ORGANIC CHEMISTRY

Enantiodivergent Pd-catalyzed C–C bond formation enabled through ligand parameterization

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Despite the enormous potential for the use of stereospecific cross-coupling reactions to rationally manipulate the three-dimensional structure of organic molecules, the factors that control the transfer of stereochemistry in these reactions remain poorly understood. Here we report a mechanistic and synthetic investigation into the use of enantioenriched alkylboron nucleophiles in stereospecific Pd-catalyzed Suzuki cross-coupling reactions. By developing a suite of molecular descriptors of phosphine ligands, we could apply predictive statistical models to select or design distinct ligands that respectively promoted stereoinvertive and stereoretentive cross-coupling reactions. Stereodefined branched structures were thereby accessed through the predictable manipulation of absolute stereochemistry, and a general model for the mechanism of alkylboron transmetallation was proposed.

Palladium-catalyzed cross-coupling reactions have revolutionized the construction of $C(sp^2)$–$C(sp^2)$ bonds. Among these cross-coupling processes, the Suzuki-Miyaura reaction has found particularly broad application owing to its extensive reaction scope, as well as the stability, availability, and low toxicity of organoboron reagents (*1*). The 2010 Nobel Prize in chemistry was awarded, in part, to recognize the transformative impact of the Suzuki cross-coupling reaction on chemical synthesis. However, although $C(sp^2)$–$C(sp^2)$ bond construction is now considered routine using the Suzuki reaction, extension of this process to the formation of $C(sp^3)$–$C(sp^2)$ bonds using alkylboron nucleophiles remains a considerable challenge. Of particular interest, a variant using secondary alkylboron nucleophiles with predictable and controllable stereospecificity would establish a powerful synthetic strategy to access molecular geometries with precise three-dimensional control, expanding the exceptional capabilities of the Suzuki reaction (Fig. 1A).

Many efforts have focused on the use of enantioenriched secondary alkylboron nucleophiles in Suzuki cross-coupling reactions (*2*–*4*). Considerable limitations remain because of slow transmetallation of the highly covalent and sterically congested $C(sp^3)$–B bond in these reagents, as well as the propensity of the resulting Pd-alkyl species to undergo β-hydride elimination-reinsertion sequences, which can result in isomerization of the alkyl group and racemization of the stereocenter. To circumvent prohibitively slow transmetallation, as well as competing β-hydride elimination-reinsertion pathways, most stereospecific Suzuki reactions have required the use of secondary alkylboron nucleophiles that are electronically activated via inclusion of a $C(sp^2)$ α-carbon, an α-heteroatom, and/or a strongly coordinating β-carbonyl group (*5*–*17*). In addition, alkylboron nucleophiles can undergo transmetallation via either stereoretentive or stereoinvertive pathways depending on the nature of the substrate, catalyst, and/or reaction conditions. In many cases, the factors controlling the dominant mechanism of transmetallation are not understood (Fig. 1B). Thus, a predictive stereochemical model for transmetallation of alkylboron reagents remains elusive.

Recently, we reported a stereospecific Pd-catalyzed cross-coupling reaction using unactivated secondary alkylboron nucleophiles (*18*). With P^tBu_3 (^{t}Bu, *tert*-butyl) as a supporting ligand, enantioenriched arylation products were obtained with transmetallation proceeding primarily via a stereoinvertive mechanism. Whereas several enlightening mechanistic studies have recently been conducted on the transmetallation of arylboron nucleophiles (*19*–*23*), these studies have not addressed the transmetallation of alkylboron nucleophiles in $C(sp^3)$–$C(sp^2)$ bond-forming processes (*24*, *25*). Thus, unactivated alkylboron nucleophiles constitute an attractive starting point from which to investigate the reaction parameters most influential to the mechanism of alkylboron transmetallation. This mechanistic work should simultaneously facilitate the development of new synthetic methods to rationally incorporate or manipulate stereocenters via cross-coupling strategies. To this end, we report a study using predictive statistical models (*26*, *27*)

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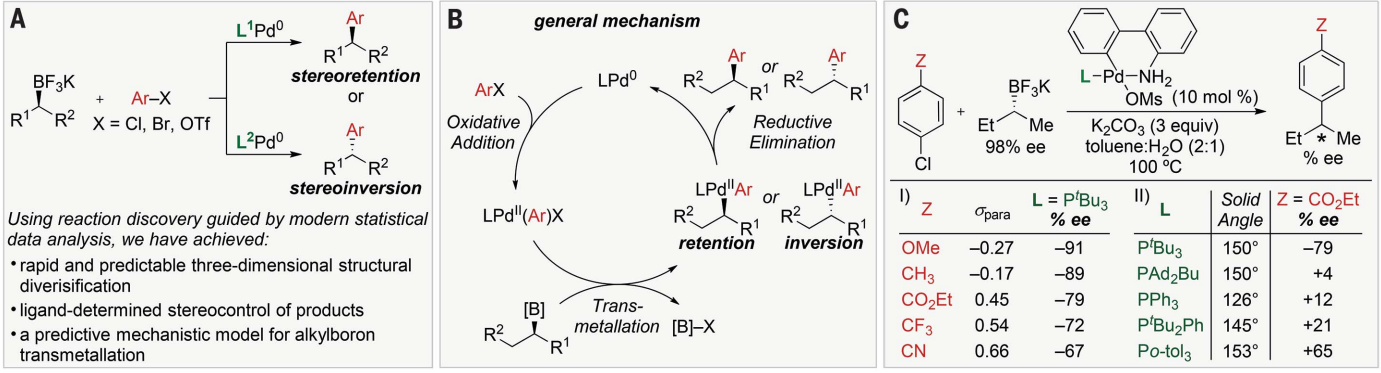

Fig. 1. Reaction development. (**A**) Enantiodivergent Suzuki reactions of secondary alkylboron nucleophiles. (**B**) General mechanism. (**C**) Initial investigation of substrate and ligand influences on stereoselectivity. A positive % ee value indicates net retention; a negative % ee value indicates net inversion. * indicates an enantioenriched stereocenter. L, ligand; Tf, trifluoromethanesulfonyl; Ar, aryl; Et, ethyl; Me, methyl; Ms, methylsulfonyl; *o*-tol, ortho-tolyl.

to relate phosphine ligand properties to stereochemical outcomes obtained from Pd-catalyzed Suzuki reactions of unactivated enantioenriched secondary alkylboron nucleophiles and aryl electrophiles. With statistical models that rely on a next-generation set of molecular descriptors, we achieved a stereoretentive Pd-catalyzed cross-coupling reaction of such nucleophiles. Furthermore, we have identified an improved ligand for the stereoinvertive variant, thus enabling an entirely ligand-controlled enantiodivergent process from a single-enantiomer organoboron nucleophile (*28*). Our statistical models also provide compelling evidence that each transmetallation pathway is intimately tied to specific electronic properties of the supporting ligand, which serves as a predictive guide to the mechanism of alkylboron transmetallation to palladium.

Initial investigations using electronically differentiated aryl chlorides with enantioenriched $^{s}BuBF_3K$ (^{s}Bu, *sec*-butyl) revealed a trend correlating diminished stereofidelity with the use of more electron-deficient coupling partners (section I of Fig. 1C). This observation suggested that subtle electronic effects could influence the mechanism of transmetallation and the resulting stereochemical outcome. Additionally, when the phosphine ligand was varied in an initial screen with a common aryl chloride electrophile, a considerable change in the reaction outcome from stereoinvertion to stereoretention was found (section II of Fig. 1C). No obvious correlation was observed between these results and the steric properties (solid angle) of the ligand. Taken together, these outcomes were difficult to interpret and inspired the use of ligand parameterization tools to provide a platform for both predictive ligand performance and mechanistic interrogation.

An expanded inventory of common phosphines with varied properties was evaluated in the Suzuki reaction of enantioenriched $^{s}BuBF_3K$ and ethyl 4-chlorobenzoate. This dataset was then subjected to correlation analysis of phosphine structural features with the stereochemical outcomes as well as the ratios of branched:linear products in these reactions. We devised a workflow and universal parameter set to describe the catalyst properties from the phosphine itself (*29*–*32*). The workflow was initiated by performing a molecular mechanics (MM) conformational search to reveal representative low-energy conformers (Fig. 2A). Next, geometry optimization of the conformers using density

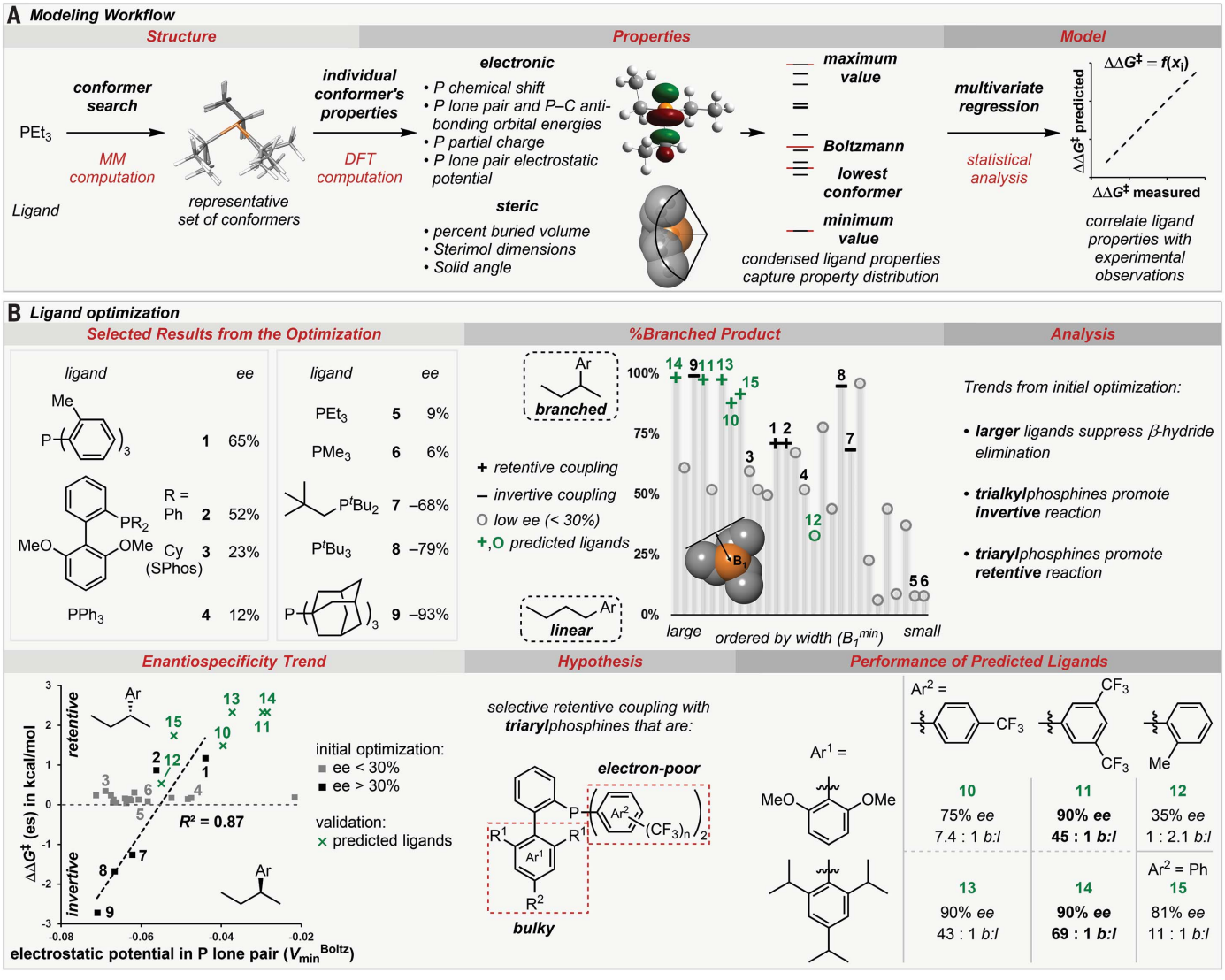

Fig. 2. Phosphine parameterization. (**A**) Workflow of parameter generation and statistical modeling. $\Delta\Delta G^{\ddagger}$, relative free energy of activation; $f(x_i)$, function of parameter x_i. (**B**) Application of phosphine parameterization to ligand optimization of the reaction shown in Fig. 1C with Z = CO_2Et. *b:l* = branched-to-linear ratio. A positive % ee value indicates net retention; a negative % ee value indicates net inversion. es, enantiospecificity; R^2, coefficient of determination.

functional theory (DFT) was followed by parameter collection. Subsequently, four descriptor subsets were defined to capture the conformational dynamics of the ligands by including the mathematical extreme descriptor values (minimum and maximum), the lowest-energy-conformer values, and the Boltzmann weighted averages. We viewed the specific treatment of representative conformers as a crucial means of describing ensemble properties such as chemical shift while also probing structural flexibility during catalysis.

The final step in the workflow involved the analysis of both the stereofidelity and the branched:linear product ratio. These two readouts

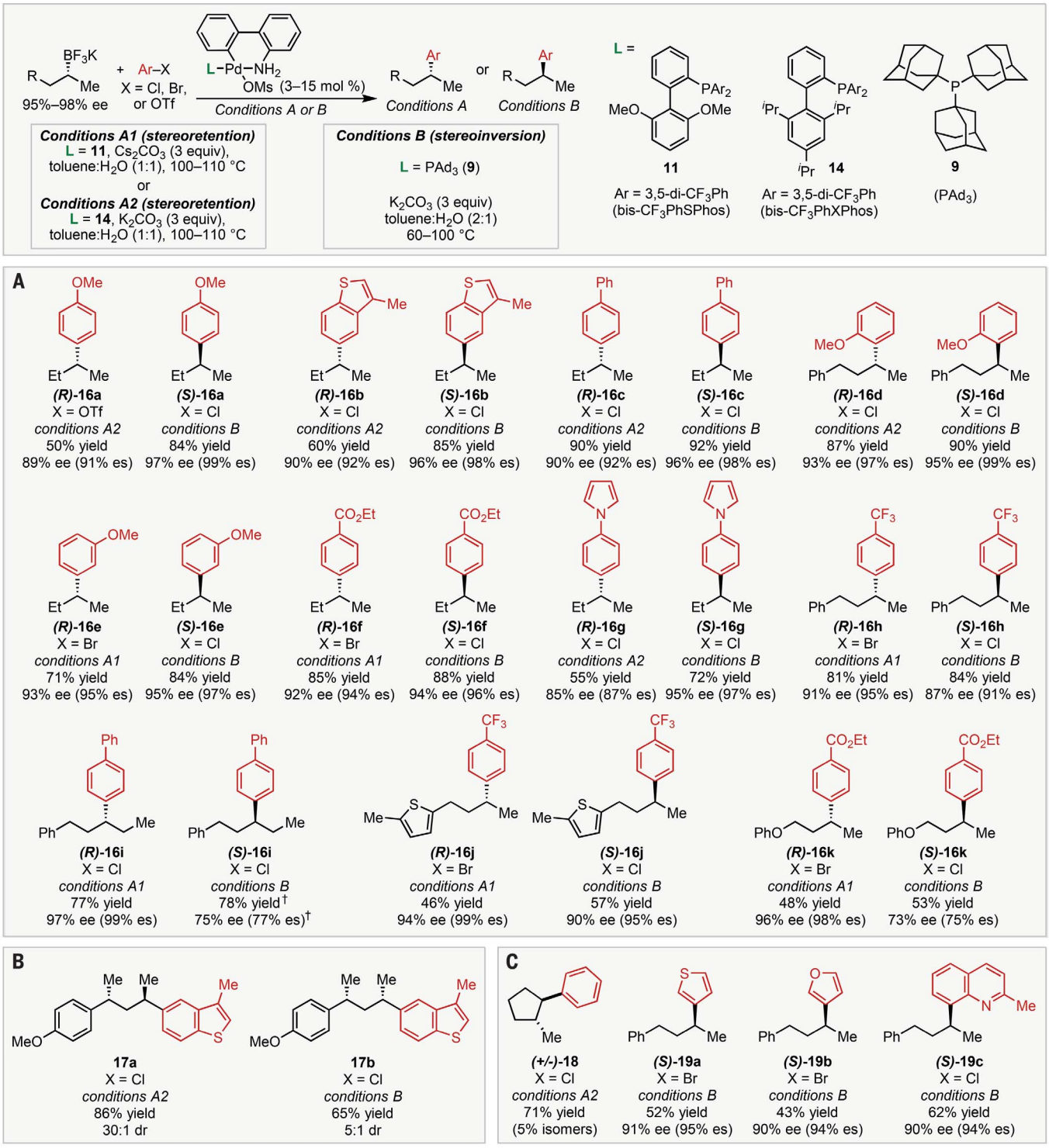

Fig. 3. Stereodivergent Pd-catalyzed cross-coupling reactions using enantioenriched alkylboron nucleophiles. The general reaction scheme is shown at the top. (**A** to **C**) Isolated yields are shown for stereoretentive and stereoinvertive cross-coupling reactions (A), diastereoselective cross-coupling reactions (B), and additional individual reactions (C). ^{i}Pr, isopropyl; dr, diastereomeric ratio. % es = % ee (final product) divided by % ee (starting material). †44% yield and 84% ee (86% es) when run at 60°C.

presumably describe two stages of the reaction mechanism (Fig. 1B): (i) the competing stereoretentive and stereoinvertive transmetallation mechanisms that determine the final stereochemistry of the cross-coupling product and (ii) the competitive β-hydride elimination-isomerization sequences that follow transmetallation. A correlation of the branched:linear ratio with the final enantiopurity of the product reveals that β-hydride elimination is responsible for both racemization and isomerization to the linear side product. Furthermore, a modest trend is observed relating the minimum width B_1 of the phosphine ligand to the branched:linear ratio (Fig. 2B). This is consistent with reports of large ligands facilitating reductive elimination over β-hydride elimination (*33*) and suggests the use of a parameterization approach to take into account the conformational flexibility of ligands.

Because the inherent selectivity of the transmetallation mechanism is masked by deleterious racemization as a consequence of β-hydride elimination, only ligands providing high selectivity were further investigated [>30% enantiomeric excess (ee), Fig. 2B]. The molecular electrostatic potential minimum in the phosphorus lone pair region (V_{min}) has been shown to correlate with the classical Tolman electronic parameter (*34*). Thus, V_{min} serves as an easily computable measure for the overall ligand electronics. A correlation between enantioselectivity and V_{min} was observed within the abridged dataset, indicating that electronic properties of the ligand determine the mechanism of transmetallation. Specifically, electron-rich trialkylphosphines promoted stereoinvertive reactions, whereas the electron-poorer triarylphosphines provided modest selectivity for stereoretention. Use of the bulky, electron-rich ligand PAd_3 (Ad, adamantyl) (**9**), which was recently reported by Carrow and co-workers (*35*), resulted in a particularly large preference for the stereoinvertive outcome. Based on these data, we hypothesized and virtually evaluated ligands for improved stereoretentive outcomes with the following features: (i) large ligand bulk to prevent β-hydride elimination and racemization and (ii) electron-deficient aryl substituents at phosphorus to promote the stereoretentive mechanism and to accelerate reductive elimination (Fig. 2B). Among the proposed ligands was a set of biaryl phosphines (**11** to **15**), as pioneered by Buchwald and colleagues (*36*), featuring various electron-deficient aryl groups at phosphorus. Gratifyingly, ligands **11** and **14** promote the alkyl Suzuki cross-coupling reaction with considerably enhanced selectivity (up to 90% ee) and minimal alkyl isomerization. Thus, parameterization-driven optimization facilitated development of a stereoretentive Suzuki reaction involving unactivated alkylboron nucleophiles. When considered alongside the introduction of **9** to achieve stereoinvertive couplings, predictable control of the absolute sense of enantioselectivity (retention or inversion) can be engendered by simply selecting the appropriate ligand.

Our stereochemical investigations of secondary alkylboron transmetallation in the Suzuki reaction suggested that both enantiomers of a cross-coupling product could be selectively accessed through use of a single enantioenriched alkylboron reagent with the proper selection of the phosphine ligand. The scope of this process is depicted in Fig. 3. Using enantioenriched, unactivated alkyltrifluoroborate nucleophiles, ligand-controlled stereoselectivity was broadly achieved in cross-coupling reactions with aryl electrophiles. Strongly π-accepting ligands bis-CF_3PhSPhos (Ph, phenyl) (**11**) and bis-CF_3PhXPhos (**14**), which emerged from our parameterization-guided optimization, preferentially promote the stereoretentive pathway, whereas strongly σ-donating ligand PAd_3 (**9**) preferentially promotes the stereoinvertive pathway. Because electron-poor palladium catalysts commonly undergo slow oxidative addition with aryl chlorides, we also evaluated aryl bromide and triflate electrophiles in reactions involving **11** and **14**. A particular highlight of this protocol is the uniformity of the conditions used for both the stereoinvertive and stereoretentive reactions: each operates in a toluene and water mixture as solvent, with a carbonate base, and no additional additives. Both reaction variants tolerated the use of electron-rich and electron-deficient aryl electrophiles, as well as an aryl electrophile bearing an ortho substituent. High stereofidelity was achieved for all of these reactions, including those involving alkylboron nucleophiles bearing thiophenyl and phenoxide substituents. Use of an alkylboron nucleophile containing a larger substituent (replacing methyl with ethyl) at the

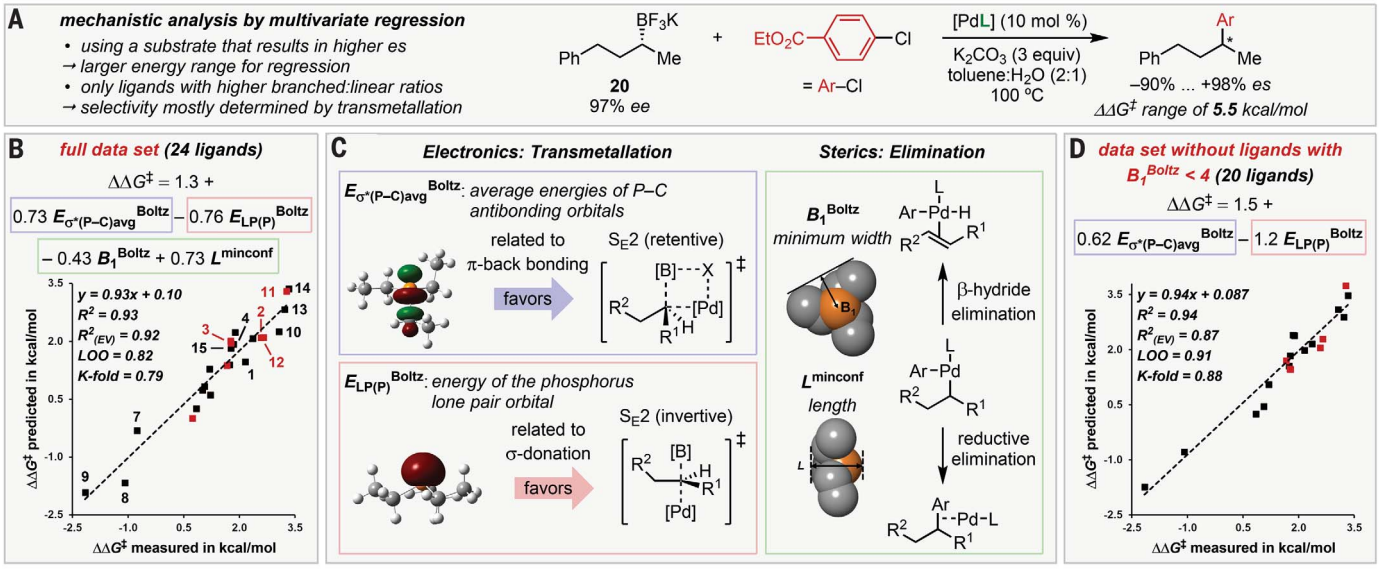

Fig. 4. Mechanistic investigation by multidimensional regression modeling. (**A**) Data from the arylation of **20** was used. [PdL] is the precatalyst as shown in Fig. 3 with varying ligands. * indicates an enantioenriched stereocenter. (**B**) Regression model containing all 24 ligands of this dataset. $E_{\sigma^*(P-C)avg}{}^{Boltz}$ is the Boltzmann-weighted average across the conformers of the average energies of the three P–C σ* antibonding orbitals in each phosphine. $E_{LP(P)}{}^{Boltz}$ is the Boltzmann-weighted average of the energy of the phosphorus lone-pair orbital. Sterimol $B_1{}^{Boltz}$ is the least width, and sterimol $L^{minconf}$ is the length of the lowest-energy conformer as seen from opposite the P substituents. Red points in the diagram indicate validation data (EV) not used in the model training. LOO, leave-one-out cross-validation score; K-fold, average threefold cross-validation score. (**C**) Illustration and interpretation of the model terms. (**D**) Regression model after removing the four smallest ligands in this dataset to exclude the influence of competitive β-hydride elimination on the data.

stereogenic center was also well tolerated (**16i**). In the absence of a methyl substituent, the stereoinvertive variant shows modestly reduced selectivity that may be improved by reducing the reaction temperature. This was partially anticipated because of the greater sensitivity of the metal fragment to steric congestion at carbon in the stereoinvertive S_E2 transmetallation mechanism. Diastereomeric products **17a** and **17b** could be generated from a single alkylboron diastereomer (*37*) using **14** and PAd_3, respectively (Fig. 3B). In these reactions, replacement of ligand **14** with PAd_3 resulted in a change in diastereoselectivity from 30:1 to 1:5, a 3.6 kcal/mol free energy of activation difference dependent only on the ligand identity. No erosion of specificity was observed for electron-deficient aryl substrates in stereoinvertive Suzuki reactions using PAd_3, in contrast to analogous reactions using P^tBu_3. Furyl and thiophenyl electrophiles are also compatible with our system (Fig. 3C). As an additional mechanistic probe, *trans*-2-methylcyclopentyltrifluoroborate was subjected to the stereodivergent reaction conditions. Because *trans*-2-methylcyclopentyltrifluoroborate is sterically impeded from undergoing stereoinvertive transmetallation, only the stereoretentive process using **14** should be mechanistically viable. Indeed, we observed that use of ligand **14** smoothly generates **18** with stereoretention, whereas use of PAd_3 results in low alkylboron conversion.

To further probe the origin of the ligand-dependent enantiodivergent process, we interrogated the mechanism of transmetallation using the parameterization strategy described above (Fig. 4). To accomplish this, phenyl-substituted substrate **20** was selected because of enhanced performance and thus a greater output range. A singular aryl chloride electrophile was chosen for this analysis to avoid potential attenuation of the ligand effects by the influence of different counterions (e.g., bromide or triflate). Additionally, 24 ligands were tested, excluding smaller ligands to reduce the complexity associated with β-hydride elimination. Multivariate linear regression revealed that most of the outputs can be expressed in two readily interpretable terms that discriminate the transmetallation pathways: the average energy of the P–C antibonding orbitals $E_{\sigma^*(P-C)}$, representative of π-back bonding, and the energy of the lone pair orbital of phosphorus $E_{LP(P)}$, a measure of the ligand's σ-donation capability (Fig. 4B). This outcome suggests that the stereoinvertive pathway is dependent on strong σ-donation from the ligand, which may stabilize a two-coordinate, cationic palladium complex. Conversely, the stereoretentive pathway is enhanced by π-back bonding, which may stabilize the coordination of a π-donor ligand X (presumably OH^-) to Pd. Including two steric descriptors such as B_1 and L (length of ligand L) improves the model fit by treating the competitive β-hydride elimination that occurs using smaller ligands and decreases the observed specificity. This becomes evident when the four smallest ligands in this dataset are removed from the analysis, which results in an excellent correlation using just the two electronic descriptors with the experimentally observed stereochemical outcomes (Fig. 4D). Multivariate regression analysis thereby provides compelling evidence for the electronic factors favoring each transmetallation mechanism and thus a guideline for future developments in stereospecific cross-coupling reactions.

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SUPPLEMENTARY MATERIALS

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The staying power of electron-poor ligands

The venerable Suzuki coupling reaction originally used palladium to pair up unsaturated carbon centers. The protocol has been widely extended to chiral saturated alkyl carbons, but control over product stereochemistry is a pressing challenge. Zhao *et al*. systematically studied how the properties of the phosphine ligands that are coordinated to the catalyst influence the stereochemical outcome. Certain electron-withdrawing phosphines favored retention of the initial configuration in chiral alkyltrifluoroborate reactants. Conversely, bulky electron-rich phosphines lead to inverted configurations in the products.

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