[11−13]

The Stille reaction is now 38, a critical age for human beings. How is it for the reaction? In this review, we try to offer a critical nonexhaustive analysis of the main advances and interesting aspects since our 2004 review, concentrating on key changes and trying to comment on some practical aspects in view of the complexities of the reaction.

2. IS THE STILLE REACTION STILL AN OPTION?

The rapid evolution of other alternative Pd-catalyzed cross-couplings begs the question whether the Stille reaction is still useful and competitive.[14] As an advantage, the Stille reaction is a mild process that tolerates a wide variety of functional groups, and for this reason, it is frequently used in the synthesis of molecules of high complexity. Furthermore, organostannanes are relatively insensitive to moisture and oxygen, allowing for harsher reaction conditions, and are accessible by numerous methods. However, the reaction adds, to the Pd concerns, that of potential Sn contamination. The problem is probably exaggerated from a strictly chemical point of view, since the toxicity of the more commonly used tri-*n*-butyltin derivatives (LD$_{50}$ in the range 100−300 mg kg^{-1}) is far lower than those of triethyl- and trimethyltin derivatives (LD$_{50}$ < 15 mg kg^{-1}),[15] but it cannot be ignored, particularly for its use in the production of pharmaceuticals. The required upper limit of Sn level by toxicologists is ~20 ppm.[16]

In this respect, it is interesting to recall the results of a study at Pfizer looking for a large-scale preparation of imidazole−

thienopyridine VEGFR kinase inhibitor for pharmaceutical purposes.[17] The key step was the coupling of the imidazole and thienopyridine fragments composing the chloropyridine intermediate shown in Figure 1. Different cross-coupling
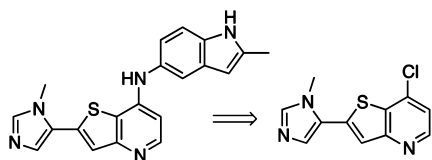
Figure 1. Retrosynthetic analysis of an imidazole−thienopyridine VEGFR kinase inhibitor through a chloropyridine key intermediate obtained by Stille coupling.

processes were attempted, but only the Stille coupling was suited to provide a robust and scalable cross-coupling method. The authors commented on a very important but often forgotten issue: "*This suggests that the wide variety of cross-coupling methods demonstrated on simpler biaryl systems is more limited when applied to complex heterocyclic systems.*" Or, could we add, when the syntheses have to be scaled.

In the same line, the comparison of the Negishi, Suzuki, and Stille methods for the synthesis of halogenated 2-chlorobithia-zoles (Figure 2) showed that the Stille reaction was the best
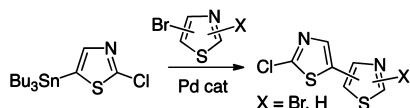
Figure 2. Synthesis of bithiazoles using Pd-catalyzed reactions in which Stille is superior to Negishi and Suzuki couplings.

cross-coupling method.[18] The Negishi method suffered from substantial side reactions leading to inseparable mixtures of products, and the Suzuki catalysis gave poor conversions.

Compared with B or Zn derivatives, the lower polarity (hence, lower basicity) and higher steric demand of Sn derivatives makes them less nucleophilic and less reactive. However, nucleophilicity is not the only virtue sought for in a nucleophilic reagent: reactivity and selectivity are often in conflict,[19] and selectivity is a must in many areas of synthesis. Stille coupling has its own position in cross-coupling catalysis. This is supported by a recent estimation of the total number of publications and patents on cross-coupling reactions through 2010/April 2014,[20] which affords the following scores and trend: Suzuki−Miyaura, 10175/15883 > Heck, 4029/5816 > Sonogashira, 3623/5689 > Stille, 2380/3537 > Negishi, 429/737 > Buchwald-Hartwig, 253/498 > Kumada-Corriu, 136/298 > Hiyama, 91/172 > carbonyl α-arylation, 113/193.

3. THE MECHANISMS: EXPERIMENTAL AND THEORETICAL STUDIES

Chemistry occurs as a competition of possible reaction pathways, whether desired or undesired, which afford more or less selective processes as a result of the competition of rates of the pathways kinetically feasible. In the simple representation of the Stille cycle often found in books (Scheme 1), the Stille process, deprived of coordination information at Pd, is composed of three steps: oxidative addition, transmetalation, and reductive elimination. It looks as simple and selective as the subway map of Sevilla (Spain): there is only one line and you

Scheme 1. A Simplified Stille Cycle
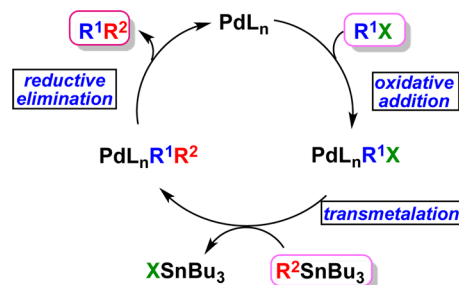
can hardly make mistakes (Figure 3). However, the true complexity of the Stille reaction reminds one of that of the


Figure 3. Maps of the subway transport. Left, Sevilla (Spain); right, Moscow (Russia).

subway maps of New York, Madrid, Paris, or Moscow. As a difference with using the subway transport, you have to make your catalytic trip with blind eyes, because you hardly see any signs. It is not that easy to take the right train, change trains at the right point, and exit at the chosen station.

This complexity is reflected in the Stille cycle shown in Scheme 2, still a poor representation of reality but at least

Scheme 2. A More Detailed Stille Cycle
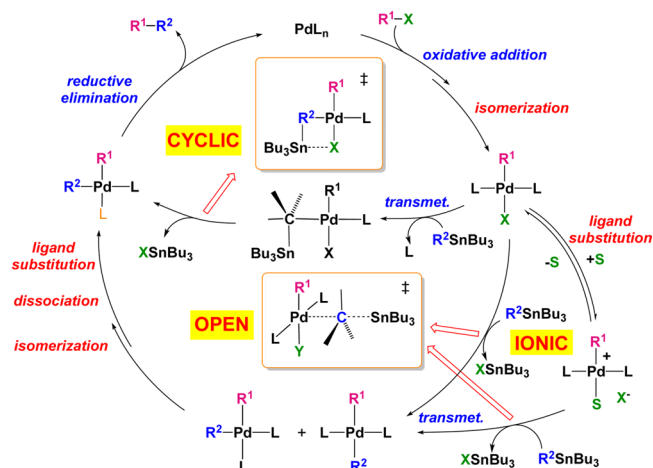
showing three important concepts sometimes forgotten: (i) It is the transition metal catalyst that does the job, obeying the rules of coordination chemistry. Ignoring coordination chemistry is like walking in a desert without a compass. (ii) A fourth type of process, isomerization, has to be considered where appropriate, as highlighted in Scheme 2, and also others,

such as ligand dissociation and ligand substitution. (iii) Although not shown in Scheme 2, some steps in the cycle are easily reversible, which can give rise to undesired byproducts, particularly when the irreversible C−C coupling step closing the cycle is too slow, allowing generation of new species via undesired (mistaken) reversible transmetalations.

It is interesting to warn that the cyclic and open pathways are part of the common mechanistic jargon in the literature, but the third pathway that we included from the beginning, the ionic pathway, is often disregarded and should be kept in mind when choosing solvents. The ionic pathway is, in fact, the most frequent subcategory of the open pathway (which can, however, proceed also through neutral species), and it is being highlighted because of its importance. We will see the importance of the open ionic pathway later on, in the section Stereoselectivity of Transmetalation: Inversion vs Retention.

Comparing Scheme 2 with the cycle proposed in our 2004 review, on the basis of only kinetic studies and observation of some intermediates, it is clear that the 2004 cycle remains essentially complete and correct, except for some details. Since then, our own DFT studies, using Ph−Br and Me_3Sn−CH═CH_2, confirmed the open and cyclic transmetalation pathways proposed, although correcting the structure of the transition state for the cyclic pathway.[21] We had proposed initially a concerted structure with penta-coordinated Pd on which formation of the square transmetalation fragment and L substitution took place simultaneously,[8] but the computational study did not find that proposed TS, and instead, it supported that, at least for the transmetalation of vinyl, transmetalation occurs in two steps: ligand substitution by the entering vinyl group (using the double bond as the entering ligand) followed by transmetalation through the TS shown in Scheme 2. The two cyclic pathways, via the old TS[7,8] or the new TS (here), have the same kinetic dependences, and this case illustrates the convenience of combining calculations and experiment in mechanistic studies for a more accurate interpretation of the data. Other mechanistic DFT studies,[22,23] some of them involving heterostannanes (Me_3SnZR_3, Z = P, As; R = Ph, Me) as nucleophiles, also support the validity of the mechanistic proposal in Scheme 2.[24,25] It is, however, important to recall that DFT studies should never replace the primary value of experimental kinetic studies because the precision of calculated energies cannot be guaranteed. An error in the calculated activation energy of 1 kcal mol^{-1}, which looks unavoidable for metal-containing molecules, means roughly a one power of 10 error in the corresponding reaction rate, which can dramatically change the prediction of the preferred pathway.[26]

Study of the retrotransmetalation reaction in Scheme 3, combining kinetic experiments and monitoring by ^{19}F NMR spectroscopy with DFT calculations, has provided definitive additional confirmation of the cyclic mechanism.[27] The complex $[PdRf_2(AsPh_3)_2]$ (Rf = 3,5-$C_6Cl_2F_3$) reacts with Bu_3SnI to produce $[PdRfI(AsPh_3)_2]$ and Bu_3SnRf. The Stille reaction is the opposite sense reaction ending with Rf−Rf coupling, but this coupling has a high activation energy for fluorinated aryls and does not take place.

This coupling frustration allows for several interesting observations: (i) The reaction in Scheme 3 proceeds smoothly, confirming that the transmetalation step is, as expected, reversible. (ii) The Stille transmetalation (from the initial reagents to $[PdRf_2L_2]$) is counter-thermodynamic (3 + 4 is more stable than 1 + 2), and for this reason, it needs the irreversible coupling step to take place so as to make the overall

Scheme 3. Retro-Stille Transmetalation Step
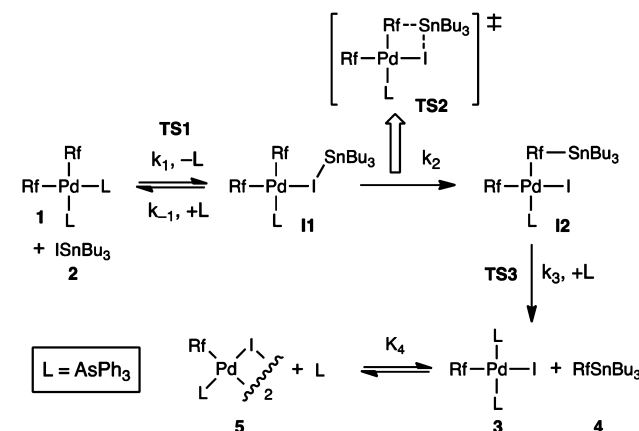
process thermodynamically favorable. (iii) A slow reductive elimination step can be rate-determining (or, as in this case, frustrate the coupling): this is an important complication, as commented above, because slow coupling will propitiate formation of undesired byproducts from undesired mistaken group exchanges in the reversible transmetalation. This explains, for instance, the observation of Bu_3SnPf (Pf = C_6F_5) in the Stille coupling of PfI and Bu_3Sn(vinyl).[9] (iv) Monitoring the retrotransmetalation allows for experimental observation of the intermediate complex $[PdRf_2(AsPh_3)(ISnBu_3)]$ (I1), which precedes the rate-determining state in the retro-Stille evolution and becomes observable.

All the rate and equilibrium constants were determined and, along with DFT calculations, provided the energy profile and the structures of the TS's in Figure 4. Note that theoretical values are $\Delta E^{\ddagger}$ and do not match the experimental $\Delta G^{\ddagger}$ values when there is important entropic contribution. Complex I1 is
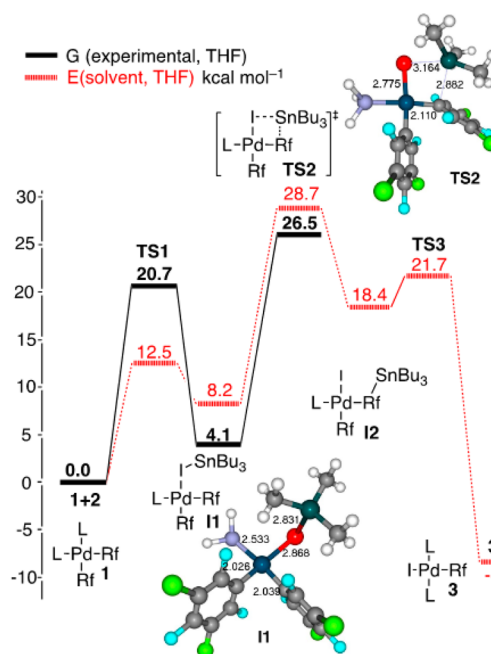
Figure 4. Profile of the retrotransmetalation reaction 1 + 2, showing experimental ΔG values in THF and calculated ΔE values (solvent) in kcal mol^{-1}. The calculated structures of the detected intermediate I1 and the transmetalation transition state TS2 are also given.

the result of ligand substitution of $AsPh_3$ by Bu_3SnI as the entering ligand, and it is the first step to form the cyclic **TS2**.

With the addition of this study, the cyclic and open mechanisms are very well supported experimentally. In fact there are now physical observations of: *cis*- and *trans*-$[PdR^1XL_2]$ products of oxidative addition (which immediately precede the cyclic or open transmetalation **TS**);[8] $[PdR^1R^2L\text{-}(XSnBu_3)]$, formed immediately after transmetalation;[27] *cis*-$[PdR^1R^2L_2]$, formed when the (Bu_3SnX) byproduct is liberated from Pd by substitution with an entering ligand;[9] and *trans*-$[PdR^1R^2L_2]$, formed in competition with its cis isomer in reactions following the open pathway.[9,10] It is very unusual that a mechanistic proposal is supported by so many physical observations.

At the time of our initial proposal of the cyclic and open mechanisms, the Stille experiments we studied started with the oxidative addition of a fluoroaryl iodide, which gives initially *cis*-$[PdR^1IL_2]$,[28] and our system happened to have a cis−trans isomerization of the oxidative addition product, which was fast compared with the transmetalation rate of the next step, so the transmetalation was studied only on the *trans*-$[PdR^1IL_2]$ complex. However, in a general case, the oxidative addition can give cis or trans complexes or a mixture of both (aryl halides give concerted cis oxidative addition, but alkyl halides often give directly trans complexes). The isomerization of these products can be slower or faster or fall in the order of rate of the transmetalation,[29] and in this case, the coexistence of transmetalations on cis and on trans oxidative addition complexes, as well as the cis or trans stereochemistry of the transmetalation itself in the open mechanism, complicates the picture: The cycle in Scheme 2 should be multiplied by two, one starting from the cis and another from the trans oxidative addition complex.

These complications have in fact been observed in the study of the coupling of RfI with $Bu_3SnC{\equiv}CPh$: The *cis*- and *trans*-$[PdRfI(PPh_3)_2]$ isomers were observed when monitoring the reaction, regardless of the election of **1** or **2** as the initial catalyst. Independent catalytic studies starting separately on each of them revealed the evolution of their isomerization, and the occurrence of transmetalations on both of them, which produced both isomers *cis*- and *trans*-$[PdRf(C{\equiv}CPh)(PPh_3)_2]$, as seen in Figure 5 for one of the monitored processes. *cis*-$[PdRf(C{\equiv}CPh)(PPh_3)_2]$ is not observed because it undergoes very fast C−C coupling to give $Rf\text{−}C{\equiv}CPh$ (which is observed), but *trans*-$[PdRf(C{\equiv}CPh)(PPh_3)_2]$ cannot couple, and it accumulated in solution due to an extremely slow isomerization to cis. Thus, the trans complex became a Pd trap that progressively captured the catalyst in that inactive form and eventually stopped the process, preventing obtaining a good yield of the desired product, $Rf\text{−}C{\equiv}CPh$.

The increasingly complicated view of the mechanisms of transition metal catalysis that these studies uncover is briefly summarized in Scheme 4. This Scheme is, in fact, deceptively simple, considering that it does not specify the several possible mechanisms of isomerization,[28,30] of transmetalation, and of reductive elimination (for instance, with or without L dissociation) hidden behind single arrows. In a more detailed mechanistic scheme, isomerization connections between cis and trans isomers should also be drawn attending to the fact that Pd complexes at different points in the cycle (as highlighted in Scheme 2) do isomerize at variable rates. Side reactions should also be considered. Full representation of all these complications would convert the cycles in a useless nightmare, and they
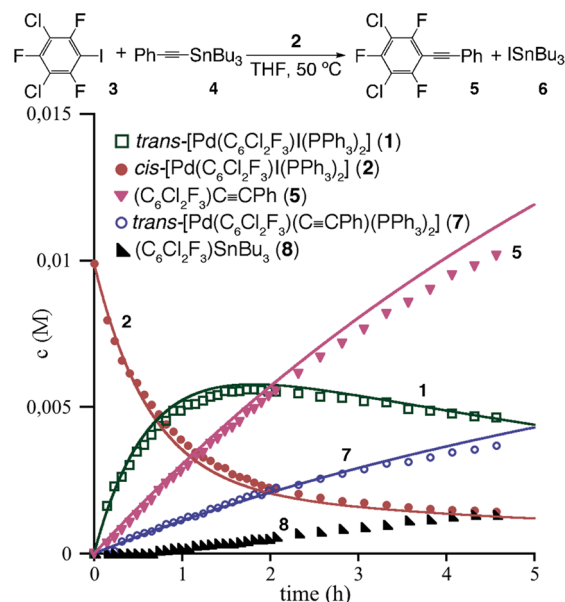
Figure 5. Concentration/time data for the reaction **3** + **4**, in THF at 323.2 K, using **2** as the initial catalyst. Note that the disappearance of **3** is not depicted and is out of the drawing limits.

Scheme 4. Mechanisms Usually Involved in Metal Catalyzed Reactions
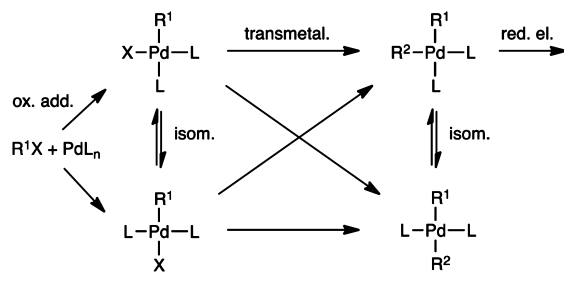
are left out of the picture, but these competitive reactions do exist and have to be kept in mind when using the simplified mechanistic information in Scheme 2.

It is obvious from the picture just discussed that any attempt to generalize palladium-catalyzed cross-coupling reactions by a simple reaction profile connecting data from different studies, or to assign in a general way the rate-determining step (or state) to a single moment of the reaction,[13c] is not realistic. Moreover, it is important to be aware that the kinetic behavior in multiequilibria systems existing in a running process is not a simple matter as well as to be conscious that the different steps can be influenced and complicated by other species present in solution that, in principle, do not pertain to the specific step under consideration.

A way to simplify the complexity of the system is to prevent the formation of isomers, which might be achieved by using chelating ligands that force cis geometry or, in a more powerful way, by using bulky ligands that hinder the coordination of a second ancillary ligand and drive the cycle via functionally tricoordinated Pd^{II} complexes. Chelating hemilabile ligands and halo-bridged dimeric complexes might also offer easy access to 3-coordination. These possibilities are discussed later. But before doing that, and notwithstanding our comment in the previous paragraph, we will make some practical quick revision of what is known for the fundamental steps of Scheme 2. For

more details and a bibliography, please refer to our 2004 review.[7]

1). Oxidative Addition. The oxidative addition of aryl iodide works easily on Pd^0 complexes with good donor ligands, such as phosphines, but bromides work worse, and chlorides or triflates usually fail. Pd^0 complexes with less-donor ligands such as $AsPh_3$ fail even with ArI and need the addition of chloride to form anionic $[PdClL_2]^-$ complexes that are easier to oxidize. Complexes with good donor bulky phosphines are more reactive, and their Pd^0 complexes often react with the difficult chloride and triflate electrophiles so that oxidative additions with aryl chlorides, triflates, tosylates, mesilates, pirazolylsulfonates, fluoroarylsulfonates, etc. have been reported in the past decade.[31]

2). Transmetalation. The cyclic mechanism requires a good bridging anionic ligand (typically a halide), and an easily leaving ligand (e.g., $AsPh_3$, furyl phosphine) will give faster transmetalation.[8] Free phosphine (e.g., from oxidation of $[Pd(PPh_3)_4]$) is very detrimental but can be sequestered with CuX salts.[28] More electronegative halides accelerate the transmetalation because they make a more electrophilic Pd^{II} center,[32] and alkaline or alkylammonium salts can be used to promote in situ halide exchange. Stannatranes are interesting reagents for the transmetalation of sp^3 carbons because the N coordination to Sn increases the nucleophilicity of the reagent (see later).[33,34]

The open and ionic mechanisms are favored for badly coordinating anionic ligands (e.g., triflate), which create highly electrophilic Pd centers, leading to fast transmetalation. The counteranion is often totally or partially displaced by even moderately coordinating solvents, such as THF, producing a more electrophilic cationic Pd^{II} center and inducing the ionic mechanism in Scheme 2. More strongly coordinating and dissociating solvents (e.g., HMPA) can also produce cationic Pd^{II} centers by halide substitution, in which case obviously, the cyclic mechanism, lacking a good bridging groups (e.g., halides) on Pd, will not operate.[9]

3). Reductive Elimination. The reductive elimination, occurring through a three-member transition state PdR^1R^2, needs the two groups involved to be mutually cis, which requires isomerization for those products of transmetalation with trans sterochemistry. The activation energy of coupling obviously depends on the groups to be coupled, following the trend C sp^3–C sp^3 > C sp^3–C sp^2 > C sp^2–C sp^2;[35] so it appears that more electron-rich carbons require higher activation energies, and strongly donor ancillary ligands might be expected to make the coupling more difficult. Moreover, nonsymmetrical complexes ($[PdR^1R^2L_2]$) have computed activation energies that are roughly the average between those of their symmetrical counterparts,[35] although experimental evidence shows that coupling rates are faster for $[PdR^1R^2L_2]$ than for $[PdR^1{}_2L_2]$ or $[PdR^2{}_2L_2]$.[36] Finally, coupling can occur on tetra-coordinated Pd complexes (also including complexes with chelating ligands),[37] or require L dissociation previous to coupling.

The role of ancillary ligands on coupling has been thoroughly studied and quantified by DFT methods (B3LYP) supported with experimental kinetics (Table 1).[38,39] In addition to the influence of the R groups ($\Delta G^{\ddagger}$ increased in the order vinyl < Ph < Me), the couplings in complexes with different ancillary ligands were computed, including the case with L = empty position, which represents the coupling in functionally tricoordinated Pd complexes formed by bulky ligands. For all

Table 1. Computed Energy Barrier ($\Delta G^{\ddagger}$, kcal mol^{-1}) for the Reductive Elimination of Me–Me Starting from the cis-$[PdMe_2(PMe_3)(L)]$ Complexes

R	L	$\Delta G^{\ddagger}$, kcal mol^{-1}
vinyl	PMe_3	11.5
Ph	PMe_3	12.8
Me	PMe_3	28.6
Me	MeCN	27.0
Me	trans-2-butene	23.0
Me	ethylene	21.7
Me	2,5-dihydrofuran	19.8
Me	3,5-dimethylenecyclopent-1-ene	15.9
Me	trans-1,2-dicyanoethylene	10.0
Me	maleic anhydride	8.6
Me	benzoquinone	5.9
Me	**empty, 3-coord**	**13.2**

the R groups, the activation free energies for the reductive elimination follow the trend illustrated in Table 1 for the Me–Me coupling. Me–Me coupling from a tricoordinated complex ($\Delta G^{\ddagger}$ = 13.2 kcal mol^{-1}) must be very fast. This is an advantageous circumstance for the use of bulky ligands. Most of the ancillary ligands lead to coupling in the tetracoordinated complex and show higher or much higher activation energies than for the tricoordinated cases, the higher for the better donor ligands.

Interestingly, olefin ligands dramatically reduce the coupling barrier, and strong π-acceptor olefins lead to $\Delta G^{\ddagger}$ values as low as 5.9 kcal mol^{-1}, in the case of benzoquinone. This means that the difficult coupling of two Me groups in a complex coordinated with one PMe_3 and one benzoquinone should still be very fast at temperatures of $-30\ ^\circ$C or lower. A support for this expectation was found in a recent study using a phosphine π-(electron withdrawing olefin) chelating ligand, in which butane was formed quickly from Et groups at $-50\ ^\circ$C.[40] There are many reactions in the literature using as the initial catalyst $[Pd(dba)_2]$ or $[Pd_2(dba)_3]$ plus some added ligand. Since some dba is displaced after oxidative addition of Pd^0 to Pd^{II}, these systems find, at the moment of coupling, the unexpected bonus that dba will contribute to reduce the coupling barrier. Of course, at the cost of some increase in the oxidative addition barrier because electron-withdrawing olefins stabilize Pd^0 against oxidation.[7,41]

4. LIGANDS IN STILLE COUPLING: BULKY PHOSPHINES, CHELATING LIGANDS, CARBENES

4.1. Bulky Phosphines. The use of electron-rich bulky phosphine ligands should be regarded as a breakthrough in the development of effective protocols for challenging Stille cross-coupling reactions.[42] For instance, XPhos and $[Pd(AcO)_2]_3$ accomplish the unprecedented Stille synthesis of biaryl compound from aryl mesylates and tosylates.[43] Bulky electron-rich proazaphosphatrane $P\{(R/R')NCH_2CH_2\}_3N$ (R/R' = ^{i}Bu, Bz) ligands (Figure 6) are very efficient in the Stille coupling of electronically diverse aryl chlorides with a variety of organotin reagents, including sterically hindered systems.[44]
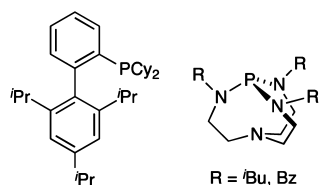
Figure 6. Structure of XPhos (left) and proazaphosphatrane (right).

In line with these results, the remarkable efficiency of P^tBu_3 led to the first effective Stille couplings of unactivated aryl and vinyl chlorides for the synthesis of a wide variety of products, including strongly hindered tetra-substituted biaryls, and Stille couplings of activated aryl chlorides and unactivated aryl bromides at room temperature.[45] Another hint of the unique behavior of P^tBu_3 was found in competition Stille experiments involving ArCl/Ar'OTf or ClC$_6$H$_4$OTf electrophiles, which revealed unexpected 43:1 selectivity for Cl—Ar reaction over Ar—OTf.[45] The same trend was found in Suzuki couplings,[46] with the also unexpected selectivity for the coupling product of the aryl chloride over the aryl triflate (Figure 7). In contrast, the expected selectivity toward the triflate coupling product was obtained using PCy$_3$ (cone angle 170°) instead of the bulkier P^tBu_3 (cone angle 182°).[47]
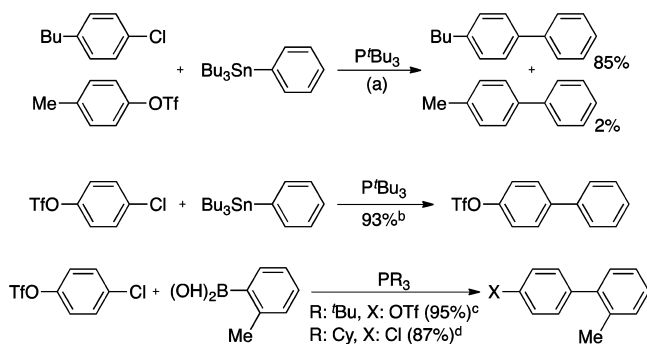

Figure 7. Inter- and intramolecular Cl/OTf competition experiments in Stille and Suzuki couplings. (a) 1.5% [Pd$_2$(dba)$_3$], 3.6% P^tBu_3, 2.2 CsF, dioxane, 60 °C; (b) 0.75% [Pd$_2$(dba)$_3$], 1.5% P^tBu_3, 2.2 CsF, dioxane, r.t.; (c) 1.5% [Pd$_2$(dba)$_3$], 3% P^tBu_3; (d) 3% [Pd$_2$(dba)$_3$], 6% PCy$_3$.

These experimental results, whether obtained from intermolecular or from intramolecular chloride/triflate competitions, along with computational studies,[48,13f] suggest that the different chemo- or regioselection occurs at the oxidative addition step and is determined by features of the Pd^0 species, such as the nucleophilicity of the ligands, the number of L ligands, their spatial requirements, their electric charge (neutral or anionic), and the polarity of the solvent. Accordingly, the more electron-rich bisligated [Pd^{0}L$_2$] complex (L = PCy$_3$) shows higher reactivity toward Ar—OTf, whereas the monoligated [Pd^{0}L] (L = P^tBu_3) is more reactive toward Ar—Cl, affording [PdArClL], although this selectivity also depends on other reaction conditions, such as the polarity of the solvent (higher polarity favors reaction of the triflate), or the presence of additives.[49]

In a more general approach, it has been shown combining gas phase experiments in an ion-trap mass spectrometer and DFT calculations, that monoligated [Pd(PAr$_2$Ar')] complexes have lower activation energies for oxidative addition of ArX (X = F, Cl, Br, I) than bisligated [Pd(PAr$_2$Ar')$_2$]. These activation

energies increase quite steeply, depending on the halide, in the order I < Br < Cl < F.[50]

Three different pathways have been proposed to explain the oxidative addition of ArX (X = Cl, Br, I) to [Pd^{0}L$_2$] complexes having phosphine ligands with different steric demands (Scheme 5):[51] (a) oxidative addition of ArX by direct reaction

Scheme 5. Mechanisms for the Oxidative Addition of ArX to [Pd^{0}L$_2$] Complexes
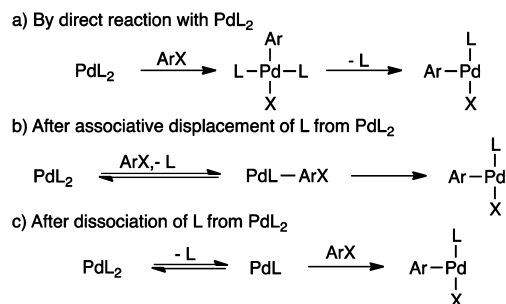
with [PdL$_2$], (b) oxidative addition of ArX after associative displacement of L from PdL$_2$, and (c) oxidative addition of ArX after dissociation of L from [PdL$_2$]. Apparently, it is the nature of the halide that determines the mechanism experimentally observed, regardless of the bulkiness of the phosphine. Thus, ArI are active enough to react irreversibly with the less active [PdL$_2$] via associative displacement of a phosphine (pathway b). In contrast, the lower reactivity of ArCl requires a dissociative mechanism to afford a more reactive monoligated [PdL] on which oxidative addition takes place (pathway c). As for ArBr, the major pathway is proposed to follow an irreversible reaction with [PdL$_2$] following either a displacement of one L (pathway b) or a direct oxidative addition (pathway a), but a minor not well-defined dissociative pathway (pathway c) seems to be also operating. Depending on the size of the phosphine, the tricoordinated kinetic product will dimerize to the corresponding halo-bridged dimer.

DFT studies on the oxidative addition of PhCl to [Pd(PR$_3$)$_2$] (R = Me, Et, ^{i}Pr, ^{t}Bu) suggest that the oxidative addition step occurs, in all cases, on monoligated species [Pd(PR$_3$)] (as in pathway c in Scheme 5). This activation energy for the transition state in which Ar—Cl interacts with the Pd^0 complex is much higher on the bisligated complex. Interestingly, the values of $\Delta G^{\ddagger}_{ox}$ are almost identical, regardless of the bulkiness of the phosphine, but the oxidation takes place only for the bulky P^tBu_3.[52] The reason for this must be that the preequilibrium dissociation of one phosphine is less unfavorable for bulky phosphine ligands, which increases their concentration under the conditions used in catalysis as compared with the smaller phosphines, affording kinetically effective concentrations that are not reached with the small phosphines, hence producing acceptable rates for the oxidation process.[53,54]

Tricoordinated Pd^{II} complexes with bulky ligands are key intermediates in cross-coupling reactions. Calculations using [PdPh(NH$_2$)(PH$_3$)] as a model complex clearly support the T-shaped geometry bearing the more σ-donor aromatic ligand trans to the vacant site as the most stable structure.[55] The strict consideration of these complexes as 14-electron tricoordinated Pd(II) complexes can be questioned; the vast majority of them show C—H,[56] or other weak[57,58] agostic coordination to the hypothetically empty coordination position on Pd, and there is

room for debate in certain cases,[59] but a few examples with amide ligands look really tricoordinated.[60] However, because of the strong π-donating ability of the lone pair in the amide nitrogen, these tricoordinated complexes cannot be said to be 14-electron.[61] Agostic interactions can be easily dissociated at very low energy cost and lead to short-lived tricoordinated intermediates with an empty low-lying Pd orbital. As a consequence, these weakly protected Pd complexes can be considered in the discussions as operationally tricoordinated for short. Their chemistry is dramatically different because they favor a 16e−14e−16e dissociative mechanism over the most common 16e−18e−16e associative substitution operating in the usual square planar Pd(II) complexes.[21] Reductive elimination is favored in these tricoordinated complexes with electron-rich phosphines bearing bulky substituents, such as P^tBu_3.[62] These phosphines happen to be electron-rich, but they facilitate the coupling because they are bulky, not because they are electron-rich. We have commented previously that electron-rich ligands making the Pd^{II} center more electron rich should be detrimental for coupling because this increases the electron density on the carbons to be coupled, making their interaction more difficult. Yet the electron richness of Pd^{II} with only three ligands (one phoshine) is less than with four ligands, and obviously, this facilitates the C···C interaction toward coupling. This consideration may also help in the understanding of the influence of bulky phosphines on facilitation of coupling in the best recent challenging coupling, which is the formation of ArF by reductive elimination from [PdArFL] (L = BrettPhos).[58]

There are many electron-rich bulky phosphines available to use, and they have revolutionized the field of cross-coupling processes. In fact, they are great assets to every step of the catalytic cycle, as illustrated by the simple sketch in Scheme 6.

Scheme 6. Sketch of the Performance of Bulky Phosphines in the Elementary Steps in Cross-Coupling Reactions

oxidative addition   *transmetalation*   *reductive elimination*
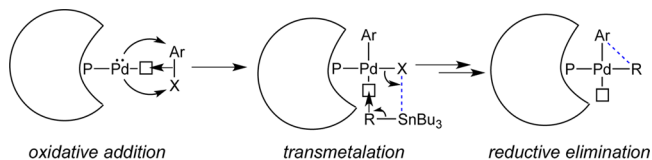
At the oxidative addition step, a monoligated Pd^0 structure offers an open space, fairly free of ligand repulsions, which facilitates the initial side-on approach of the Ar−X bond to Pd (a nucleophilic attack to Pd by the electron pair of that bond); the electron richness of the phosphine provides efficient electron back-donation to the σ^* Ar−X orbital so that the oxidative addition is completed even for reagents with very low nucleophilicity of the Ar−X bond.

At the transmetalation step, the nucleophilic attack of the stannane occurs on a tricoordinated Pd center, which is always more electrophilic than an equivalent tetracoordinated center with one additional donor ligand. This facilitates the reaction with less-strong tin nucleophiles. It is worth commenting that tricoordination at transmetalation is particularly beneficial for Stille (and presumably for the Hiyama) processes because of the low nucleophilicity of tin derivatives due to the low polarity of the Sn−C bond and the high volume of the tin reagent, as compared with Zn, B, and other derivatives. Moreover, the S_N2 transmetalation does not require the displacement of a leaving group (there is no need to pay for the displacement of the fourth ligand, inexistent or being at most an agostic interaction

or the bridge in a dimer). As an extra bonus, the problem associated with the formation of cis and trans isomers that we have shown in Schemes 2 and 4 does not exist in tricoordinated complexes.

Finally, at the reductive elimination step, tricoordinated complexes have very low coupling barriers (on the order of 13 kcal mol^{-1} for Me−Me coupling, as discussed before). It is the combination of these virtues that makes the electrophilic bulky phosphines almost unbeatable for Stille processes, were it not for their high prices and their sensitivity to oxidation.

4.2. Chelating and Pincer Ligands. Chelating ligands could be thought of as an alternative, less expensive solution to the problem of undesired isomers because they force in Pd the cis geometry required for the final cross-coupling. However, since early times,[63] the few scattered studies report negative results,[64] with very rare exceptions.[65] There are several possible reasons for the bad performance of diphosphines (PP). The diphosphines are difficult to dissociate and will stabilize tetracoordinated intermediates. Thus, they can sequester Pd^0 in the form $[Pd(PP)_2]$, which is very resistant to oxidation. They will also make the transmetalation step difficult because it often requires dissociation of one coordinated ligand to make room for the entering R^2 coming with the tin reagent (Scheme 2). The same difficulty to release one end of a chelating ligand will also create a high activation barrier to reductive elimination.[13c,66]

Pd complexes with pincer ligands have also been tried in the Stille reaction, and some of them have an extraordinary activity that will not be further discussed here because the catalysis is due to the formation of nanoparticles.[67]

4.3. Carbene Ligands. Although very fashionable ligands in other fields (e.g., Au^I catalysis), only rare examples of the use of an in situ-prepared $[Pd(OAc)_2]_3$/NHC·HCl/TBAF system[68] or well-defined *trans*-dihalopalladium complexes bearing only one bulky NHC (nitrogen heterocyclic carbene) and a second easy leaving ligand (e.g., Pd-PEPPSI-Ipent) have proved effective in Stille cross-coupling.[69] A recent review on these systems is available.[70] In contrast, there are no synthetic reports using biscarbene complexes, and it has been nicely shown that the presence of two carbenes on Pd blocks the transmetalation step.[71]

5. STEREOSELECTIVITY OF TRANSMETALATION: INVERSION VS RETENTION

The double possibility to drive the transmetalation step of chiral stannanes taking advantage of the two conformational consequences of the cyclic (retention) and the open and ionic (inversion) pathways is an interesting possibility that seems not to have been consciously tested, but there are a few papers using chiral stannanes in the Stille reaction, which will be analyzed here in light of the mechanistic possibilities in Scheme 2. The chiral stannanes used are easily accessible α-heterosubstituted stannanes, except for the seminal work of Stille and the azastannatrane derivatives in Table 2. The use of chiral C(sp^3) α-stannylated electrophiles affords insight into the transmetalation mechanism because the stereoselectivity of the whole reaction depends on this step, since the reductive elimination takes place with retention of the configuration at sp^3 carbons. Thus, the stereochemistry found in the coupling products should report whether a cyclic or an open mechanism is operating. Table 2 gathers the reactions using Pd exclusively as the catalyst, and a chiral stannane.

Table 2. Stereoselective Pd Catalyzed Stille Couplings

chiral stannane	electrophile	cat (mol%) solvent, T(°C) inversion /retention
	Ph—C(=O)Cl	[PdCl(CH$_2$Ph)(PPh$_3$)$_2$](4%) HMPA, 65 ≥ 65% stereospecificity **inversion**[a 72]
94%ee	ArX (X: I, Br)	[Pd(PPh$_3$)$_4$] (8%) DMF, 60–75 **complete inversion** (90-94% ee for different aryls)[73]
98%ee	PhI	[PdCl$_2$(dppe)] (10%) THF, 45 **complete retention** (98% ee)[74]
	Ph—CH=CH—I	[PdCl$_2$(dppe)] (10%) THF, 45 **complete retention**[b 74]
Bu$_3$Sn	PhBr	[Pd(PPh$_3$)$_4$] (5%) dioxane, 80 **complete retention** (99% ee)[75]

[a]As indicated by Stille. [b]No ee data specified in the reference article, although the authors comment that complete retention of configuration is observed.

Retention of the configuration in entries 3, 4 might be expected because the conditions (less polar and not very coordinating solvents: for example, THF; polar index, 4.0; dioxane, polar index, 4.8) are perfect for the oxidative addition product [PdArXL$_2$] to follow a cyclic transmetalation. In contrast, in the reactions in entries 1 and 2, partial or complete inversion is reported, as expected for an open mechanism, despite the fact that the presence of halide in the oxidative addition intermediate should also induce retention. The reason for this apparent contradiction is found in the effect of solvents on the [PdArXL$_2$] complexes. As shown in the cases in Table 3, better coordinating polar solvents such as HMPA, NMP, and

Table 3. Speciation of Palladium Complexes under Different Conditions

Y	solvent	n	complexes in solution
Cl, Br, OTf	HMPA	2	[HMPA—Pd(L)(L)—R^1]$^+$ Y$^-$
Cl	HMPA	0	[HMPA—Pd(L)(L)—R^1]$^+$ Cl$^-$ 62.5% / [HMPA—Pd(L)(HMPA)—R^1]$^+$ Cl$^-$ 17.5% / Cl—Pd(L)(HMPA)—R^1 20%
I	NMP	0	I—Pd(L)(L)—R^1
OTf	NMP	0, 2	[NMP—Pd(L)(L)—R^1]$^+$ OTf$^-$
Cl, Br, I	THF	0	Y—Pd(L)(L)—R^1

presumably DMF are able to displace the halide ligand from [PdArXL$_2$] to give a more electrophilic cationic complex and drive the reaction via the ionic pathway in Scheme 2, which implies inversion of configuration. Interestingly, in his seminal paper, Stille found major but only partial inversion in HMPA, which fits well with the mixture of covalent and ionic species found in HMPA for a related Pd^{II} complex under the conditions of Stille (n = 0), suggesting competition of cyclic and ionic mechanisms.

The scope of enantioselective Stille cross-coupling has been widened by the use of copper(I) salts as cocatalysts, which can play two different roles. It has been demonstrated that cooper salts can act as ligand scavengers, mitigating the autoretardation by free phosphine of the rate-determining associative trans-metalation (for instance, when [PdL$_4$] is used as catalyst).[76] In this case, the copper salt should not participate in the catalytic cycle and this copper effect does not lead to any difference in the stereochemical outcome. However, the copper effect may have another component based on the existence of Sn/Cu transmetalation processes. In fact, copper salts alone are able to catalyze Stille-like cross-coupling reactions without the assistance of palladium (Table 4). All the examples of palladium-free copper-catalyzed Stille-like reactions found in the literature are consistent with retention and are believed to operate via a Cu^I/Cu^{III} cycle similar to the Pd^0/Pd^{II} classic Stille cycle.[77] It is risky and premature to accept the Cu/Pd comparison or to take these findings as a general behavior because all the reactions tested have been carried out in relatively low polar solvents, and all the stannanes bear an oxygen substituent at α-C.

Finally, Table 5 collects reactions using Pd as the catalyst and Cu salts as the cocatalysts. With the previous data in mind, the question is, does copper participate in a bimetallic Pd/Cu catalysis? With just one exception, using a special ligand, all the articles report retention. An inspection of the reaction conditions shows that the ligand used is a phosphine, and the Cu salt has a stoichiometric, 2:1, or higher Cu/Pd ratio. This suggests that the reactions are operating with a phosphine-scavenging copper effect, which is known to have an accelerating effect.[76] Whether the copper salt participates with palladium in a bimetallic catalytic cycle (as we will report later for gold) or is only Cu catalysis, or Pd catalysis, or both competing, cannot be ascertained with the data available because under the conditions used, in all cases, retention should be expected, regardless of the mechanism.

6. BIMETALLIC Pd/Au STILLE CATALYSIS

Bimetallic catalysis refers here to catalytic protocols that use two different metals in two catalytic cycles, usually connected by a transmetalation step (this excludes tandem processes). This field has been recently reviewed.[88] The potential of the bimetallic Au/Pd pair has been evaluated under different conditions in a model Stille reaction between p-CF$_3$C$_6$H$_4$I and Bu$_3$SnAr, in which transmetalation is the rate-determining step.[89] What we want to comment on here, the effect of gold cocatalysis, can be illustrated by the selected reactions in Table 6: a dramatic beneficial effect of the presence of gold is noted as the bulkiness of the Ar group to be transmetallated increases. This clearly points to a mechanistic change. Note that in the reactions studied, Pd and Au use the same AsPh$_3$ ligand and are added as fully coordinated complexes, so any potential ligand scavenging by gold (as observed in the copper effect by Cu^I salts) is excluded.

Table 4. Stereoselective Cu Catalyzed Stille Couplings

Chiral stannane	Electrophile	Cat (mol%) solvent, T (°C) inversion /retention
(pyrrolidine thiocarbamate, R–CH(SnBu₃)–O–C(=S)–N)	BocHN–CH(R)–C(=O)–S-p-NO₂Ph	CuTC (5–20%) dioxane, 100 **retention**[a 78]
F₃C–C₆H₄–C(=O)–O–CH(R)–SnBu₃ (R = CH₂C(=O)OMe or alkene chain); Bu₃Sn	R'–C≡C–CH=CH–Br (R' = triisopropylsilyl); F₃C–C₆H₄–C(=O)–O–CH(R)(CH₃)	CuTC (20%) dioxane, 90 **retention**[a 79]
Ph(CH₂)₂–epoxide–SnBu₃ (two diastereomers)	Cl–C(=S)–O–Ph	Cu₂S (8%) THF, 70 **retention**[a 80]
(pyrrolidine thiocarbamate on dioxolane) SnBu₃	cis-alkenyl with –COOMe and –Br	CuCN (7%) THF, 50 **retention**[a 81]
X-PG / R–CH(SnBu₃)	Allyl, vinyl, aryl halides	CuCN (8%) THF, 45 **retention**[a 82]
(acetonide–SnBu₃ carbamates / thiocarbamates)	Allylic, cinnamylic, propargylic, acetylenic halides	CuI (7–10%) THF, 50 **retention**[a 83]
PTCO / Ph(CH₂)–CH(SnBu₃)	Ph–CH=CH–CH₂–I	CuTC (100%) THF, 23 **retention** (98% de)[84]
PTCO / (dioxolane)–CH(SnBu₃)	Ph–CH=CH–I	CuTC (100%) THF, −20 **retention** (95% ee)
NⁱPr₂ / Ph–CH₂–CH(SnBu₃)–O–C(=O)	Acid chlorides allyl bromides	CuCN (10%) toluene, 70 **retention** (94–98%[b])[85]

[a] No ee data is specified in the reference article, but the authors comment that complete retention of configuration is observed. [b] Stereoselectivity value.

Table 5. Stereoselective Pd/Cu Catalyzed Stille Couplings

Chiral stannane	Electrophile	Cat (mol%) Solvent, T (°C) inversion / retention
ᵗBu–S(=O)(=O)–NH–CH(Ar)(SnBu₃), R	Ph–C(=O)–Cl	[Pd₂(dba)₃] (5%) CuCN (5–10%) TTMPP (20%) toluene, 70 **inversion**[a 64b]
(N-Boc pyrrolidine)–Sn–N bicyclic, 99% ee	Br–C₆H₄–CN	[Pd(dba)₂] (5%) CuCl (200%) KF (200%) JackiePhos (10%) MeCN, 60 **retention** (96% ee)[34]
(azastannatrane) Ph(CH₂)₂–CH(CH₃), 94% ee	2-bromopyridine; 6-bromo-2-methylquinoline	[Pd(dba)₂] (5%) CuCl (200%) KF (200%) JackiePhos (10%) MeCN, 60 **retention** (91–92% ee)[34]
Bu₃Sn–CHD–OBz	Ph–C(=O)–Cl	[PdCl₂(PPh₃)₂] (4.5%) CuCN (10.5%) toluene, 70 **retention** (99% ee)[75]
Bu₃Sn–CHD–NPhth	Ph–C(=O)–Cl	[Pd(PPh₃)₄] (4%) CuCN (8%) toluene, 75 **retention** (98% ee)
Bu₃Sn–CHD–NPhth	PhBr	[PdCl₂(PPh₃)₂] (8%) CuCN (16%) dioxane, 90 **retention** (52% ee)
Bu₃Sn–CHD–NPhth	PhBr	[PdCl₂(PPh₃)₂] (8%) CuCN (16%) toluene, 90 **retention** (69% ee)
(bicyclic lactone)–SnBu₃, OBn	Ph–C(=O)–Cl	[PdCl₂(PPh₃)₂] (4%) CuCN (8%) toluene, 95 **retention**[a 86]
(BnO tris-benzyl sugar)–OR–CH(SnBu₃)	Cl–C(=S)–O–Ph	[PdCl₂(dppf)] (8%) CuCN (8%) toluene, 90 **retention**[a 65a]
OBz / CH₃(CH₂)₆–CH(SnBu₃), 94% ee	Ph–C(=O)–Cl	[PdCl₂(PPh₃)₂] (4%) CuCN (8%) toluene, 75 **retention**[a 87]

[a] No ee data is specified in the reference article but the authors comment that complete inversion/retention of configuration is observed.

These couplings could probably be carried out efficiently using bulky phosphines, but the cocatalized reaction is interesting because it shows very clearly one side of the Achilles heel of the classical Stille transmetalation: bulky groups are difficult to transmetallate due to their low nucleophilicity, originating in the low polarity of the Sn−C bonds, but severely worsened by the steric hindrance when two Pd[II] and Sn[IV] compounds, each with four ligands, have to come close to each other in the transmetalation transition state. This steric problem is alleviated in the Sn[IV] to Au[I] transmetalation because Au[I] is linear and also in the subsequent Au[I]-to-Pd[II] transmetalation.[90] Quantitative values for this sequential Sn/Au/Pd double transmetalation of a 2-Me-naphtyl group, leading to the product in Table 6, entry 7 via gold-cocatalyzed Stille coupling were obtained by DFT methods and are shown in Scheme 7 and in Figure 8. The activation energy in MeCN for the Sn/Pd transmetalation is 36.6 kcal mol⁻¹, which in practice means a forbidden pathway. The other two transmetalations, Sn/Au (25.5 kcal mol⁻¹) and Au/Pd (21.4 kcal mol⁻¹), indicate a somewhat slow but perfectly feasible process.

Scheme 8 depicts together the classic (black) and the Au cocatalyzed (pink) Stille cycles. The yields at identical reaction times observed in Table 6 indicate that for simple aryls, the two reaction rates are not very different (entries 1, 2), but just one ortho substituent suffices to produce a large rate detriment, and two substituents make the classic Stille impossible, while the cocatalyzed version keeps running (entries 3−8).
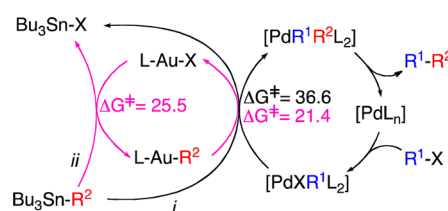
Table 6. Stille Au Co-Catalyzed Reactions

$$\text{Bu}_3\text{Sn-Ar} + \text{I}\!-\!\!\bigcirc\!\!-\text{CF}_3 \xrightarrow[\text{MeCN, 80 °C}]{\text{[Pd], [Au], LiCl}} \text{Ar}\!-\!\!\bigcirc\!\!-\text{CF}_3$$

Entry	Au co-cat	ArC$_6$H$_4$CF$_3$	time (h)	yield (%)
1	yes		5	83
2	**no**		**5**	**68**
3	yes		6	89
4	**no**		**6**	**4**
5	yes		24	84
6	**no**		**24**	**< 1**
7	yes		24	90
8	**no**		**24**	**< 1**

Scheme 7. DFT Calculated Pathway for the Sn to Au Transmetalation
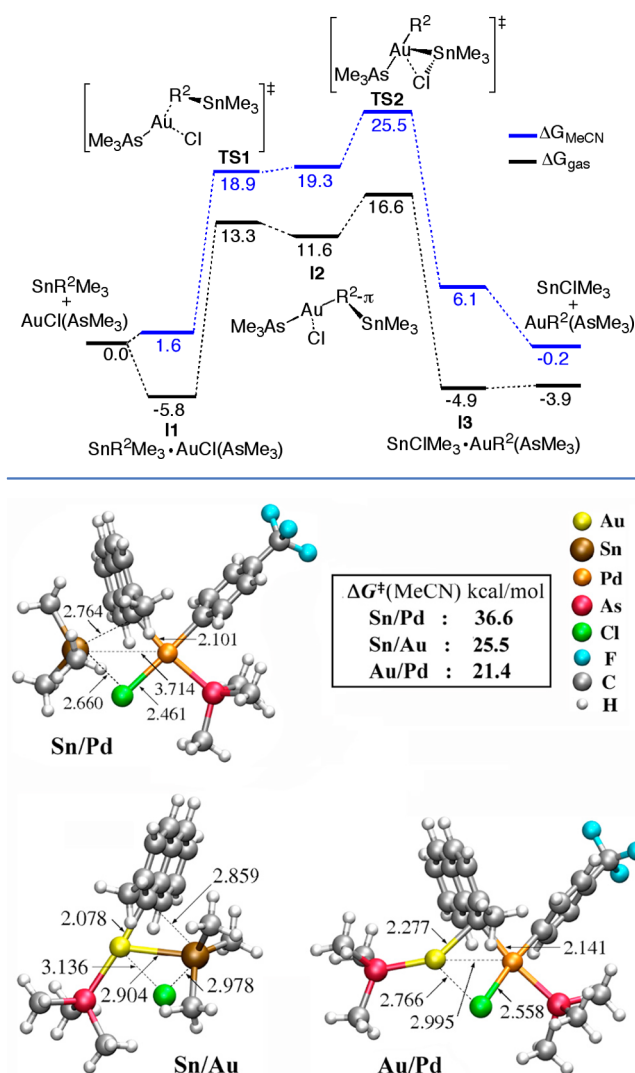
Figure 8. Transition states and $\Delta G^{\ddagger}$ for the transmetalations (R^1 = p-CF$_3$C$_6$H$_4$; R^2 = 2-Me-naphtyl; X = Cl).
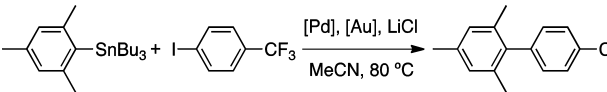
The optimization with synthetic purposes of one of the precedent reactions (between p-CF$_3$C$_6$H$_4$I and Bu$_3$SnMes with a gold cocatalyst) supplied very interesting information about the decisive role of ligands in the classic and in the Au cocatalyzed Stille reaction (Table 7).[71] Using the same donor in

Scheme 8. Classic and Cocatalyzed Stille Processes[a]

[a]$\Delta G^{\ddagger}$ values are for the coupling in Figure 8.

Table 7. Effects of the Different Ligands in the Initial Pd and Au Cocatalysts for a Stille Reaction

$$\bigcirc\!\!-\text{SnBu}_3 + \text{I}\!-\!\!\bigcirc\!\!-\text{CF}_3 \xrightarrow[\text{MeCN, 80 °C}]{\text{[Pd], [Au], LiCl}} \bigcirc\!\!-\!\!\bigcirc\!\!-\text{CF}_3$$

entry	Pd cat Au cat	time (h)	yield (%)
1	[PdCl$_2$(AsPh$_3$)$_2$] [AuCl(AsPh$_3$)]	24	84
2	[PdCl$_2$(PPh$_3$)$_2$] [AuCl(PPh$_3$)]	310	96
3	[PdCl$_2$(IDM)$_2$] [AuCl(IDM)]	48	0
4	[PdCl$_2$(AsPh$_3$)(IDM)] [AuCl(IDM)]	48	89

both catalysts, AsPh$_3$ and PPh$_3$ give active catalysis, which is faster with AsPh$_3$ (entry 1) and slower but better protected against decomposition with PPh$_3$ (entry 2). In dramatic contrast, the carbene ligand IDM blocks the catalysis (entry 3). The result in entry 4 demonstrates that it is the Pd complex [PdCl$_2$(IDM)$_2$] that is blocking the catalysis because at transmetalation, Pd needs at least one easy leaving ligand; in entry 4, AsPh$_3$ plays this role of easy leaving ligand, and the catalysis works perfectly. As we had suggested before, this experiment proves that two carbenes on Pd are incompatible with transmetalation under mild conditions. In [AuCl(IDM)], IDM does not disturb the catalysis because Au does not need to release L during the transmetalation (at their transition states, Au is tri- or tetracoordinated and does not release any ligand). Having in mind that the ligands can scramble between metals until they find their preferred coordination site and this scrambling can be fast or slow, a judicious and appropriate choice of the ligand–metal pairs is necessary in bimetallic catalysts in order to start with the best combination.

7. RESEARCH TOWARD GREENER STILLE PROCESSES

The classic and most extended routine procedure to remove most organotin byproducts is washing off the organic phase with an aqueous solution of potassium fluoride and filtration of the insoluble organotin fluoride. However, the washed product can still contain ~5% weight of tin.[91] The concern about the toxicity of tin derivatives has led to pursuing several ideas to face the problem. These can be classified in four main approaches: (i) catalytic use of stannanes, (ii) use of polymer immobilized stannanes, (iii) ionic-liquid-supported and phosphonium-supported Stille reactions, and (iv) utilization of molecular stannanes that are fully recyclable or less toxic.

Because some reviews are available,[13d,92] we will comment only on the main lines to approaching the problem.

(i). Catalytic Use of Stannanes. This is a most interesting idea, although of limited application so far because the formation of the tin transmetallating agent is a consequence of the hydrostannation of an alkyne; the scope of this reaction, catalytic in tin, is limited to the coupling of vinyl substrates (Scheme 9).[93] The regeneration of tin (whether molecular or

Scheme 9. Tin Catalytic Stille Cross-Coupling
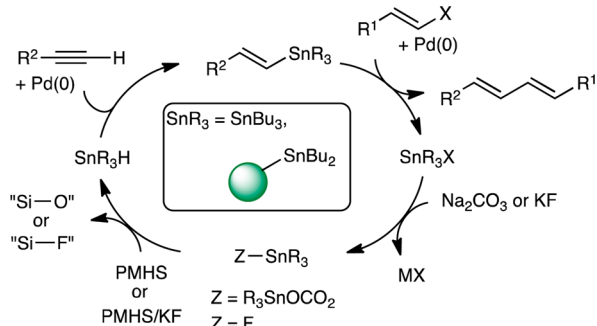
polymer-supported) is based on the use of polymethylhydrosiloxane (PMHS) with or without added KF[94] to produce R_3SnH, which reacts with the alkyne to give a vinyl stannane. In fact, this approach, initially developed by Maleczka, also uses the benefits of other protocols discussed below, and affords values of tin contamination in the range of 5−60 ppm.[95]

(ii). Use of Polymer-Immobilized Stannanes. A common strategy to handle contaminant molecules is to support them in polymers.[13d] As far as leaching is not a problem, this approach offers an easy way to recover and, in some cases, recycle the contaminant reagent. This method was initially applied by Kuhn and Newmann[96] and later beautifully elaborated by Nicolaou into an intramolecular process leading to the synthesis of (S)-zearalenone.[97]

Immobilized polystyrene vinyl or phenyl stannanes have been successfully used in Stille cross-coupling reactions with aryl- and heteroaryl halides.[98] In the case of phenyl stannanes, treatment of the used polymer with 2,4,6-trimercapto-s-triazine (to remove the palladium deposit in the polymer after the first cycle), followed by a reaction with PhMgBr, allowed for regeneration and recycling of the polymer but the activity of the recycled polymer decreased severely after more than four cycles.[98b]

More tunable, stannylated polymers with different solubilities ranging from quite soluble to insoluble have been recently obtained by direct vinylic polymerization or copolymerization of norbornene-type stannylated monomers. Some of these polymers are recyclable reagents in the Stille reaction (Scheme 10).[99] The manipulations along the cycle, depending on the solubility or insolubility of the product in step B, are indicated in the scheme. Some reactions have been tested for recyclability up to six times, with yields dropping only from 81% in the first run to 69% in the sixth run, and tin contamination is down to 15−50 ppm with the insoluble polymer.[100]

(iii). Ionic-Liquid-Supported and Phosphonium-Supported Stille Reactions. Similar to the polymer-supported tin reagents, ionic-liquid-supported[101] and phosphonium-supported[102] tin reagents (Figure 9) have been prepared and used in the Stille cross-coupling. Their use is aimed, as discussed for the case of polymers, at facilitating the separation

**Scheme 10. Recycling of Stannylated Polynorbornenes Reagents in Stille Cross-Coupling Reactions**
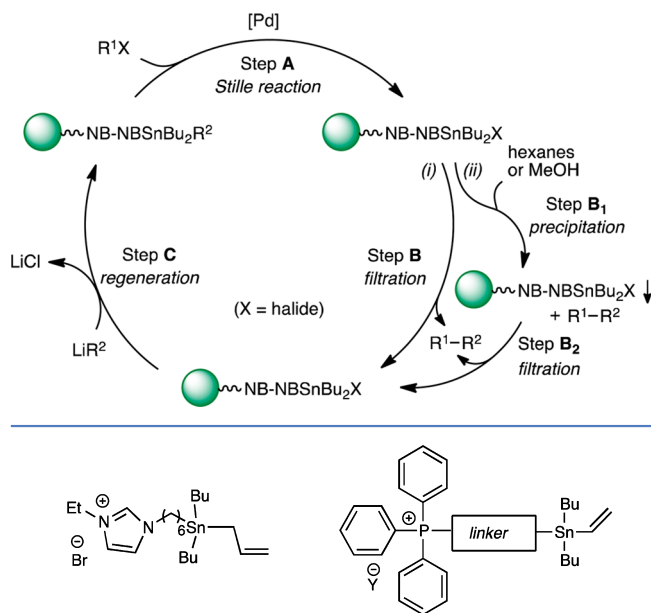
ionic liquid supported organotin reagent   triarilphosphonium supported organotin reagent

Figure 9. Ionic liquid or phosphonium supported vinylstannanes.

or recycling of the tin byproducts. Lowering of tin contents in the coupling products to values lower than 3 ppm is achieved.

(iv). Utilization of Fully Recyclable, Or Less Toxic Molecular Stannanes. Azastannatranes are very interesting tin reagents: on one hand, N coordination to Sn increases the nucleophilicity of the reagent;[33,34] on the other, protocols have been developed that allow for complete separation and recycling of the tin byproduct. A well-known application was reported by Merck chemists in the synthesis of an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) carbapenem.[103] Recently, azastannatranes have been used for the sp^3−sp^2 Stille coupling of chiral secondary alkyls with aryl halides. Interestingly, the reactions occur with retention of configuration (Scheme 11).[34]

Scheme 11. sp^3−sp^2 Stille Coupling of Chiral Secondary Alkyls with Aryl Halides
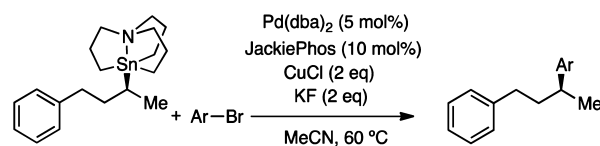
The use of less toxic but less reactive monoalkyl bisamido tin compounds derived from Lappert's stannylene $Sn[N(SiMe_3)_2]_2$ is also interesting because the coupling products are relatively free of tin contamination since the inorganic trifluorotin byproducts can be easily removed by simple filtration. The process has been applied in cross-coupling reactions with halides[104] and triflates[105] with <1% of $[Pd(PPh_3)_4]$ or $[Pd_2(dba)_3]$[106] using the protocol described in Scheme 12. It has been found that the best results are obtained under ligand-free conditions.[106]

Scheme 12. Stille sp³−sp² Coupling by TBAF Activation of Alkyltin Reagents
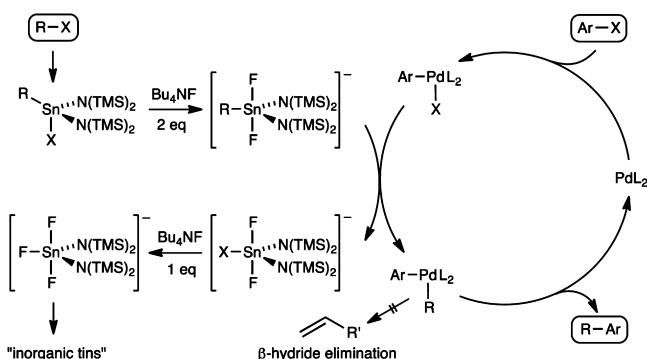
CONCLUSION

Thirty-eight years after its introduction, the Stille catalysis looks in good shape. We know now better how it works, what we can expect from it, and what we should not. Stannanes keep being dependable reagents for delicate syntheses, and there are ways to heat up their sometimes too mild character (nucleophilicity) when needed. It is clear that just for this, the Stille reaction is destined to have a permanent position in the cross-coupling team. But there are opportunities for other variations of the Stille process and also some aspects that deserve more studies, particularly those related to enantioselectivity and control of toxicity. It will be interesting to see how far these items can be developed in the near future.

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Notes
The authors declare no competing financial interest.

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ABBREVIATIONS

VEGFR, vascular endothelial growth factor receptors; Rf, 3,5-dichlorotrifluorophenyl; Pf, pentafluorophenyl; dba, dibenzylideneacetone; OTf, trifluoromethanesulfonate; BrettPhos, 2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl; JackiePhos, 2-di[3,5-bis(trifluoromethyl)phenylphosphino]-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl; HMPA, hexamethylphosphoramide; DMF, dimethylformamide; NMP, N-methyl-2-pyrrolidone; PTCO, pyrrolidinylthiocarbamoyl; CuTC, copper(I) thiophene-2-carboxylate; TTMPP, tris(2,4,6-trimethoxyphenyl)phosphine; dppf, 1,1-bis(diphenylphosphino)ferrocene; NPhth, phthalimido derivative; IDM, 1,3-dimethylimidazol-2-ylidene; PMHS, polymethylhydrosiloxane; NHC, nitrogen heterocyclic carbene

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