

Cu-Controlled Enantiodivergence in Pd-Catalyzed Stille Cross-Coupling Reactions

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Abstract: We report enantiodivergent Pd-catalyzed cross-coupling reactions between enantioenriched alkylcarbastannatrane nucleophiles and aryl electrophiles in which the stereochemical course of the reaction is dictated by the inclusion or omission of a Cu(I) additive. Using a new electron-deficient biarylphosphine ligand (MaPhos), a previously unknown stereoinvertive pathway for the transmetalation of unactivated and benzylic secondary alkylstannanes to Pd has been uncovered. When a Cu(I) salt is included in the reaction, the stereochemical course of the reaction changes from stereoinvertive to stereoretentive. Thus, both enantiomers of the cross-coupling product can be accessed in high enantiopurity using a single achiral ligand. Mechanistic investigations suggest that net-stereoretentive alkyl transfer, in the presence of Cu(I), results from consecutive stereoretentive transmetalations from tin to copper and copper to palladium. In contrast, direct alkyl transmetalation from tin to palladium proceeds primarily via a stereoinvertive pathway that is facilitated by the presence of electron-deficient ligands. Both experiment and DFT computations agree that ligand electronic properties play an important role in dictating the stereochemical course of direct (copper-free) alkyl transmetalation from tin to palladium. DFT results additionally reveal the governing structural features and interactions that promote the stereoinvertive transmetalation pathway in the copper-free reaction using MaPhos.

Introduction

Incorporation of C(*sp*³)-rich domains into molecular structure is a powerful strategy to modulate pharmacokinetic properties and bioavailability of a drug candidate.^[1,2] Synthetic methods to install stereogenic C(*sp*³) centers are particularly important as they also enable the manipulation of three-dimensional chemical space, which greatly expands the molecular complexity accessible for evaluation.^[3] Accordingly, there has been increased focus on the development of new strategies to rationally install and manipulate stereogenic centers.^[4,5] Our lab and several other research groups have pursued a stereospecific C(*sp*³)-C(*sp*²) cross-coupling approach towards manipulation of stereogenic centers in which configurationally stable, enantioenriched, main group organometallic nucleophiles are employed in Pd-catalyzed cross-coupling reactions with C(*sp*²) electrophiles.^[6–12] In principle,

stereospecific cross-coupling reactions involving enantioenriched main group organometallic nucleophiles can proceed with net-retention or net-inversion of configuration at the stereogenic center, depending on the relative accessibility of the stereoretentive S_E2 and stereoinvertive S_E2 transmetalation pathways (Figure 1).^[10,13–31] However, a single stereochemical outcome is usually achieved through this strategy, which is dictated by the absolute stereochemistry of the enantioenriched nucleophile and the stereochemical course of transmetalation. Thus, preparation of both individual enantiomers of a main group organometallic nucleophile is generally required for both enantiomers of a cross-coupling product to become accessible. Examples of enantiodivergent cross-coupling reactions where both individual enantiomers of a cross-coupling product can be selectively generated from a single-enantiomer nucleophile are rare and remain a formidable challenge as efficient access to two fundamentally different transmetalation pathways must be achieved.^[32–37] Additionally, because transmetalation of alkyl groups is commonly facilitated by the presence of specific activation modes in the structure of the alkyl nucleophile (e.g., $C(sp^2)$ α -carbon or heteroatomic α -substituent),^[10] accessing both stereochemical outcomes for an unactivated enantioenriched nucleophile is a particularly challenging goal.

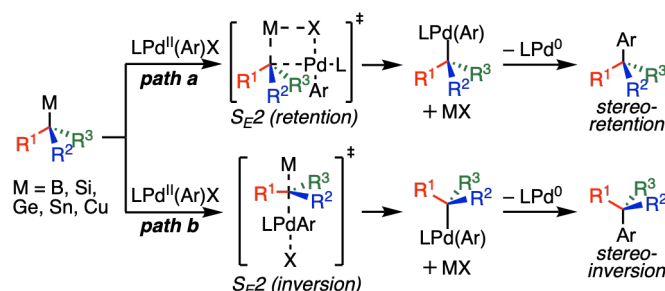


Figure 1. Stereoretentive and stereoinvertive transmetalation pathways in Pd-catalyzed cross-coupling reactions.

In our previous studies of stereospecific Stille couplings, we demonstrated that unactivated enantioenriched secondary alkylcarbostannatranes^[38–42] (**1**) undergo stereoretentive Pd-catalyzed cross-coupling reactions when JackiePhos (**2**) is employed as the supporting ligand and a Cu(I) salt is included as a co-transmetalating agent (Figure 2a).^[43–45] However, stereoinvertive transmetalation of an unactivated enantioenriched secondary alkylstannane remains unprecedented in Pd-catalyzed cross-coupling reactions. Prior demonstrations of net-stereoinvertive alkyl transmetalation from tin to palladium by Stille^[46] (Figure 2b) and Hoppe^[16] (Figure 2c) have each required the presence of an activating group (α -sp² carbon and/or remote coordinating group) to engage the stereoinvertive transmetalation mechanism.^[10] Based on our observation that unactivated enantioenriched secondary alkylcarbostannatranes undergo a direct net-stereoinvertive fluorination reaction when exposed to SelectFluor (Figure 2d),^[47] it seemed plausible that direct stereoinvertive transmetalation to a Pd(II) complex could likewise be achieved using unactivated enantioenriched secondary alkylcarbostannatranes nucleophiles under the correct conditions. This would thereby provide a general mechanism to effect a stereoinvertive outcome in stereospecific Pd-catalyzed Stille reactions. Herein, we report a new electron-deficient biarylphosphine ligand that supports a previously unknown stereoinvertive transmetalation of unactivated alkylcarbostannatranes to palladium (Figure 2e). When the same ligand is employed alongside CuCl as an additive, remarkably, the stereoretentive transmetalation pathway becomes operative. Thus, a single ligand can support enantiodivergent Pd-catalyzed cross-coupling reactions where the stereochemical course of transmetalation is determined by the presence or absence of a Cu(I) additive.

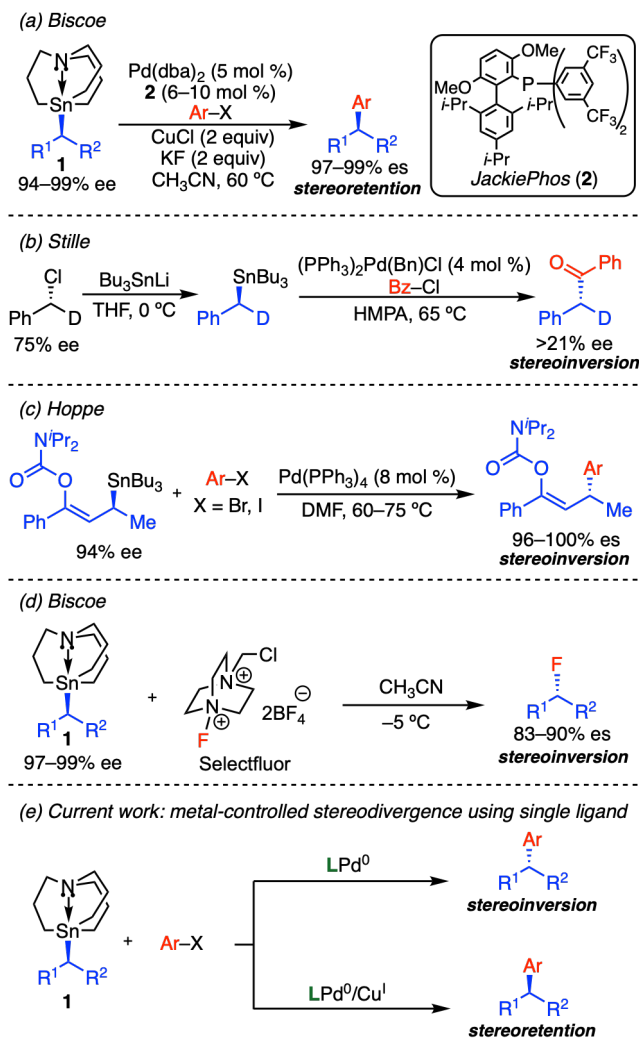


Figure 2. (a) Stereoretentive Pd-catalyzed Stille reaction using enantioenriched carbastannatranes. (b, c) Stereoinvertive Pd-catalyzed Stille reactions. (d) Direct stereoinvertive electrophilic fluorination of enantioenriched carbastannatranes. (e) Metal-controlled enantiodivergent Pd-catalyzed Stille reactions.

Results and Discussion

We have previously observed that electron-deficient biarylphosphine ligand JackiePhos (**2**) is capable of promoting the stereospecific (net-stereoretentive) Pd-catalyzed arylation of unactivated secondary carbastannatranes when a Cu(I) salt is included as an additive.^[43–45] However, in the absence of a Cu(I) additive, low yields of the corresponding cross-coupling product were observed. Upon revisiting this copper-free reaction, we were surprised to find that the low yield of cross-coupling product was generated with a minor preference for the stereoinvertive transmetalation pathway (Figure 3, entry 1). This observation suggested that a stereoinvertive alkyl transmetalation pathway from tin to palladium was viable, though not strongly favored, using JackiePhos as the supporting phosphine ligand. An exhaustive evaluation of ligands showed that bis- $\text{CF}_3\text{PhXPhos}$ (**4**), a ligand previously designed by our group to promote the *stereoretentive* transmetalation of secondary alkyltrifluoroborate nucleophiles,^[35] is reasonably effective at promoting the stereoinvertive transmetalation (–70% es) of unactivated secondary alkylcarbastannatranes **3** (Figure 3, entry 2). The improved yield and enantiospecificity observed from use of ligand **4** in place of JackiePhos (**2**) suggests that the stereoinvertive Cu-free pathway is more sensitive to the steric properties of the ligand than the stereoretentive Cu-containing pathway. Based on our previous findings that the electronic properties of a phosphine ligand can dictate the stereochemical course of transmetalation for unactivated enantioenriched alkylboron nucleophiles,^[35] we hypothesized that electronic control may likewise be operational for the transmetalation of unactivated enantioenriched alkylcarbastannatranes. Accordingly, we prepared new biarylphosphine derivatives of **4** in which additional CF_3 units were incorporated into the phosphine-bearing ring of the biaryl group. Use of these new ligands (**5** and **6**)^[48] resulted in an enhanced preference for the

stereoinvertive transmetalation pathway that correlated to the number of CF₃ units installed. Biarylphosphine ligand **6** (MaPhos) proved optimal for this reaction, affording –89% es favoring the stereoinvertive pathway (Figure 3, entries 4–6). This process constitutes the first example of a net-stereoinvertive Stille cross-coupling reaction using unactivated secondary alkylstannanes. Remarkably, when CuCl was added to the reaction and acetonitrile employed as a solvent, a complete switch in the stereochemical course of the reaction was achieved, with high selectivity (+98% es) now observed for the stereoretentive transmetalation pathway (Figure 3, entry 7). Previously, JackiePhos (**2**) was identified as the sole ligand capable of supporting efficient transmetalation of unactivated secondary alkylcarbostannatranes in Cu(I)-mediated Pd-catalyzed cross-coupling reactions. However, our current results indicate that MaPhos (**6**) is capable of selectively supporting both stereoinvertive and stereoretentive transmetalation pathways, thus enabling an enantiodivergent Pd-catalyzed coupling process where the stereochemical course of the reaction is primarily dictated by the inclusion or omission of a Cu(I) additive.

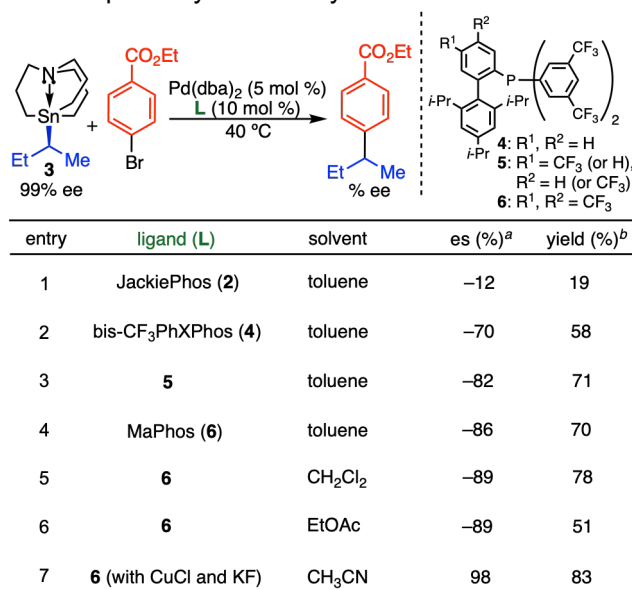


Figure 3. Influence of phosphine ligand on the stereochemical outcome of Pd-catalyzed cross-coupling reactions using enantioenriched alkylcarbostannatrane **3**. ^a Enantiospecificity (es) = (ee_{product}/ee_{starting material}) × 100%; negative % es indicates net stereoinversion. ^b GC yields using *n*-dodecane as an internal standard.

Cu-controlled enantiodivergence was broadly achieved in Pd-catalyzed cross-coupling reactions of enantioenriched, unactivated alkylcarbostannatrane nucleophiles and aryl electrophiles when MaPhos (**6**) was employed as the supporting ligand (Figure 4). To promote the stereoinvertive cross-coupling pathway, reactions were conducted with MaPhos (**6**) in the absence of a Cu(I) additive (Figure 4, conditions B). We found that use of ethyl acetate as solvent afforded higher yields for electron-rich and electron-neutral electrophiles, while use of dichloromethane as solvent afforded higher yields for electron-deficient electrophiles. However, only a nominal change in enantiospecificity for the stereoinvertive pathway was observed when the solvent was switched from ethyl acetate to dichloromethane. For the coupling partners examined, selectivity for the stereoinvertive pathway could generally be achieved with enantiospecificities (% es) that ranged from the mid/high 80s to low 90s. Selectivity for the direct stereoinvertive transmetalation of alkylcarbostannatranes to Pd was highest for cross-coupling reactions involving electron-deficient aryl electrophiles (e.g., (*R*)-**7c**, (*R*)-**7d**, and (*R*)-**7j**). Cross-coupling reactions employing electron-rich aryl electrophiles (e.g., (*R*)-**7f** and (*R*)-**7k**) and those involving nucleophiles bearing functional groups capable of weak coordination to palladium (e.g., (*R*)-**7p** and (*R*)-**7r**) displayed slightly lower selectivity for the stereoinvertive reaction course. We additionally observed that the presence of a free alcohol on the alkylcarbostannatrane nucleophile shut down the stereoinvertive pathway ((*R*)-**7s**). However, the presence of an ortho substituent on the electrophile was extremely well tolerated by the stereoinvertive mechanism, with 2-bromotoluene ((*R*)-**7o** and (*R*)-**7q**) providing the highest selectivity for the stereoinvertive pathway of all electrophiles investigated.

To promote the stereoretentive cross-coupling pathway, reactions were conducted with MaPhos (**6**) in the presence of CuCl and KF at rt, using acetonitrile as solvent (Figure 4, conditions A). Inclusion of a fluoride source^[49] is not a requirement for these reactions and has little impact on enantiospecificity (see ESI), but typically leads to slightly higher yields (ca. 5–10%). In general, enantiospecificity for the stereoretentive pathway using MaPhos (**6**) was high (>95% es). Selectivity for the stereoretentive transmetalation pathway displayed little dependence on the electronic properties of the electrophilic or nucleophilic coupling partners. Electron-rich and electron-deficient

electrophiles as well as electrophiles and nucleophiles bearing coordinating functional groups all engaged in cross-coupling reactions with excellent selectivity for stereoretention when CuCl was included. The primary limitation associated with the Cu-promoted stereoretentive pathway using MaPhos (**6**) pertained to low cross-coupling yields that accompanied use of some electron-rich electrophiles (e.g. (*S*)-**7i** and (*S*)-**7t**). In these instances, JackiePhos (**2**) could be employed in place of MaPhos (**6**) to increase yield without adversely affecting enantiospecificity.

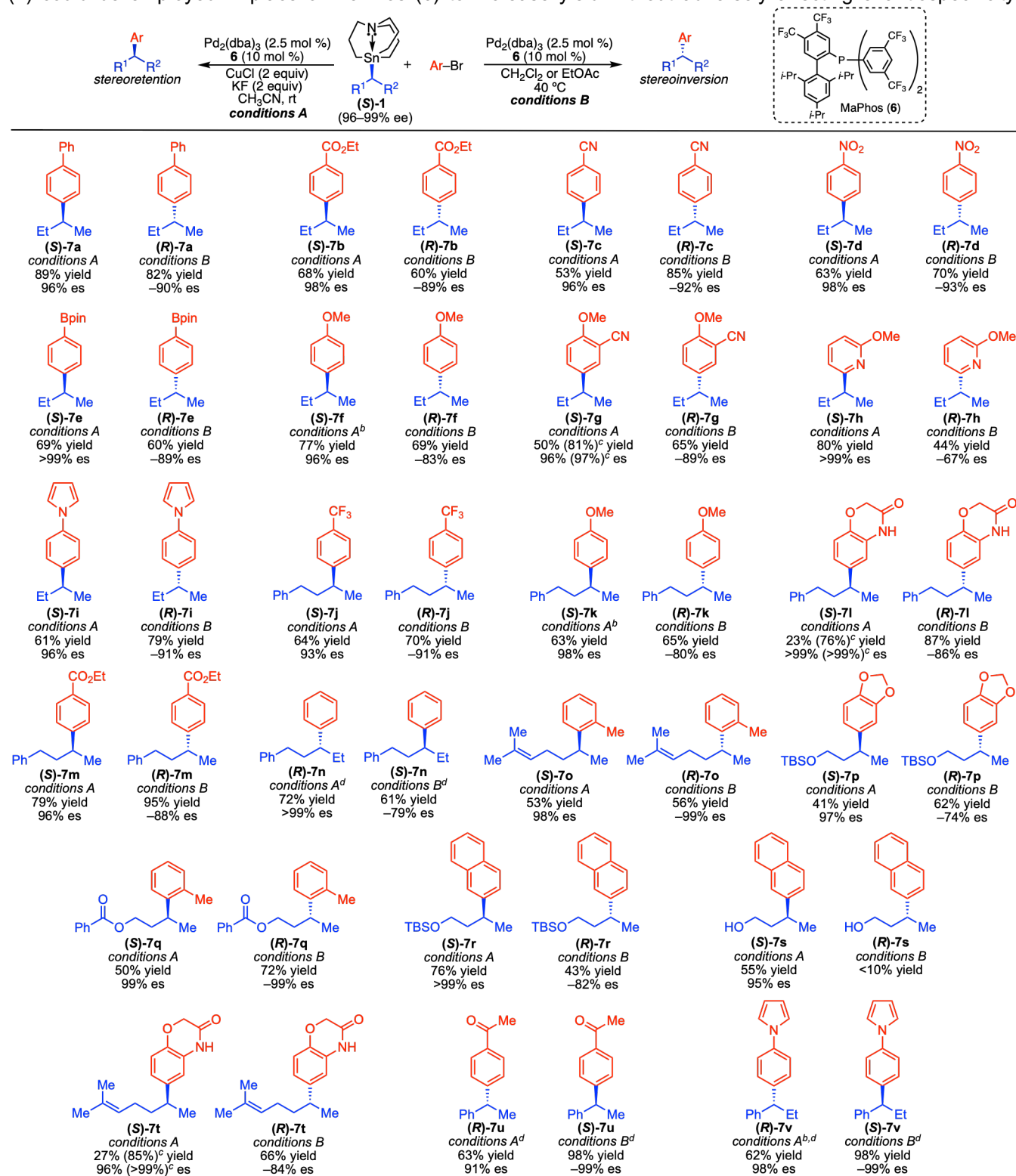


Figure 4. Enantiodivergent Pd-catalyzed cross-coupling reactions of enantioenriched secondary alkylcarboastannatranes and aryl halides using MaPhos as a supporting ligand. ^a All reactions were conducted in duplicate on a 0.2 mmol scale. ^b ArI used in place of ArBr. ^c JackiePhos used in place of MaPhos. ^d Using (*R*)-**1** in place of (*S*)-**1**.

Though we primarily focused on the use of unactivated enantioenriched alkylcarbostannatranes in these reactions, we also examined the use of enantioenriched benzylic carbostannatranes in Cu-controlled enantiodivergent reactions (see Figure 4, **7u** and **7v**). Using MaPhos (**6**) as a supporting ligand and identical reaction conditions as those employed for unactivated alkylcarbostannatranes, enantioenriched benzylic carbostannatranes undergo stereoinvertive cross-coupling reactions with remarkably high stereofidelity and in excellent yield. Use of our copper-mediated conditions with benzylic carbostannatranes results in similarly high enantiospecificity for the stereoretentive transmetalation pathway. It is particularly noteworthy that the same reaction conditions successfully promote enantiodivergent reaction pathways for both activated and unactivated nucleophiles. In the ligand-controlled enantiodivergent Suzuki process previously reported by our lab,^[35] the stereoretentive and stereoinvertive pathways both failed when benzylic organoboronates were employed as nucleophiles. This suggests that our Cu-controlled enantiodivergent Stille approach may be broadly applicable to other classes of activated enantioenriched organostannane nucleophiles.

We employed Density Functional Theory (DFT) to study the origins of stereocontrol in the copper-free stereoinvertive Pd-catalyzed Stille cross-coupling reaction using MaPhos (**6**) (Figure 4, conditions B). PBE with Grimme's D3BJ empirical dispersion correction and the 6-31G*/LANL2DZ basis set/effective core potential was used as implemented in Gaussian 16.^[50] All computations were performed with SMD solvation using dichloromethane as solvent and thermal corrections at 40 °C. We exhaustively sampled the configurations and conformations of the ligand-sphere in the stereo-determining transition state for transmetalation. Transition structures involving both *syn*- and *anti*-relationships between the carbostannatrane group and the bromine, as well as *cis*- and *trans*-relationships between the nucleophile and the phosphine ligand were computed. The most stable retention and inversion transition structures found for the formation of product **7d** are shown in Figure 5. There was a uniform preference for the *trans* structures, presumably because these minimize steric repulsion between atoms involved in the bond-forming process and the sterically encumbered MaPhos (**6**) ligand, while also avoiding the destabilizing electronic effect of having the strongly sigma-donating electrophile aryl and phosphine groups *trans* to each other (*trans* influence).^[51] The **Retention** transition structure in Figure 5 results in the disfavored stereoretentive product, while the **Inversion** transition structure yields the favored stereoinvertive product, with energy barriers of 17.6 and 14.8 kcal/mol, respectively ($\Delta\Delta G^\ddagger = 2.8$ kcal/mol). This is consistent with the experimentally observed preference for the stereoinvertive pathway (2.0 kcal/mol, –93% es).

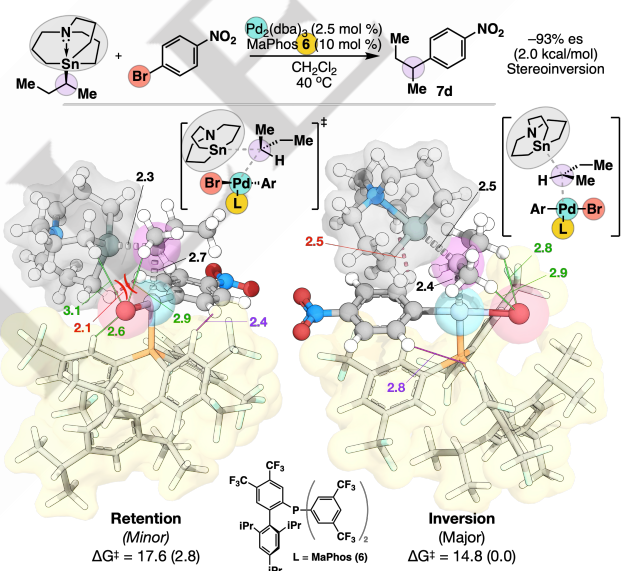


Figure 5: Computed transition structures of the stereoretentive (left) and stereoinvertive (right) transmetalation processes in the copper-free Pd-catalyzed Stille cross-coupling using MaPhos (**6**) to form product **7d**. Energies in kcal/mol and distances in Ångströms. Transition structure distances are shown in black, stabilizing electrostatic interactions in green, destabilizing electrostatic interactions in purple, and selectivity-determining steric contact in red.

Stereoretentive alkyl transmetalation in Pd-catalyzed Stille reactions has previously been reported to proceed via a closed transition state involving simultaneous Sn–C bond cleavage, C–Pd bond formation, and Pd to Sn halogen transfer (Figure 6, top left).^[52] Our computations suggest that the stereoretentive transmetalation of a secondary alkylcarbostannatrane from Sn to Pd proceeds via an open transition state in a stepwise process in which the Sn–C bond breaks concomitantly with formation of the C–Pd bond, with the halide remaining stationary and not transferring from Pd to Sn in the same transition state (Figure 6, top right). Moreover, the stereoretentive

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transition state in our process adopts a bent configuration in which the Sn and Br groups are distal (4.0 Å), well beyond the distance expected for a direct halogen-transfer process. The corresponding Wiberg bond index between the Sn and Br was zero (~ 0.001), suggesting minimal, if any, covalent bonding interactions. Consistent with this interpretation, the Pd–Br distance remains essentially unchanged between the transition and post-transition structures. CHELPG charge analysis revealed the presence of significant electrostatic interactions between the positively charged Sn and negatively charged Br (+0.6 and -0.4 , respectively).

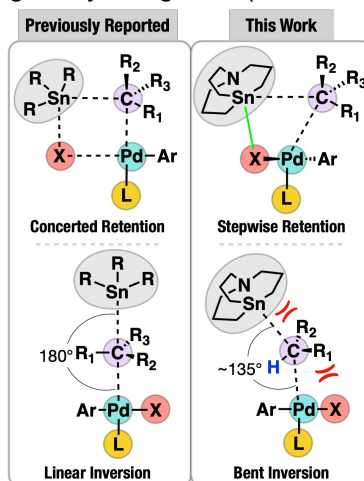


Figure 6: Stereoretentive transmetalation transition state models (top) and stereoinvertive models (bottom) for copper-free Pd-catalyzed Stille reactions using secondary alkylcarbostannatranes. Previously proposed models shown on the left, and the DFT discovered transition state models on the right. Transition state bonds are dashed black lines, electrostatic interactions in green, and destabilizing interactions indicated in red.

Stereoinvertive alkyl transfer from alkylmetal nucleophiles^[10,53–55] is commonly proposed to proceed via a $C(sp^2)$ -hybridized transition state involving a linear 180° arrangement between atoms involved in bond formation and bond breaking (Figure 6, bottom left).^[10] However, we and others have shown that the geometry of stereoinvertive alkyl transfer can deviate significantly from linearity, especially when the transferring alkyl group is non-symmetrically substituted.^[25] Our results again reveal a bent stereoinvertive transition state, presumably because this geometry minimizes steric repulsion by bending towards the sterically minimal substituent (i.e., hydrogen) of the transferring alkyl group (Figure 6, bottom right).

The preference for inversion over retention in the copper-free process can be attributed to interactions involving the two ortho $C(sp^2)$ –H atoms from the aryl group of the electrophilic coupling partner. In the disfavored retention transition state, one of these hydrogens lies within 2.1 Å of the carbostannatrane $C(sp^3)$ –H (Figure 5, red dashed line), suggesting a repulsive steric interaction. The other hydrogen is involved in a repulsive electrostatic interaction with a $C(sp^2)$ –H on the MaPhos biaryl ring ortho to the phosphorous atom, at a distance of 2.4 Å (thin purple line; NBO charges of +0.269 and +0.281, respectively). In contrast, the trans arrangement of the carbostannatrane and palladium in the inversion transition structure eliminates the steric repulsion while increasing the distance between the electrostatically repulsive groups (both distances now ≥ 2.5 Å).

To further probe the origins of stereospecificity, we examined the impact of ligand electronic properties on the transmetalation pathways. When the less electron-deficient phosphine ligand bis- $CF_3PhXPhos$ (**4**), which is virtually isosteric to MaPhos (**6**) around the phosphine center, is employed, diminished selectivity for the stereoinversion pathway is observed experimentally (Figure 3; -70% es vs -86% es for **4** and **6**, respectively for product **7b**). Consistent with these results, the computed preference for stereoinversion decreases from 2.8 kcal/mol to 1.2 kcal/mol when MaPhos (**6**) is replaced with **4**. To understand the diminished stereoinversion selectivity observed with less electron-deficient ligand bis- $CF_3PhXPhos$ (**4**), we computed a three-part distortion-interaction analysis of each transition structure.^[56] Each structure was fragmented into three separate components: the alkylcarbostannatrane, the aryl ligand, and the Pd(Br)-phosphine complex. Surprisingly, the distortion-interaction energies of the favored stereoinversion transition structures are virtually identical for the two ligands (Figure 7, bottom). This strongly suggests that the change in selectivity originates from the disfavored retention transition structures. In the stereoretentive pathway, we found that distortion energies of the alkylcarbostannatrane and electrophilic aryl fragment are very similar (9.8 and 3.8 vs 9.6 and 4.0 kcal/mol for ligands **4** and **6**, respectively; Figure 7, top). In contrast, the distortion and interaction energies of the Pd–Br–phosphine fragment differ significantly (5.7 vs 9.9 for distortion and -18.1 vs -20.7 kcal/mol for interaction energies, respectively). Examination of the retention transition structures for both phosphine ligands revealed that the steric repulsion between one ortho $C(sp^2)$ –H bond of the aryl ligand and a carbostannatrane $C(sp^3)$ –H are essentially identical for the two phosphine ligands, with both interactions occurring at the same distance of 2.10 Å (Figure 5, left, red). However, electrostatic

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repulsions between the other ortho C(sp²)–H of the aryl ligand and the C(sp²)–H of the upper aryl ring of the phosphine ligand differ significantly. For both ligands, the NBO charges of the ortho C(sp²)–H of the electrophilic aryl are identical (+0.269). However, for MaPhos (**6**), the corresponding ligand C(sp²)–H is more positively charged and located at a shorter distance, leading to greater electrostatic repulsion. Specifically, the NBO charge on the ortho C(sp²)–H of the upper aryl ring of MaPhos **6** is +0.281 at a distance of 2.44 Å (Figure 5, left, purple). In contrast, the more electron rich ligand **4** exhibited a smaller positive charge (+0.267) at a slightly greater distance (2.48 Å). Taken together, these results suggest that electronic factors play a subtle but important role in dictating the stereochemical outcome of the copper-free Pd-catalyzed cross-coupling reactions, not through direct perturbation of the electronic character of the Pd catalyst, but through non-bonding interactions involving the phosphine ligand.

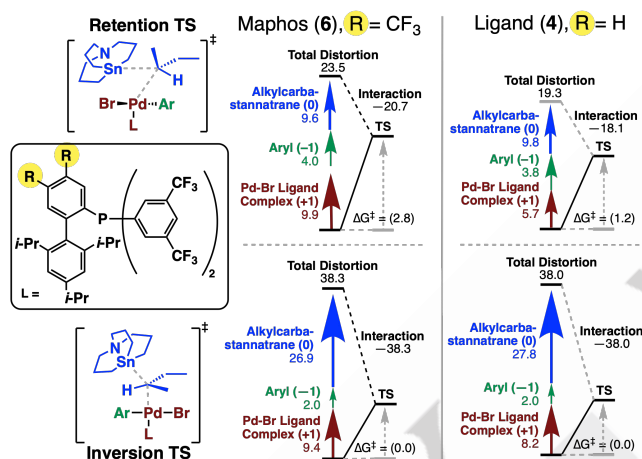


Figure 7. Use of distortion-interaction analyses to probe the influence of ligand electronics on the stereochemical course of alkylcarbastannatransmetalation to Pd^{II} oxidative addition complexes supported by MaPhos (**6**) and by less electron-deficient ligand bis-CF₃PhXPhos (**4**). Energies in kcal/mol.

To experimentally corroborate these electronic effects on the observed stereoselection in Pd-catalyzed cross-coupling reactions using MaPhos (**6**), we conducted a Hammett analysis of the enantiomeric ratios obtained for cross-coupling reactions using electronically differentiated aryl bromides (Figure 8). Relative selectivities for the stereoinvertive pathway displays excellent correlation to Hammett parameters, with electron-deficient substituents enhancing preference for the stereoinvertive pathway more so than electron-rich substituents. When less electron-deficient ligand bis-CF₃PhXPhos (**4**) was used in place of MaPhos (**6**), diminished net selectivity for the stereoinvertive pathway was observed alongside increased sensitivity to the electronic properties of the aryl electrophile ($\rho = 0.61$ for **4**, vs. $\rho = 0.42$ for **6**). Thus, it appears that the electronic properties of the ligand and aryl electrophile combine to dictate the stereochemical outcome of transmetalation to Pd. These results are consistent with our computational studies, which predict that the electronic properties of the aryl electrophile and phosphine ligand result in electrostatic interactions that are primarily responsible for the energy difference between the stereoinvertive and stereoretentive pathways for direct (Cu-free) transmetalation to Pd.

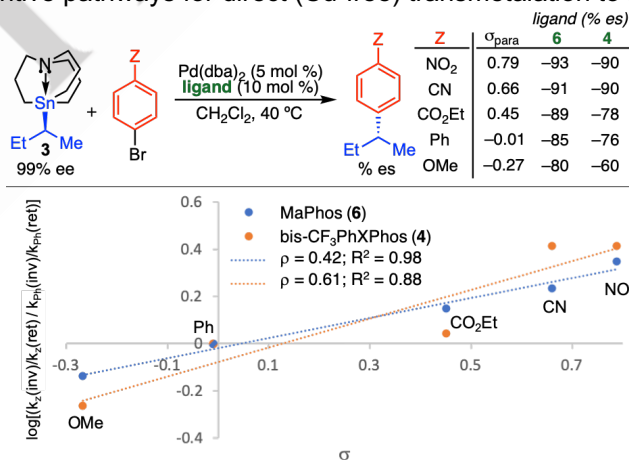


Figure 8. Hammett plot showing electronic effects on selectivity ($K_{\text{inv}}/K_{\text{ret}}$) of transmetalation pathways.

Transmetalation of activated enantioenriched secondary alkylstannanes to copper has been shown to proceed primarily via a stereoretentive pathway.^[57–64] These precedents, alongside our prior observation that *t*-

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butylcarbostannatrane can undergo successful Cu-supported Pd-catalyzed cross-coupling reactions,^[44] suggested that Cu-supported Pd-catalyzed alkyl Stille reactions likely achieve net-stereoretention via a mechanistic course involving double stereoretention as opposed to double stereoinversion. To more definitively probe the stereochemical outcome for transmetalation of unactivated secondary alkyl units from carbostannatrane to copper, we investigated the use of enantioenriched alkylcarbostannatrane **8** in a Cu-mediated acylation reaction. Because the alkylcopper species formed via transmetalation of alkylstannanes to copper(I) thiophene-2-carboxylate (CuTC) are known to undergo acylation reactions with thioester electrophiles,^[64] we chose CuTC as the Cu(I) source for our initial studies using thioester **9** as the electrophilic coupling partner (Figure 9). In the absence of a palladium catalyst, the Cu-mediated acylation of enantioenriched alkylcarbostannatrane **8** proceeds with net retention of absolute stereochemistry and in excellent yield using CuTC (Figure 9a). The same stereochemical outcome was achieved using our previously reported Pd-catalyzed acylation conditions with CuCl as the Cu(I) source (Figure 9b).^[44] When CuCl was used in the absence of a Pd catalyst, **10** was again formed with high preference for the stereoretentive transmetalation pathway (Figure 9c). These stereochemical outcomes are entirely consistent with a stereoretentive transmetalation of unactivated alkylcarbostannatranes to Cu(I), which necessitates double stereoretention when a MaPhos-ligated Pd catalyst is also involved (Figure 10). In contrast, direct transmetalation of unactivated alkylcarbostannatranes to a MaPhos-ligated Pd(II) complex proceeds preferentially via a stereoinvertive pathway when in the absence of a Cu(I) co-transmetalating agent. We propose that use of a polar solvent promotes transmetalation from tin to copper,^[65] thus ensuring a net-stereoretentive outcome (Figure 10, path a) while also minimizing the chance for direct (stereoinvertive) transmetalation from tin to palladium (Figure 10, path b). Thus, MaPhos (**6**) can support both stereochemical courses depending on the presence/absence of a Cu(I) additive and the solvent employed.

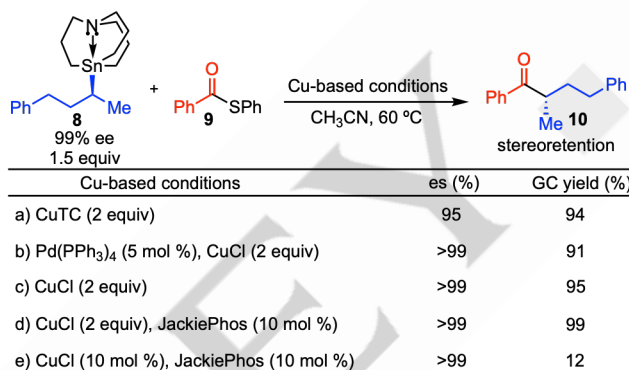


Figure 9. Stereochemical Studies of Sn/Cu Transmetalation.

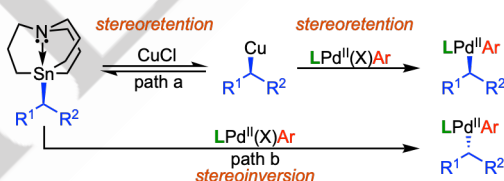


Figure 10. Proposed transmetalation pathways (L = MaPhos) for net-stereoretentive and net-stereoinvertive coupling reactions.

Conclusion

In conclusion, we have developed enantiodivergent Pd-catalyzed Stille cross-coupling reactions between unactivated enantioenriched secondary alkylcarbostannatranes and aryl halides. The stereoinvertive and stereoretentive transmetalation pathways are each supported by the novel electron-deficient biarylphosphine ligand MaPhos (**6**), with the stereochemical course of the reaction determined primarily by the presence or absence of CuCl as a co-transmetalating agent. Under Cu-free conditions, MaPhos (**6**) supports direct, stereoinvertive alkyl transfer from tin to palladium, thus enabling the first stereoinvertive Stille coupling of unactivated alkylstannane nucleophiles. The stereoinvertive transmetalation pathway appears to be under electronic control with strongly electron-withdrawing ligands enhancing selectivity for stereoinversion. DFT results agree with experiments, showing the stereoinversion pathway to be preferred over the stereoretention. More importantly, the computational

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results reveal that subtle, yet significant interactions not only govern the stereospecificity of this reaction but also suggest how the ligand identity may influence selectivity through electronic interactions. Conversely, in the presence of CuCl, stereoretentive transmetalation of unactivated alkylcarbostannatranes is selectively achieved via a double stereoretention mechanism. The described enantiodivergent cross-coupling method thus provides a facile strategy to access both enantiomers of a cross-coupling product from a single-enantiomer precursor. Additionally, these enantiodivergent reaction conditions could be directly extended to reactions involving activated benzylic carbostannatranes, suggesting that the approach may be more broadly applicable to other classes of electronically activated carbostannatranes. Accordingly, we expect that our enantiodivergent cross-coupling strategy will serve as an enabling tool to rapidly access new stereochemically diversified molecular structures.

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Keywords: enantiodivergence • Pd catalysis • Stille cross-coupling • carbostannatranes • transmetalation

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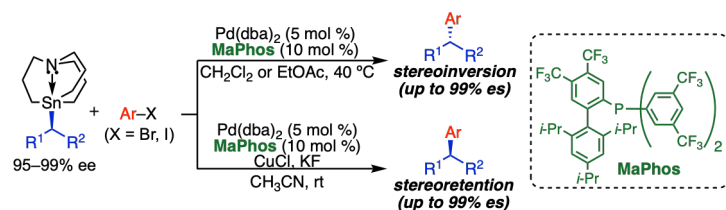
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We report an enantiodivergent Pd-catalyzed cross-coupling reaction between enantioenriched alkylcarbostannatrane nucleophiles and aryl electrophiles in which the stereochemical course of the reaction is dictated by the inclusion or omission of a Cu(I) additive. Using the new electron-deficient biarylphosphine ligand **MaPhos**, stereoretentive and stereoinvertive transmetalation pathways can each be selectively accessed.