Development and Molecular Understanding of a Pd-Catalyzed Cyanation of Aryl Boronic Acids Enabled by High-Throughput Experimentation and Data Analysis

Journal Article

Author(s):

De Jesus Silva, Jordan ; Bartalucci, Niccolò; Jelier, Benson ; Grosslight, Samantha; Gensch, Tobias; Schünemann, Claas; Müller, Bernd; Kamer, Paul C.J.; Copéret, Christophe ; Sigman, Matthew S.; Togni, Antonio

Publication date:

2021-12

Permanent link:

<https://doi.org/10.3929/ethz-b-000515010>

Rights / license:

[Creative Commons Attribution 4.0 International](#)

Originally published in:

Helvetica Chimica Acta 104(12), <https://doi.org/10.1002/hlca.202100200>

Development and Molecular Understanding of a Pd-Catalyzed Cyanation of Aryl Boronic Acids Enabled by High-Throughput Experimentation and Data Analysis

Jordan De Jesus Silva,^a Niccolò Bartalucci,^a Benson Jelier,^a Samantha Grosslight,^b Tobias Gensch,^{b, c} Claas Schünemann,^d Bernd Müller,^d Paul C. J. Kamer,^d Christophe Copéret,^{*a} Matthew S. Sigman,^{*b} and Antonio Togni^{*a}

^a Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 1–5, CH-8093 Zürich, Switzerland, e-mail: ccoperet@ethz.ch; Antonio.togni@inorg.chem.ethz.ch

^b Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States, e-mail: matt.sigman@utah.edu

^c Department of Chemistry, TU Berlin, Straße des 17. Juni 135, DE-10623 Berlin, Germany

^d Leibniz-Institute for Catalysis e. V., Albert-Einstein-Straße 29a, DE-18059 Rostock, Germany

Dedicated to the late Prof. Paul C. J. Kamer

© 2021 The Authors. Helvetica Chimica Acta published by Wiley-VHCA AG. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

A synthetic method for the palladium-catalyzed cyanation of aryl boronic acids using bench stable and non-toxic *N*-cyanosuccinimide has been developed. High-throughput experimentation facilitated the screen of 90 different ligands and the resultant statistical data analysis identified that ligand σ -donation, π -acidity and sterics are key drivers that govern yield. Categorization into three ligand groups – monophosphines, bisphosphines and miscellaneous – was performed before the analysis. For the monophosphines, the yield of the reaction increases for strong σ -donating, weak π -accepting ligands, with flexible pendant substituents. For the bisphosphines, the yield predominantly correlates with ligand lability. The applicability of the designed reaction to a wider substrate scope was investigated, showing good functional group tolerance in particular with boronic acids bearing electron-withdrawing substituents. This work outlines the development of a novel reaction, coupled with a fast and efficient workflow to gain understanding of the optimal ligand properties for the design of improved palladium cross-coupling catalysts.

Keywords: aryl boronic acids, cyanation, data analysis, high-throughput experimentation, ligand design, palladium.

Introduction

Aryl nitriles are ubiquitous structural motifs that constitute an integral part of numerous dyes, agrochemicals, herbicides, pharmaceuticals and natural products.^[1–6] Furthermore, the cyano group serves as a valuable precursor for a plethora of functional group transformations in the synthesis of various compounds

such as aldehydes, amines, carboxylic acids or heterocycles.^[7–9] Therefore, the transition metal-catalyzed (Pd, Cu, Ni, Co, Rh) formation of aromatic nitriles has been studied extensively over the last few decades,^[10–24] stimulated by the development of new, less toxic and readily-available cyano sources.^[25,26] However, the design of these catalytic reactions remains mostly serendipitous due to the multidimensionality of the reaction conditions, among which ligand selection is a significant challenge.

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/hlca.202100200>

In this context, robotized high-throughput experimentation (HTE) methods have been utilized to accelerate the acquisition of data on large libraries of formulations and build robust structure–activity relationships (SAR), ultimately enabling the identification of well-performing catalytic systems.^[27–29] These robotized approaches are particularly auspicious as they enable obtaining reproducible data sets that, in concert with statistical analysis tools, allow for correlating reaction outputs to specific physico-chemical properties.^[30–32] While random forest models have recently gained attention for being excellent for prediction,^[33] such models often tend to be difficult to interpret.^[34] Hence alternative, multivariate linear and polynomial regression analyses enjoy popularity in both industry and academia,^[35] owing to their ease of interpretability.^[36–38]

Herein, we describe the development of a palladium-catalyzed electrophilic cyanation of aryl boronic acids, using bench stable *N*-cyanosuccinimide as the cyanating agent (see Scheme 1,1). A combined HTE-data analysis strategy was applied to identify effective ligands for this transformation and to determine a structure–activity relationship between yield and readily accessible ligand descriptors. In this study, we evaluated 90 ligands, highlighting *Buchwald*-type monophosphines and *Xantphos*-type bisphosphines as the most efficient ligands for this reaction, and revealing σ -donating abilities and ligand lability, as key parameters, which govern the observed reaction yields of the desired product.

Results and Discussion

Preliminary Screening for Optimal Reaction Conditions

Among the electrophilic 'CN' transfer reagents, *N*-CN reagents have been extensively employed in the literature given their low toxicity and bench-stability.^[39–42] We prepared a selection of *N*-CN reagents (Figure 1), encompassing different classes of organic compounds: *N*-cyanoheterocyclic reagents **NCN1**–**NCN3**, *N*-cyanoimides (**NCN4**, **NCN5**) and *N*-cyanoimines **NCN6**. The C–CN aryl nitrile bond formation was carried out using palladium as the metal source and aryl boronic acids as typical substrates in *Suzuki–Miyaura* cross-coupling reaction conditions.^[43–45]

As a first step, we sought to verify the stability of the six *N*-CN reagents wherein only *N*-cyanoimides **NCN4** and **NCN5** were found to be stable in 1,4-dioxane at 100 °C after two hours in the presence of a

Figure 1. *N*-CN reagents considered for the Pd-catalyzed cross-coupling cyanation of aryl boronic acids.

base (see Supporting Information for more information). Even though *N*-cyanoimides have been known in the literature since the 1870s^[46] and are commercially available,^[47] their use as electrophilic cyanation reagents has not yet been well-explored.^[13,48,49] Preliminary screening of the reaction conditions was carried out (see Table S1 for more details), allowing us to identify *Buchwald*'s Palladium G3 pre-catalyst,^[50] 1,4-dioxane as solvent, potassium phosphate as base and **NCN4** as the cyanation reagent as optimal reaction components for further investigation.

The tolerance of the reaction towards different perturbations was also investigated. Interestingly, the presence of free ^-CN in the reaction mixture was found to be detrimental for the conversion, as no product formation was detected, possibly due to catalyst poisoning (formation of unreactive $Pd(II)(CN)_x$ intermediates^[51–53]). This observation supports the assumption that *in situ* formation of nucleophilic cyanide is not involved in the reaction mechanism. By carrying out the reaction in the presence of O_2 , formation of biphenyl as the main product was detected as a result of homocoupling of the aryl boronic acid, a commonly observed process.^[54,55] While the addition of exogenous water (3 equiv.) to the mixture led to a decrease in yield (see Table S1), the use of dry reaction conditions severely hampered the reaction (for experiments on the optimal water quantity, see Figure S1). This observation is presumably linked to the state of hydration of boronic acids, that can undergo dehydration to their less reactive dimeric

HTE Study

1. Pd-catalyzed cyanation of 4-fluorophenylboronic acid

2. Ligand library

3. Results of the catalytic cyanation

Scheme 1. Design of the HTE study (1.), ligand library (2.) and catalytic results (3.) for the cyanation of 4-fluorophenylboronic acid. *For bidentate ligands, 10 mol-% were used. Ar^F = 3,5-(CF_3)-Ph; Ar^F = 2,3,4,5,6-F-Ph.

and trimeric (boroxine) forms under anhydrous conditions.^[56–58] Indeed, commercial ‘boronic acids’ are often mixtures of all these forms in various ratios, and up to one equivalent of water is needed to reform the boronic acid required for the reaction. For the purposes of subsequent ligand screening and substrate scope, commercial, non-dried solvent (ca. 180 ppm H₂O) and base were found to yield reproducible and satisfactory results.

Ligand Screening under Optimized Reaction Conditions

In order to study the impact of ligand structure on the cyanation reaction, a diverse array of 90 prototypical ligands used in cross-coupling reactions was selected for evaluation due to their broad range of steric and electronic properties. However, the design matrix does incorporate overlapping feature space, which should facilitate the identification of uncorrelated structural features that determine the catalytic outcome (see Scheme 1). For simplicity, the library is subdivided into three categories: monophosphines **A1–A33**, bisphosphines **B1–B45** and miscellaneous ligands **C1–C12**. All catalyst formulations were prepared by mixing 1 equiv. boronic acid, 1.5 equiv. *N*-cyanosuccinimide, 2.5 mol-% palladium precatalyst,^[50] 5 or 10 mol-% ligand (for bidentate or monodentate ligands, resp.) and 20 mol-% potassium phosphate in 1,4-dioxane. The preparation of the mixtures was automated by a liquid handling robot operated inside an inert (N₂) atmosphere purge box (see the *Supporting Information* for details). The mixtures were then heated to 120 °C for 12 h, and the reaction yield was analyzed through quantification of the products by gas chromatography/mass spectrometry. All tests were performed in triplicate, including ligand **B1** in every 96-reaction run to assess (batch-to-batch) reproducibility of the results. Outliers within the triplicate runs were evaluated by examining the coefficient of variation,^[59] that should be below 20% and were discarded for the average yield without outliers (see Table S2).

Among all ligands in the library, the bisphosphine category leads to the greatest percentage of high-yielding entries, where tests using ligands **B1–B3**, **B7**, **B8**, **B14** and **B35** afforded the cross-coupling product in >80% yield. Interestingly, the majority of those entries are Xantphos-type ligands,^[60,61] a privileged class popularly applied in numerous reactions.^[62] In the monophosphine category, the highest yields are found with dialkylbiaryl phosphines.^[63] Specifically, yields >55% were afforded using dicyclohexylbiaryl phosphines **A3–A6** and **A9**. However, tests using *tert*-

butyl analogues **A16–B23** led to significantly lower yields (< 25%), possibly pointing at the significant role of the alkyl substituents on generating high-yielding catalysts. Reactions using ligands from the miscellaneous group, e.g., NHCs **C1–C2**, diamines **C3–C5** and phosphites or phosphoramidites **C6–C9**, generally gave poor yields. In this ligand group, only tests with Triphos (**C12**) afforded the product in high yield (85%).

Parametrization

In order to delineate which ligand properties influence the reaction yield, we sought to apply statistical methods used in some of our groups.^[36] We limit the discussion below primarily to monophosphines (**A**) and bisphosphines (**B**), because these categories contain the highest yielding entries and incorporated subsets of structurally related ligands that should facilitate statistical analyses. For the monophosphine group **A**, all physicochemical descriptors were extracted from the *kraken* discovery platform.^[64] For the bisphosphine group **B**, a workflow was initiated by performing conformer searches on the corresponding PdCl₂ adducts using xTB/crest^[65–68] and followed by structural refinement by DFT on the lowest energy conformer. Descriptors were extracted for the complexes and from separate single-point calculations on the stand-alone ligand without PdCl₂. Subsequently, the origin of increased product formation is investigated by statistical models starting from preliminary identification of univariate trends within subsets of the ligand categories, followed by application of multivariate linear regression analysis. The general workflow to correlate the reaction yields to molecular descriptors of bisphosphine ligands is presented in Figure 2.

Descriptors of the Phosphines

Phosphines are amongst the most extensively studied ligands in homogenous catalysis.^[69] Pioneering work by Tolman in this regard have provided a guide to interrogate the donor and steric properties of PR₃ ligands, hence enabling systematic fine tuning of ligand properties with a some degree of predictability.^[70,71] The bonding in phosphine ligands is constituted of two major components: σ -donation of the phosphine lone pair to an empty metal orbital and π -backdonation from a filled metal orbital to antibonding σ^* -orbitals of the phosphine–substituent bonds. The bulkiness of the phosphine ligand is important to modulate the binding to the metal center

Figure 2. Parametrization of the bisphosphine ligands and selected calculated molecular descriptors.

and facilitate association/dissociation as well as the ligation state (how many ligands are bound to the metal for monodentate phosphine ligands^[64]). We sought to calculate descriptors that would address these features.

Monophosphine Descriptors. The donating properties were assessed relative to the molecular electrostatic potential minimum in the phosphine lone pair region (V_{min}), the natural bond orbital (NBO) derived atomic charges of phosphorus (q_{O}), P–C bonding $\sigma_{\text{(P-C)}}$ ($E\sigma_{\text{(P-C)}}$, $\text{Occ}_{\text{(P-C)}}$) and antibonding $\sigma^*_{\text{(P-C)}}$ ($E\sigma^*_{\text{(P-C)}}$, $\text{Occ}_{\text{(P-C)*}}$) NBO energies and occupancies. Additional parameters included HOMO/LUMO energies, SOMO energies of the radical cation/anion, NBO energies of the phosphorus lone pair ($E_{\text{LP(P)}}$), molecular dipole (μ) and pyramidalization (Pyr). The steric influence of the

phosphine ligands was assessed using Verloop's Sterimol parameters (L , B_1 , B_5),^[72] and the proximal ($\%V_{\text{bur}}$) and distal ligand volume.^[73,74] Additionally, some descriptors were collected for the minimum (*min*), maximum (*max*), Boltzmann (*Boltz*) and minimum buried volume (*vburmin*) valued conformers. All of these parameters are accessible from the *kraken* database.

Bisphosphine Descriptors. In addition to the descriptors used for the monophosphines, ligand parameters specific to the PdCl₂ adduct were assessed to describe the bidentate nature of the ligands. Included are the bite angle α_{PPdP} , the Pd–Cl ($d_{\text{Pd-Cl}}$) and Pd–P ($d_{\text{Pd-P}}$) distances. The values are all presented in the *Supporting Information*.

Analysis of the Monophosphines

We first explored the analysis of monophosphines **A** independently, seeking to relate calculated electronic and steric properties of the ligands to the experimentally determined yield. Generation of a univariate correlation matrix (see Figure S40) revealed modest correlations with R^2 values not exceeding 0.45. Hence, closer analysis of a series of structurally similar ligands was explored, to probe the electronic and steric impact on different subclasses in our correlations. The focus was set on three subclasses: *Buchwald*-type dialkylbiaryl phosphines with either cyclohexyl (**A1**–**A12**) or *tert*-butyl substituents (**A16**–**A23**) and simple trisubstituted alkyl/aryl phosphines (**A27**–**A33**). Unfortunately, no compelling conclusions could be obtained through splitting of the monophosphine data set **A**, apart from identifying the dicyclohexylbiaryl subset as highest yielding ligand family (see Figure S41).

To gain a better understanding on how phosphine steric and electronic features relate to reaction performance, multivariate linear regression analysis was performed to investigate the cooperative effect of steric and electronic parameters on the yield response, focusing on the ligands (**A1**–**A14**, **A16**–**A19**, **A24**–

A26, **A30**, **A31** and **A33**) remaining after removal of inactive entries with yields below 5% (less than one turnover). The robustness of the model is tested by evaluating a validation set not used in the model training and internal-validation techniques (LOO, leave-one-out cross-validation score; k -fold, average fourfold cross-validation score) after feature standardization, yielding good scores for all cases consistent with a well-validated model.^[27–29,75] The significance of each of the represented effects is given by the coefficients of the normalized descriptors in the trained model.

The multivariate regression analysis of the monophosphine ligands produced a model that features one electronic and one steric parameter, as well as one interaction term (see Figure 3). The steric descriptor $QV_{\text{tot,min}}^{\text{Boltz}}$ describes the lowest quadrant total volume arising from the buried volume analysis. Given the negative coefficient, this steric descriptor correlates lower steric bulk to higher yields, possibly relating to an easily accessible additional coordination to the ligated catalyst. The interaction term $E_{\text{SOMO,rc}}^{\text{Boltz}}:V_{\text{tot}}(z+)^{\text{vburminconf}}$ could relate to the σ -donor ability of the phosphine (the SOMO energy of the radical cation is largely correlated to the nucleophilicity of a phosphine, as can be assessed by looking

Figure 3. Multivariate linear regression model to predict yield for ligands **A1**–**A14**, **A16**–**A19**, **A24**–**A26**, **A30**, **A31** and **A33** with depiction of parameters within the multivariate model.

at correlations of this descriptor with for instance E_{HOMO} in the larger *kraken* discovery platform^[64] as a function of the total volume occupied in the $z+$ hemisphere, which is the part of the metal coordination sphere that points away from the phosphine ligand. Its coefficient indicates that it is the defining parameter of the model and can be viewed as the ability to modulate the fine balance of σ -donation and sterics required for the coordination/decoordination to/from palladium. The average occupancy of the P–C bonds $\text{Occ}_{(\text{P}-\text{C})\text{avg}}^{\text{Boltz}}$ is a probe of the overall electronic state at phosphorus (the occupancy is most strongly correlated with the *HOMO*–*LUMO* gap). Together with $E_{\text{SOMO},\text{rc}}^{\text{Boltz}}$, this descriptor captures the electron-richness/ donation of the ligand, wherein generally less electron-rich ligands (smaller values for $\text{Occ}_{(\text{P}-\text{C})\text{avg}}^{\text{Boltz}}$) lead to increased yields.

Considering the statistical model, the yield of the cyanation reaction depends heavily on the stereo-electronic properties of the ligands. One possible interpretation is that flexible, moderately large ligands like the dicyclohexylbiaryl phosphines can efficiently bind to the palladium center through a σ -bonding interaction, while being bulky enough to favor dissociation of at least one phosphine ligand. When the ligand sterics increase, the σ -bonding interaction to the metal is hindered and the π -acidity compensates to weakly interact with the metal, as can be seen for the di-*tert*-butylbiaryl phosphines and the simple alkyl/aryl phosphines. This hypothesis holds true for the adamantyl phosphines **A13**–**A15** and explains the low yield obtained with phosphites and phosphoramidites **C6**–**C8**, that are weak σ -donors, but strong π -acceptors. The importance of ligand lability also explains the low yields observed for non-phosphinic ligands **C1**–**C5**, that usually form strong metal–ligand bonds and do not easily dissociate.

Analysis of the Bisphosphines

In an analogous approach to the one applied for the monophosphine set **A**, a series of structurally similar ligands was chosen to analyze the effect of sterics and electronics on a subclass of the bisphosphine set **B**. The Xantphos-derivatives (**B1**–**B17**) were particularly interesting to investigate as they represent over one third of all ligands in group **B** and cover a broad range of yields (0–93%). In a first attempt, univariate correlations with the ligands in *cis*-PdCl₂ were explored, but the R^2 values of the univariate correlation matrix did not exceed 0.54 (see *Figure S42*). Inability to model ^{*t*}Bu-Xantphos **B17** as a *cis*-complex and crystal-

lographic evidence of Xantphos-type square-planar palladium complexes in *trans* configuration,^[76,77] inspired the hypothesis that parametrizing ligands as *trans*-complexes might be required. Indeed, treating ligands **B4**, **B5**, **B10**, **B12**, **B13** and **B15**–**B17**, all affording less than 21% yield, as *trans*-PdCl₂ complexes improved univariate correlations significantly (see *Figure S43*). In particular, the inverse correlation with the longest palladium–chlorine bond length $d_{\text{Pd}-\text{Cl}}^{\text{max}}$ (see *Figure 4,a*) displayed a good coefficient of determination ($R^2=0.77$). This descriptor may represent the *cis*- or *trans*-influence of the bidentate ligand,^[78–80] a measure of the lability of ligands that are *cis* or *trans* to other ligands, which is manifested by the elongation of the respective metal–ligand bond.

Exploration of reactivity thresholds was carried out to classify Xantphos-type ligands as *active* or *inactive* in the cyanation of aryl boronic acids. Previous studies by the Doyle and Sigman groups have demonstrated that threshold analyses could successfully be used to classify ligands according to their reactivity for several Ni and Pd-catalyzed cross-coupling reactions.^[81] A sharp reactivity cliff could be found with the largest P–C antibonding energy of the ligand ($E\sigma^*_{(\text{P}-\text{C})\text{max}}$) at a threshold value of 0.237 Hartree, allowing us to bin the outcomes accurately (see *Figure 4,b*): all ligands above 0.237 were classified as *active* (white area), whereas the ones with values below were classified as *inactive* (gray area). The cutoff for inactive entries has been set, as mentioned before, to 5% yield (less than one turnover), hence dividing the plot in areas with true negatives (below 0.237, below 5%) and false negatives (below 0.237, above 5%). As previously discussed,^[82] $E\sigma^*_{(\text{P}-\text{C})}$ is a measure for the π -acidity of the ligand, wherein larger values correspond to weaker π -accepting properties. Hence, the threshold value indicates a propensity towards avoiding metal-to-ligand π -backdonation as observed for the monophosphine group **A** (*vide supra*). Compellingly, this result provides the foundation to suggest most *trans*-coordinated complexes as active isomers, except for **B5** and **B12**, where both isomers lie below the threshold. It should be noted however, that *cis*-**B5** lies on the threshold line and may likely be a false positive.

Given the popularity of Xantphos-type ligands,^[60,61] a more detailed analysis through multivariate regression was performed using the ligand classified as *active* following the threshold analysis (see *Figure 4,c*). The produced model includes all dicyclohexyl- and diphenyl-derivatives (**B1**–**B14** and **B16**), but omits **B4**,

Figure 4. a) Univariate correlation between yield [%] and $d_{(Pd-Cl)}^{max}$ with *cis* and *trans*-modeled complexes. b) Threshold analysis according to $E\sigma^*_{(P-C)max}^L$ with *cis* and *trans*-modeled complexes. c) Multivariate linear regression model to predict yield for Xantphos-type ligands **B1–B3**, **B5–B14** and **B16**.

B15 and **B17** as low-yielding strongly *trans* chelating ligands. The model features the electronic descriptors d_{Pd-Cl}^{max} and $E\sigma^*_{(P-C)min}^L$, representing again the *trans*-effect and the π -acidity of the ligand, respectively, as previously discussed. The yield increases with decreasing maximum palladium–chlorine bond length, which can be interpreted as weaker *cis/trans*-influence. In contrast, lower π -acidity is correlated with higher yields as previously observed for the dicyclohexyl biaryl phosphines. Hence, both terms potentially describe the necessity of at least one weakly binding phosphine of the bidentate Xantphos-type ligand, in line with the well-known hemi-lability exhibited by those ligands.^[83,84]

To gain further insight into the key parameters required for high yields in the bisphosphine group **B**, a more general statistical analysis encompassing non-Xantphos-like ligands was carried out (see Figure 5). After performing a classification with the same parameter used for the Xantphos ligand subset, the threshold value for $E\sigma^*_{(P-C)max}^L$ remained at 0.237 Hartree (Figure 5,a). Three ligands (**B37**, **B44** and **B45**) appear to be false negatives, likely due to omission of steric interactions that might be significant (as **B37** and **B44** have cyclohexyl and phospholane substituents, resp.). Furthermore, the threshold suggests *trans*-**B25** to be the active isomer but is incapable of distinguishing the *active* isomer for SPANPhos (**B29**). Nevertheless, proximity to the threshold value and literature precedents

suggest the respective *trans*-complexes to be favored.^[85,86]

Using the insights from the threshold analysis regarding *cis*- or *trans*-configuration of the entries, the %yield response was evaluated through multivariate regression analysis (Figure 5,b). Apart from ligands **B1–B3**, **B5–B14** and **B16** (*vide infra*), the model includes the biphenyl and binaphthyl derivatives **B18–B23**, the variable chain length bisphosphines **B33**, **B34**, **B36–B40** and **B45**, as well as **B27–B30**, covering 32 of the 45 ligands in set **B**. The obtained model includes the electronic parameters $d_{(Pd-Cl)}^{avg}$, $E\sigma^*_{(P-C)max}^L$, $NBO_{LP(P)S\%}^{min}$ and $Occ_{(P-C)}^{avg}$, as well as the steric descriptor $L_{P-frame}^{min}$. The first electronic term, the average palladium–chlorine bond length $d_{(Pd-Cl)}^{avg}$, in juxtaposition with the previously addressed maximum bond length, has a positive correlation with yield. This likely arises from the fact that only one of the two phosphine ligands in the bisphosphine needs to engage in a strong bonding interaction with the palladium metal, thus leading to a stronger *cis/trans*-influence. This observation is further supported by the correlation with $NBO_{LP(P)S\%}^{min}$, the lowest s-character percentage of either of the two phosphorus lone pairs, which is the consequence of the hybridization of the phosphorus and thus σ -donation. Here, an increase in yield is promoted by having a strong σ -donating phosphine. In contrast, $E\sigma^*_{(P-C)max}^L$, the largest P–C antibonding energy of the ligand, is responsible for an increase in yield with higher energies and hence, lower

Figure 5. a) Threshold analysis of the bisphosphine dataset **B** with $E\sigma^*(P-C)_{\max}^L$, including computed *cis* and *trans* complexes. b) Multivariate linear regression model to predict yield for bisphosphine ligands **B1–B3**, **B5–B14**, **B16**, **B18–B25**, **B28–B30**, **B33**, **B34**, **B36–B40** and **B45**. c) Depiction of parameters within the multivariate model.

π -acidity. The overall electron-richness of the phosphine shows a detrimental effect on yield as indicated by the negative coefficient on $Occ_{(P-R)}^{avg}$, the average occupancy of the phosphorus non-framework carbon atom σ -bond. Having lower values for more delocalized systems (aryl vs. alkyl substituents), this descriptor hints again at the importance of having at least one phosphine coordinated. The steric parameter $L_{P-frame}^{min}$, the minimum *Sterimol* length on the phosphorus framework carbon bond, describes the fine balance of sterics required for efficient catalysis. Yield increases with an increase of the framework size, following the same trend observed with the mono-

phosphine set **A**, where increased bulk likely facilitates de-coordination.

Considering the relevant descriptors in the multivariate models, a parallel scenario to the one described for the monophosphine group **A** becomes apparent. The yield of the cyanation reaction is modulated by a balance of σ -bonding, π -bonding and steric interactions, where strong binding to the palladium metal is disfavored. Given the bidentate nature of the bisphosphines, lability of one of the phosphine ligands seems to be crucial as shown by d_{Pd-Cl} , likely owing to the possibility of facilitating *cis-trans* isomerism of the square-planar complexes or opening a coordination site for incoming

reactants.^[77,87] This hypothesis would explain the low yields observed with Cy-Xantphos **B15**, *t*Bu-Xantphos **B17** and PNP pincer ligand **C10** that form stable *trans* square planar complexes with strong phosphorus–palladium bonds.^[76,88] The hypothesis also holds true for 20F-dppe **B41** and the bisphosphite **C9**, that are weak σ -donors, but strong π -acceptors. Curiously, dppp **B35** failed to be incorporated into the statistical analysis, although shorter chain length bisphosphines dppm **B33** and dppe **B34**, as well as longer chain analogue dppb **B36** fit in well. A possible explanation would be the anaerobic oxidation of dppp, commonly observed under similar reaction conditions,^[89–92] that would yield a phosphine oxide that is more labile than its parent compound.^[93,94] Following the same argument, the surprisingly high yield of Triphos (**C12**) can be rationalized, as this ligand consists of tethered dppp moieties.

Taking the analyses from both mono- and bisphosphines into consideration, the yield of the cyanation reaction appears to be governed by the same phenomena in both ligand subsets. Essentially, the models suggest that ligands should efficiently bind to the metal (higher σ -donation abilities favored), while maintaining the ability to decoordinate easily hence it is disfavored by strong π -acids and favored by the flexibility/sterics of the ligand. As yield is a combination of complex kinetic events including competitive off cycle processes and catalyst deactivation events, the observed correlations presumably indicate that the ligand characteristics simultaneously modulate activity and stability of the catalyst. This is most likely connected to the dynamic ligation state of the complex during catalysis that controls both rates (see Figure 5). In this arena, structurally-responsive ligands (SRL) like Buchwald dialkyl biaryls and Xantphos-type ligands excel as they are able to stabilize the metal in their L2 state while their well-known hemilability opens up a coordination site (L1 state) that may be needed to enable catalysis (see Scheme 2).^[83,84]

Substrate Scope

Given the promising results involving Xantphos-type ligands, we sought to investigate the applicability of this reaction to a wider scope of boronic acids using simple and commercially available Xantphos (**B1**). We explored the scope of 32 aryl boronic acids as substrates for the aryl cyanation reaction using the optimized reaction conditions and **B1** as the ligand. To our delight, the protocol was found to be applicable

Scheme 2. Structurally-responsive ligand behavior for Buchwald dialkyl biaryls and Xantphos-type ligands.

to a broad range of aryl boronic acids with electron donating and withdrawing functional groups (Scheme 3). We started our investigation from simple, monosubstituted aromatic rings: electron donating substituents like *tert*-butyl **2a** and methoxy **2c** in *para*-position were found to be suitable for this transformation, affording the corresponding benzonitriles in moderate to very good yields (47 % and 81 %, resp.). 4-Biphenylboronic acid (**1b**) was functionalized to form the corresponding 4-phenylbenzonitrile (**2b**) in fair yield (54 %). Interestingly, electron-withdrawing substituents seemed to be well tolerated in these reaction conditions, as aryl boronic acids bearing cyano **1d**, aldehyde **1e**, ester **1g**, trifluoromethyl **1i** and **1j** as well as trifluoromethoxy **1h** moieties all underwent cyanation in good to excellent yields (75–96 %). The preference towards electron withdrawing substituents is seldom observed for electrophilic cyanation protocols,^[42] which usually prefer electron-rich substrates.^[13,95,96] This could potentially hint at a mechanism involving an Umpolung of CN, leading to the expected behavior of CN in typical cross-coupling cyanations.^[97]

The free carboxylic acid moiety was found to be unsuitable for this protocol, as 4-carboxybenzonitrile (**2f**) was detected only in trace amounts (4 %), possibly due to protonation of K_3PO_4 required to activate the Pd G3 precatalyst.^[98,99]

Nitro-substituted benzonitriles **2k** and **2l** deserve special mention, as their formation was accompanied by the generation of dinitrobiphenyl byproducts, as a result of a homocoupling side reaction. The oxidative homocoupling was reported to be favored in the

Scheme 3. Scope of the aryl nitriles **2** obtained by the cyanation of aryl boronic acids **1** with the optimized reaction conditions. The reaction was performed on a 1.0 mmol scale, $[ArB(OH)_2] = 25$ mM. Yields of isolated products (NMR yields reported in parentheses).^[a] Yield of isolated product only. ¹H-NMR yield could not be determined due to signal overlapping.^[b] The yield was determined by ¹H- or ¹⁹F-NMR spectroscopy on the crude mixture, due to the volatility of the product (1,2,4,5-tetrafluorobenzene employed as an internal standard).^[c] Reaction conditions: 0.85 mmol $ArB(OH)_2$, 1.8 equiv. SuccNCN, 6 mol-% Pd G3, 6 mol-% Xantphos, 24 mol-% K_3PO_4 .^[d] Isolated in a mixture with inseparable impurity. See *Supporting Information* for further information.^[e] Trace amount detected with GC/MS.

presence of oxidants such as nitrates.^[100] These by-products, albeit present in small amounts (*ca.* 5–10%), appear to have very similar electronic features to the corresponding benzonitrile products, rendering their separation complicated (see *Supporting Information* for further details). The functional group tolerance in the case of different heteroatom-containing substituents was also investigated. Thioether moieties appeared to be compatible with the catalytic conditions, as 3-methylthiobenzonitrile (**2m**) was isolated in 54% yield, while the more electron-donating dimethylamino-substituted aryl boronic acid was converted to **2n** in poor yield (34%).

The compatibility of halide substituents with the reaction conditions requires further discussion. While 4-fluoro- and 4-chlorophenylboronic acid were both successfully converted to benzonitriles **2r** and **2o**, respectively, the formation of 4-bromobenzonitrile (**2p**) was only observed in trace amounts. GC/MS

Analysis of the crude mixtures of **1o** and **1p** revealed traces of 4-halobiphenyl being formed, most likely resulting from oxidative addition of the carbon–halogen bond of the starting material to the palladium catalyst as supported by the decrease in yield in the order $F > Cl > Br$.

Poly-substituted, fluorinated aromatic substrates were screened, affording benzonitriles **2s–2w** in variable yields (5–88%). While fluoroaryl boronic acids containing methyl, ketone and ester moieties underwent cyanation in good yields (71, 75 and 88% NMR yield, resp.), polyfluoro-substituted boronic acids **1s–1t** proved to be difficult substrates, as their incompatibility with the basic environment is well-documented in the literature.^[101–103] The reaction conditions were also suitable for more structurally complex substrates such as **2x**, which was isolated in 66% yield.

Cyanation of polycyclic derivatives 1-naphthyl and 2-naphthylboronic acid led to the successful isolation

of products **2y** and **2z**, while the benzodioxole derivative **2aa** could only be observed in trace amounts.

Finally, we investigated the applicability of the protocol to heteroaromatic substrates. Unfortunately, such substrates were not well tolerated under the reaction conditions. When 2-thienylboronic acid was employed as a substrate, only a small amount of thiophene-2-carbonitrile (**2ab**) could be detected by NMR analysis of the crude (23%). Instead, no formation of nitriles **2ac–2af** was observed with the nitrogen-containing heterocycles, suggesting that catalyst poisoning by these substrates may be occurring.^[104,105]

Conclusions

In summary, we have developed a practical protocol for the palladium-catalyzed electrophilic cyanation of aryl boronic acids using bench stable *N*-cyanosuccinimide as cyanating agent. Further insight into the established reaction was sought by using 90 different ligands and performing each reaction in triplicate in a robotized high-throughput approach, highlighting *Buchwald*-type dicyclohexyl biaryl phosphines and *Xantphos*-type bisphosphines as ideal ligands. Multivariate linear regression analysis allowed us to determine σ -donation, π -acidity and sterics of the ligands to be essential in promoting high reaction yields. In the monophosphine group, strong σ -bonding interactions, weak π -acidic character and flexibility of the ligands modulate the increase in yield by matching sterics and electronics required for the coordination/decoordination to and from palladium. In the bisphosphine group, the yield depends on the ability of the bidentate ligands to dissociate at least with one phosphine, as described by the detrimental effects of π -acidity, but beneficial contribution of increased sterics to promote higher yields, likely owing to promotion of *trans/cis* isomerism or opening of a coordination site to the incoming substrates. Given the excellent reaction yields obtained with *Xantphos*, the applicability of the designed reaction to a wider substrate scope was investigated with **B1**, demonstrating good functional group tolerance with boronic acids bearing electron-withdrawing substituents. To conclude, this work provides a valuable, potentially less toxic alternative to traditional cyanation reaction and the structure–activity relationships serve as base for further mechanistic investigations on this type of reactions.

Supplementary Material

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/hlca.2100200>. Experimental procedures, identification of optimal water amount, catalytic data, plots of the performed data analysis, NMR spectra, modeling details can be found in a PDF file. Xyz-files of the calculated ligands in a ZIP file, mono- and bisphosphine datasets as an XLSX file.

Acknowledgements

J. D. J. S. was supported by the *National Research Fund*, Luxembourg (AFR Individual Ph.D. Grant 12516655). *M. S. S.* acknowledges financial support from NSF under the CCI Center for Computer Assisted Synthesis (CHE-1925607). The support and resources from the Center for High Performance Computing at the University of Utah are gratefully acknowledged. Open access funding provided by Eidgenössische Technische Hochschule Zurich.

Author Contribution Statement

J. D. J. S. and *N. B.* contributed equally to this work. *J. D. J. S.*, *N. B.* and *B. J.* designed the experiments. *N. B.* designed and performed the substrate scope. *J. D. J. S.* performed calculations on the bisphosphines and modelling of the data. *S. G.* performed calculations on bisphosphines. *T. G.* performed calculations on the monophosphines. *P. J. K.*, *B. M.* and *C. S.* synthesized *Xantphos*-type ligands. Initial drafts were written by *J. D. J. S.* and *N. B.* Further editing of the manuscript was conducted by *J. D. J. S.*, *T. G.*, *M. S. S.*, *C. C.* and *A. T.* All authors have given approval to the final version of the manuscript.

References

- [1] F. F. Fleming, 'Nitrile-containing natural products', *Nat. Prod. Rep.* **1999**, 16, 597–606.
- [2] S.-I. Murahashi, 'Three Carbon–Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives', Georg Thieme Verlag, Stuttgart, New York, 2004.
- [3] L. H. Jones, N. W. Summerhill, N. A. Swain, J. E. Mills, 'Aromatic chloride to nitrile transformation: medicinal and synthetic chemistry', *MedChemComm* **2010**, 1, 309–318.
- [4] F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, 'Nitrile-Containing Pharmaceuticals: Efficacious Roles of

- the Nitrile Pharmacophore', *J. Med. Chem.* **2010**, 53, 7902–7917.
- [5] C. Torborg, M. Beller, 'Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries', *Adv. Synth. Catal.* **2009**, 351, 3027–3043.
- [6] A. Kleemann, J. Engel, B. Kutscher, D. Reichert, 'Pharmaceutical Substances – Syntheses, Patents and Applications of the most relevant APIs', 5th Edition, Georg Thieme Verlag, Stuttgart, New York, 2009.
- [7] A. J. Fatiadi, 'Preparation and synthetic applications of cyano compounds', Chapt. 26 in 'Triple-Bonded Functional Groups (1983): Supplement C: Part 2, Volume 2', Eds. S. Patai, Z. Rappoport, John Wiley & Sons Ltd., Chichester, 1983, pp. 1057–1303.
- [8] R. C. Larock, 'Comprehensive Organic Transformations: A Guide to Functional Group Preparations', Wiley-VCH, New York, Chichester, 1997.
- [9] Z. Rappoport, 'The Chemistry of the Cyano Group', John Wiley & Sons Ltd., London, 2010.
- [10] G. P. Ellis, T. M. Romney-Alexander, 'Cyanation of aromatic halides', *Chem. Rev.* **1987**, 87, 779–794.
- [11] M. Sundermeier, A. Zapf, M. Beller, 'Palladium-Catalyzed Cyanation of Aryl Halides: Recent Developments and Perspectives', *Eur. J. Inorg. Chem.* **2003**, 3513–3526.
- [12] P. Anbarasan, T. Schareina, M. Beller, 'Recent developments and perspectives in palladium-catalyzed cyanation of aryl halides: synthesis of benzonitriles', *Chem. Soc. Rev.* **2011**, 40, 5049–5067.
- [13] P. Anbarasan, H. Neumann, M. Beller, 'A General Rhodium-Catalyzed Cyanation of Aryl and Alkenyl Boronic Acids', *Angew. Chem. Int. Ed.* **2011**, 50, 519–522.
- [14] G. Zhang, X. Ren, J. Chen, M. Hu, J. Cheng, 'Copper-Mediated Cyanation of Aryl Halide with the Combined Cyanide Source', *Org. Lett.* **2011**, 13, 5004–5007.
- [15] J. Kim, H. J. Kim, S. Chang, 'Synthesis of Aromatic Nitriles Using Nonmetallic Cyano-Group Sources', *Angew. Chem. Int. Ed.* **2012**, 51, 11948–11959.
- [16] G. Yan, J. Yu, L. Zhang, 'Recent Progress in the Research of the Transition-Metal-Catalyzed C–CN Bonds Coupling Reactions', *Chin. J. Org. Chem.* **2012**, 32, 294–303.
- [17] J. Li, L. Ackermann, 'Cobalt-Catalyzed C–H Cyanation of Arenes and Heteroarenes', *Angew. Chem. Int. Ed.* **2015**, 54, 3635–3638.
- [18] Y. Zhu, L. Li, Z. Shen, 'Cu–Catalyzed Cyanation of Arylboronic Acids with Acetonitrile: A Dual Role of TEMPO', *Chem. Eur. J.* **2015**, 21, 13246–13252.
- [19] G. Yan, Y. Zhang, J. Wang, 'Recent Advances in the Synthesis of Aryl Nitrile Compounds', *Adv. Synth. Catal.* **2017**, 359, 4068–4105.
- [20] P. Yu, B. Morandi, 'Nickel-Catalyzed Cyanation of Aryl Chlorides and Triflates Using Butyronitrile: Merging Retrohydrocyanation with Cross-Coupling', *Angew. Chem. Int. Ed.* **2017**, 56, 15693–15697.
- [21] D. Zhao, P. Xu, T. Ritter, 'Palladium-Catalyzed Late-Stage Direct Arene Cyanation', *Chem* **2019**, 5, 97–107.
- [22] U. S. Kanchana, T. V. Mathew, G. Anilkumar, 'Recent advances and prospects in the nickel-catalyzed cyanation', *J. Organomet. Chem.* **2020**, 920, 121337.
- [23] G. Zhang, S. Chen, H. Fei, J. Cheng, F. Chen, 'Copper-Catalyzed Cyanation of Arylboronic Acids Using DDQ as Cyanide Source', *Synlett* **2012**, 23, 2247–2250.
- [24] S. Pimparkar, A. Koodan, S. Maiti, N. S. Ahmed, M. M. M. Mostafa, D. Maiti, 'C–CN bond formation: an overview of diverse strategies', *Chem. Commun.* **2021**, 57, 2210–2232.
- [25] A. E. Ahmed, M. Y. H. Farooqui, 'Comparative toxicities of aliphatic nitriles', *Toxicol. Lett.* **1982**, 12, 157–163.
- [26] A. M. Nauth, T. Opatz, 'Non-toxic cyanide sources and cyanating agents', *Org. Biomol. Chem.* **2019**, 17, 11–23.
- [27] P. S. Engl, C. B. Santiago, C. P. Gordon, W.-C. Liao, A. Fedorov, C. Copéret, M. S. Sigman, A. Togni, 'Exploiting and Understanding the Selectivity of Ru–N-Heterocyclic Carbene Metathesis Catalysts for the Ethenolysis of Cyclic Olefins to α,ω -Dienes', *J. Am. Chem. Soc.* **2017**, 139, 13117–13125.
- [28] J. De Jesus Silva, M. A. B. Ferreira, A. Fedorov, M. S. Sigman, C. Copéret, 'Molecular-level insight in supported olefin metathesis catalysts by combining surface organometallic chemistry, high throughput experimentation, and data analysis', *Chem. Sci.* **2020**, 11, 6717–6723.
- [29] M. A. B. Ferreira, J. De Jesus Silva, S. Grosslight, A. Fedorov, M. S. Sigman, C. Copéret, 'Noncovalent Interactions Drive the Efficiency of Molybdenum Imido Alkylidene Catalysts for Olefin Metathesis', *J. Am. Chem. Soc.* **2019**, 141, 10788–10800.
- [30] C.-C. Tsai, C. Sandford, T. Wu, B. Chen, M. S. Sigman, F. D. Toste, 'Enantioselective Intramolecular Allylic Substitution via Synergistic Palladium/Chiral Phosphoric Acid Catalysis: Insight into Stereoinduction through Statistical Modeling', *Angew. Chem. Int. Ed.* **2020**, 59, 14647–14655.
- [31] J. J. Henle, A. F. Zahrt, B. T. Rose, W. T. Darrow, Y. Wang, S. E. Denmark, 'Development of a Computer-Guided Workflow for Catalyst Optimization. Descriptor Validation, Subset Selection, and Training Set Analysis', *J. Am. Chem. Soc.* **2020**, 142, 11578–11592.
- [32] S. G. Robinson, M. S. Sigman, 'Integrating Electrochemical and Statistical Analysis Tools for Molecular Design and Mechanistic Understanding', *Acc. Chem. Res.* **2020**, 53, 289–299.
- [33] D. T. Ahneman, J. G. Estrada, S. Lin, S. D. Dreher, A. G. Doyle, 'Predicting reaction performance in C–N cross-coupling using machine learning', *Science* **2018**, 360, 186–190.
- [34] R. Guha, 'On the interpretation and interpretability of quantitative structure–activity relationship models', *J. Comput.-Aided Mol. Des.* **2008**, 22, 857–871.
- [35] N. R. Draper, H. Smith, 'Applied regression analysis', Wiley India Pvt. Ltd., New Delhi, 2019.
- [36] C. B. Santiago, J.-Y. Guo, M. S. Sigman, 'Predictive and mechanistic multivariate linear regression models for reaction development', *Chem. Sci.* **2018**, 9, 2398–2412.
- [37] J. P. Reid, M. S. Sigman, 'Comparing quantitative prediction methods for the discovery of small-molecule chiral catalysts', *Nat. Chem. Rev.* **2018**, 2, 290–305.
- [38] J. P. Reid, M. S. Sigman, 'Holistic prediction of enantioselectivity in asymmetric catalysis', *Nature* **2019**, 571, 343–348.
- [39] Y. Yang, S. L. Buchwald, 'Copper-Catalyzed Regioselective *ortho* C–H Cyanation of Vinylarenes', *Angew. Chem. Int. Ed.* **2014**, 53, 8677–8681.

- [40] T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu, Y. Fu, 'Rhodium-Catalyzed Directed C–H Cyanation of Arenes with *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide', *J. Am. Chem. Soc.* **2013**, *135*, 10630–10633.
- [41] P. Anbarasan, H. Neumann, M. Beller, 'A Convenient Synthesis of Benzonitriles via Electrophilic Cyanation with *N*-Cyanobenzimidazole', *Chem. Eur. J.* **2010**, *16*, 4725–4728.
- [42] J. Schörgenhumer, M. Waser, 'New strategies and applications using electrophilic cyanide-transfer reagents under transition metal-free conditions', *Org. Chem. Front.* **2016**, *3*, 1535–1540.
- [43] N. Miyaura, K. Yamada, A. Suzuki, 'A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides', *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
- [44] N. Miyaura, A. Suzuki, 'Stereoselective synthesis of arylated (*E*)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst', *J. Chem. Soc. Chem. Commun.* **1979**, 866–867.
- [45] N. Miyaura, A. Suzuki, 'Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds', *Chem. Rev.* **1995**, *95*, 2457–2483.
- [46] H. Möller, 'Die Cyanamidverbindungen der Bernsteinsäure', *J. Prakt. Chem.* **1880**, *22*, 193–222.
- [47] R. W. Stephens, L. A. Domeier, 'N-Cyanoimides via the Cyanation of Imides', *Synth. Commun.* **1991**, *21*, 2025–2032.
- [48] A. B. Pawar, S. Chang, 'Cobalt-Catalyzed C–H Cyanation of (Hetero)arenes and 6-Arylpurines with *N*-Cyanosuccinimide as a New Cyanating Agent', *Org. Lett.* **2015**, *17*, 660–663.
- [49] X. Wang, M. Makha, S.-W. Chen, H. Zheng, Y. Li, 'GaCl₃-Catalyzed C–H Cyanation of Indoles with *N*-Cyanosuccinimide', *J. Org. Chem.* **2019**, *84*, 6199–6206.
- [50] N. C. Bruno, M. T. Tudge, S. L. Buchwald, 'Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions', *Chem. Sci.* **2013**, *4*, 916–920.
- [51] K. Takagi, T. Okamoto, Y. Sakakibara, A. Ohno, S. Oka, N. Hayama, 'Nucleophilic Displacement Catalyzed by Transition Metal. III. Kinetic Investigation of the Cyanation of Iodobenzene Catalyzed by Palladium(II)', *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3177–3180.
- [52] K. D. Dobbs, W. J. Marshall, V. V. Grushin, 'Why Excess Cyanide Can Be Detrimental to Pd-Catalyzed Cyanation of Haloarenes. Facile Formation and Characterization of [Pd(CN)₃(H)]^{2−} and [Pd(CN)₃(Ph)]^{2−}', *J. Am. Chem. Soc.* **2007**, *129*, 30–31.
- [53] S. Erhardt, V. V. Grushin, A. H. Kilpatrick, S. A. Macgregor, W. J. Marshall, D. C. Roe, 'Mechanisms of Catalyst Poisoning in Palladium-Catalyzed Cyanation of Haloarenes. Remarkably Facile C–N Bond Activation in the [(Ph₃P)₄Pd]/[Bu₄N]⁺ CN[−] System', *J. Am. Chem. Soc.* **2008**, *130*, 4828–4845.
- [54] C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, 'Mechanism of the Palladium-Catalyzed Homocoupling of Arylboronic Acids: Key Involvement of a Palladium Peroxo Complex', *J. Am. Chem. Soc.* **2006**, *128*, 6829–6836.
- [55] M. Moreno-Mañas, M. Pérez, R. Pleixats, 'Palladium-Catalyzed Suzuki-Type Self-Coupling of Arylboronic Acids. A Mechanistic Study', *J. Org. Chem.* **1996**, *61*, 2346–2351.
- [56] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, 'Catalysts for Suzuki–Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure', *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
- [57] J. A. Jordan-Hore, J. N. Sanderson, A.-L. Lee, 'Mild and Ligand-Free Pd(II)-Catalyzed Conjugate Additions to Hindered γ -Substituted Cyclohexenones', *Org. Lett.* **2012**, *14*, 2508–2511.
- [58] T. Senda, M. Ogasawara, T. Hayashi, 'Rhodium-Catalyzed Asymmetric 1,4-Addition of Organoboron Reagents to 5,6-Dihydro-2(1*H*)-pyridinones. Asymmetric Synthesis of 4-Aryl-2-piperidinones', *J. Org. Chem.* **2001**, *66*, 6852–6856.
- [59] C. E. Brown, 'Coefficient of Variation', in 'Applied Multivariate Statistics in Geohydrology and Related Sciences', Ed. C. E. Brown, Springer Berlin Heidelberg, Berlin, Heidelberg, 1998, pp. 155–157.
- [60] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, 'New Diphosphine Ligands Based on Heterocyclic Aromatics Inducing Very High Regioselectivity in Rhodium-Catalyzed Hydroformylation: Effect of the Bite Angle', *Organometallics* **1995**, *14*, 3081–3089.
- [61] S. Hillebrand, J. Bruckmann, C. Krüger, M. W. Haenel, 'Bidentate phosphines of heteroarenes: 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene', *Tetrahedron Lett.* **1995**, *36*, 75–78.
- [62] P. W. N. M. van Leeuwen, P. C. J. Kamer, 'Featuring Xantphos', *Catal. Sci. Technol.* **2018**, *8*, 26–113.
- [63] D. S. Surry, S. L. Buchwald, 'Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide', *Chem. Sci.* **2011**, *2*, 27–50.
- [64] T. Gensch, G. dos Passos Gomes, P. Friederich, E. Peters, T. Gaudin, R. Pollice, K. Jorner, A. Nigam, M. Lindner D'Addario, M. S. Sigman, A. Aspuru-Guzik, 'A Comprehensive Discovery Platform for Organophosphorus Ligands for Catalysis', *ChemRxiv Preprint* **2021**, 10.26434/chemrxiv.12996665.v1.
- [65] S. Grimme, C. Bannwarth, P. Shushkov, 'A Robust and Accurate Tight-Binding Quantum Chemical Method for Structures, Vibrational Frequencies, and Noncovalent Interactions of Large Molecular Systems Parametrized for All spd-Block Elements (*Z*=1–86)', *J. Chem. Theory Comput.* **2017**, *13*, 1989–2009.
- [66] C. Bannwarth, S. Ehlert, S. Grimme, 'GFN2-xTB—An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions', *J. Chem. Theory Comput.* **2019**, *15*, 1652–1671.
- [67] S. Grimme, 'Exploration of Chemical Compound, Conformer, and Reaction Space with Meta-Dynamics Simulations Based on Tight-Binding Quantum Chemical Calculations', *J. Chem. Theory Comput.* **2019**, *15*, 2847–2862.
- [68] P. Pracht, F. Bohle, S. Grimme, 'Automated exploration of the low-energy chemical space with fast quantum chemical methods', *Phys. Chem. Chem. Phys.* **2020**, *22*, 7169–7192.

- [69] P. C. J. Kamer, P. W. N. M. van Leeuwen, 'Phosphorus(III) Ligands in Homogeneous Catalysis Design and Synthesis', John Wiley & Sons Ltd., The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom, 2012.
- [70] C. A. Tolman, 'Electron Donor–Acceptor Properties of Phosphorus Ligands. Substituent Additivity', *J. Am. Chem. Soc.* **1970**, 92, 2953–2956.
- [71] C. A. Tolman, 'Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis', *Chem. Rev.* **1977**, 77, 313–348.
- [72] A. Verloop, W. Hoogenstraaten, J. Tipker, 'Development and Application of New Steric Substituent Parameters in Drug Design', Chapt. 4 in 'Drug Design', Vol. 7, Academic Press, New York, NY, 1976, pp. 165–207.
- [73] H. Clavier, S. P. Nolan, 'Percent buried volume for phosphine and *N*-heterocyclic carbene ligands: steric properties in organometallic chemistry', *Chem. Commun.* **2010**, 46, 841–861.
- [74] A. C. Hillier, W. J. Sommer, B. S. Yong, J. L. Petersen, L. Cavallo, S. P. Nolan, 'A Combined Experimental and Theoretical Study Examining the Binding of *N*-Heterocyclic Carbenes (NHC) to the Cp^*RuCl ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) Moiety: Insight into Stereoelectronic Differences between Unsaturated and Saturated NHC Ligands', *Organometallics* **2003**, 22, 4322–4326.
- [75] V. Mougél, C. B. Santiago, P. A. Zhizhko, E. N. Bess, J. Varga, G. Frater, M. S. Sigman, C. Copéret, 'Quantitatively Analyzing Metathesis Catalyst Activity and Structural Features in Silica-Supported Tungsten Imido–Alkylidene Complexes', *J. Am. Chem. Soc.* **2015**, 137, 6699–6704.
- [76] H. Kooijman, A. L. Spek, M. Caporali, D. Vogt, P. W. N. M. van Leeuwen, CCDC 857447: Experimental Crystal Structure Determination 2012, <https://www.ccdc.cam.ac.uk/structures/search?id=doi:10.5517/ccxs7lh&sid=DataCite>.
- [77] J. Yin, S. L. Buchwald, 'Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery that Xantphos Can Be Trans-Chelating in a Palladium Complex', *J. Am. Chem. Soc.* **2002**, 124, 6043–6048.
- [78] C. W. Fryer, J. A. S. Smith, 'A *cis*-influence in square-planar palladium and platinum complexes', *J. Organomet. Chem.* **1969**, 18, 35–38.
- [79] G. B. Kauffman, 'Il'ya Il'ich Chernyaev (1893–1966) and the trans effect', *J. Chem. Educ.* **1977**, 54, 86.
- [80] K. M. Anderson, A. G. Orpen, 'On the relative magnitudes of *cis* and *trans* influences in metal complexes', *Chem. Commun.* **2001**, 2682–2683.
- [81] S. Newman-Stonebraker, S. Smith, J. Borowski, E. Peters, T. Gensch, H. Johnson, M. S. Sigman, A. Doyle, 'Linking Mechanistic Analysis of Catalytic Reactivity Cliffs to Ligand Classification', *ChemRxiv Preprint* **2021**, 10.26434/chemrxiv.14388557.v1.
- [82] S. Zhao, T. Gensch, B. Murray, Z. L. Niemeyer, M. S. Sigman, M. R. Biscoe, 'Enantiodivergent Pd-catalyzed C–C bond formation enabled through ligand parameterization', *Science* **2018**, 362, 670–674.
- [83] G. M. Adams, A. S. Weller, 'POP-type ligands: Variable coordination and hemilabile behaviour', *Coord. Chem. Rev.* **2018**, 355, 150–172.
- [84] J. M. Blacquiere, 'Structurally-Responsive Ligands for High-Performance Catalysts', *ACS Catal.* **2021**, 11, 5416–5437.
- [85] O. Jacquet, N. D. Clément, C. Blanco, M. M. Belmonte, J. Benet-Buchholz, P. W. N. M. van Leeuwen, 'SPANphos Ligands in Palladium-Catalyzed Asymmetric Fluorination', *Eur. J. Org. Chem.* **2012**, 4844–4852.
- [86] Z. Freixa, M. S. Beentjes, G. D. Batema, C. B. Dieleman, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, J. Fraanje, K. Goubitz, P. W. N. M. van Leeuwen, 'SPANphos: A C_2 -Symmetric *trans*-Coordinating Diphosphane Ligand', *Angew. Chem. Int. Ed.* **2003**, 42, 1284–1287.
- [87] D. A. Redfield, J. H. Nelson, 'On the Mechanism of *Cis*-*Trans* Isomerization for Square Planar Complexes of the Type ML_2X_2 ', *J. Am. Chem. Soc.* **1974**, 96, 6219–6220.
- [88] M. Feller, E. Ben-Ari, M. A. Iron, Y. Diskin-Posner, G. Leituss, L. J. W. Shimon, L. Konstantinovski, D. Milstein, 'Cationic, Neutral, and Anionic PNP Pd^{II} and Pt^{II} Complexes: Dearomatization by Deprotonation and Double-Deprotonation of Pincer Systems', *Inorg. Chem.* **2010**, 49, 1615–1625.
- [89] V. V. Grushin, 'Synthesis of Hemilabile Phosphine–Phosphine Oxide Ligands via the Highly Selective Pd-Catalyzed Mono-oxidation of Bidentate Phosphines: Scope, Limitations, and Mechanism', *Organometallics* **2001**, 20, 3950–3961.
- [90] V. V. Grushin, 'Mixed Phosphine–Phosphine Oxide Ligands', *Chem. Rev.* **2004**, 104, 1629–1662.
- [91] Z. Csákai, R. Skoda-Földes, L. Kollár, 'NMR investigation of $\text{Pd}(\text{II})$ – $\text{Pd}(0)$ reduction in the presence of mono- and ditertiary phosphines', *Inorg. Chim. Acta* **1999**, 286, 93–97.
- [92] C. Amatore, A. Jutand, A. Thuilliez, 'Formation of Palladium(0) Complexes from $\text{Pd}(\text{OAc})_2$ and a Bidentate Phosphine Ligand (dppp) and Their Reactivity in Oxidative Addition', *Organometallics* **2001**, 20, 3241–3249.
- [93] A. Bader, E. Lindner, 'Coordination chemistry and catalysis with hemilabile oxygen-phosphorus ligands', *Coord. Chem. Rev.* **1991**, 108, 27–110.
- [94] C. S. Slone, D. A. Weinberger, C. A. Mirkin, 'The Transition Metal Coordination Chemistry of Hemilabile Ligands', in 'Progress in Inorganic Chemistry', Ed. K. D. Karlin, Vol. 48, John Wiley & Sons Ltd., Hoboken, NJ, USA, 1999, pp. 233–350.
- [95] Z. Shu, W. Ji, X. Wang, Y. Zhou, Y. Zhang, J. Wang, 'Iron(II)-Catalyzed Direct Cyanation of Arenes with Aryl(cyano) iodonium Triflates', *Angew. Chem. Int. Ed.* **2014**, 53, 2186–2189.
- [96] D.-G. Yu, T. Gensch, F. de Azambuja, S. Vázquez-Céspedes, F. Glorius, 'Co(III)-Catalyzed C–H Activation/Formal $\text{S}_{\text{N}}\text{-Type}$ Reactions: Selective and Efficient Cyanation, Halogenation, and Allylation', *J. Am. Chem. Soc.* **2014**, 136, 17722–17725.
- [97] J. L. Klinkenberg, J. F. Hartwig, 'Reductive Elimination from Arylpalladium Cyanide Complexes', *J. Am. Chem. Soc.* **2012**, 134, 5758–5761.
- [98] A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, B. Tarbit, 'Palladium-Catalyzed Cross-Coupling Reactions of Pyridylboronic Acids with Heteroaryl Halides Bearing a Primary Amine Group: Synthesis of Highly

- Substituted Bipyridines and Pyrazinopyridines', *J. Org. Chem.* **2005**, 70, 388–390.
- [99] P. Meier, S. Legrauerant, S. Müller, J. Schaub, 'Synthesis of Formylphenylpyridinecarboxylic Acids Using Suzuki–Miyaura Coupling Reactions', *Synthesis* **2003**, 551–554.
- [100] D. J. Koza, E. Carita, 'An Efficient High Yielding Approach for the Homocoupling of Aryl Boronic Acids', *Synthesis* **2002**, 2183–2186.
- [101] T. Kinzel, Y. Zhang, S. L. Buchwald, 'A New Palladium Precatalyst Allows for the Fast Suzuki–Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids', *J. Am. Chem. Soc.* **2010**, 132, 14073–14075.
- [102] P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King, G. C. Lloyd-Jones, 'Base-Catalyzed Aryl-B(OH)₂ Protodeboronation Revisited: From Concerted Proton Transfer to Liberation of a Transient Aryl Anion', *J. Am. Chem. Soc.* **2017**, 139, 13156–13165.
- [103] C. A. Malapit, J. R. Bour, C. E. Brigham, M. S. Sanford, 'Base-free nickel-catalysed decarbonylative Suzuki–Miyaura coupling of acid fluorides', *Nature* **2018**, 563, 100–104.
- [104] N. Kudo, M. Perseghini, G. C. Fu, 'A Versatile Method for Suzuki Cross-Coupling Reactions of Nitrogen Heterocycles', *Angew. Chem. Int. Ed.* **2006**, 45, 1282–1284.
- [105] K. L. Billingsley, K. W. Anderson, S. L. Buchwald, 'A Highly Active Catalyst for Suzuki–Miyaura Cross-Coupling Reactions of Heteroaryl Compounds', *Angew. Chem. Int. Ed.* **2006**, 45, 3484–3488.

Received September 30, 2021

Accepted October 1, 2021