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

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Abstract

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 steric factors 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.

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 intensively over the last few decades,10-22 constantly stimulated by the development of new, less toxic and readily-available cyano sources.23-24 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. 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.25-27 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.28-30 While recently, random forest models have gained attention for being excellent for prediction,31 such models often tend to be difficult to interpret.32 Hence alternative, multivariate linear and polynomial regression analyses enjoy great popularity in both industry and academia,33 owing to their ease of interpretability.34-36

Herein, we describe 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 approach was used to identify key ligands and to trace 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.\(^{37-40}\) We prepared a selection of N-CN reagents (Figure 1), encompassing different classes of organic compounds: N-cyanoheterocyclic reagents NCN1–3, N-cyanoimides (NCN4–5) 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.\(^{41-43}\)

![Figure 1. N-CN reagents considered for the Pd-catalyzed cross-coupling cyanation of aryl boronic acids.](Image)

As a first step, we sought to verify the stability of the six N-CN reagents wherein only N-cyanoimides NCN4–5 were found to be stable in 1,4-dioxane at 100 °C after 2 hours in the presence of a base (see SI for more information). Even though N-cyanoimides have been known in the literature since the 1870s\(^ {44}\) and are commercially available,\(^ {45}\) their use as electrophilic cyanation reagents has not yet been well-explored.\(^ {13,46}\) 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,\(^ {47}\) 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. 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.\(^ {48-49}\) While the addition of exogenous water (3 equiv.) to the reaction 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 amount, 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 and trimeric (boroxine) forms under anhydrous conditions.\(^ {50-52}\) Indeed, commercial “boronic acids” are often mixtures of all these forms in various ratios, and up to 1 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 H\(_2\)O) 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 A1–33, bisphosphines B1–45 and miscellaneous ligands C1–12. All catalyst formulations were prepared by mixing 1 equiv. boronic acid, 1.5 equiv. N-cyanosuccinimide, 2.5 mol% palladium precatalyst,57 5 or 10 mol% ligand (for bidentate or monodentate ligands, respectively) and 20 mol% potassium phosphate in 1,4-dioxane. The preparation of the reaction mixtures was automated by a liquid handling robot operated inside an inert (N₂) atmosphere purge box (see the SI for details). The reaction 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 to assess reproducibility of the results (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 B1–3, B7–8, B14 and B35 afforded the cross-coupling product in >80% yield. Interestingly, the majority of those entries are XantPhos-like ligands,53–54 a privileged class popularly used in numerous reactions.55 In the monophosphine category, the highest yields are found with dialkylbiaryl phosphines.56 Specifically, yields >55% were afforded using dicyclohexylbiaryl phosphines A3–6 and A9. However, tests using tert-butyl analogues A16–23 lead to significantly lower yields (<25%), pointing at a significant influence of the alkyl substituents on generating active catalysts. Reactions using ligands from the miscellaneous group, e.g., NHCs C1–2, diamines C3–5 and phosphites or phosphoramidites C6–9, generally gave poor yields. In this ligand group, only tests with TriPhos C12 afforded the product in high yield (85%).
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$_3$)$_2$-Ph; Ar$^{F5}$ = 2,3,4,5,6-F$_5$-Ph.
Parametrization

In order to delineate which ligand properties influence the reaction yield, we sought to apply statistical methods used in some of our groups.\textsuperscript{34} 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.\textsuperscript{57} For the bisphosphines group B, a workflow was initiated by performing conformational searches on the corresponding PdCl\textsubscript{2} adducts using xTB/crest\textsuperscript{58-61} 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 PdCl\textsubscript{2}. 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 Scheme 2.

Scheme 2. Parametrization of the monophosphine ligands and selected calculated molecular descriptors.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{computational_workflow.png}
\caption{Computational Workflow for Bisphosphines}
\end{figure}

1. Ligand Structure Optimization and Descriptor Collection

For the monophosphine group A, all physicochemical descriptors were extracted from the kraken discovery platform.\textsuperscript{57} For the bisphosphines group B, a workflow was initiated by performing conformational searches on the corresponding PdCl\textsubscript{2} adducts using xTB/crest\textsuperscript{58-61} 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 PdCl\textsubscript{2}. 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 Scheme 2.

Scheme 2. Parametrization of the monophosphine ligands and selected calculated molecular descriptors.

2. PdCl\textsubscript{2} Adduct and Free Ligand Descriptors

- **PdCl\textsubscript{2} Adduct**
  - Structural Descriptors ($d_{Pd-Cl}$, $d_{Pd-C}$, Bite Angle $\alpha$)

- **General Descriptors**
  - Frontier MOs
  - NBO Analyses
  - Sterimol $L$, $B_1$, $B_2$ for every $P-C$ bond

Descriptors of the phosphines

Phosphines are amongst the most extensively studied ligands in homogenous catalysis.\textsuperscript{62} Pioneering work by Tolman in this regard have provided a guide to interrogate the donor and steric properties of PR\textsubscript{3} ligands, hence enabling systematic fine tuning of ligand properties with a some degree of predictability.\textsuperscript{63-64} 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 and facilitate association/dissociation as well as the speciation (how many ligands are bound to the metal for monodentate phosphine ligands). 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 (\(V_{\text{min}}\)), the natural bond orbital (NBO) derived atomic charges of phosphorus (\(q_0\)), P-C bonding \(\sigma(P-C)\) (\(E_{\sigma(P-C)}\)) and antibonding \(\sigma^*(P-C)\) (\(E_{\sigma^*(P-C)}\)) NBO energies. Additional parameters included HOMO/LUMO energies, NBO energies of the phosphorus lone pair (\(E_{\text{LP(P)}}\)), molecular dipole (\(\mu\)) and pyramidalization (Pyr). The steric influence of the phosphine ligands was assessed using Verloop’s Sterimol parameters (\(L, B_1, B_5\))\textsuperscript{65} and the proximal (%\(V_{\text{bar}}\)) and distal ligand volume.\textsuperscript{66-67}

Bisphosphine descriptors. In addition to the descriptors used for the monophosphines, ligand parameters specific to the PdCl\(_2\) adduct were assessed to describe the bidentate nature of the ligands. Included are the bite angle \(\alpha_{\text{PPdP}}\), 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 S\textsuperscript{40}), 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 (\(A_{1-12}\)) or tert-butyl substituents (\(A_{16-23}\)) and simple trisubstituted alkyl/aryl phosphines (\(A_{27-33}\)). Unfortunately, no compelling conclusions could be obtained through splitting of the monophosphine data set \(A\), apart from identifying the dicyclohexyl biaryl subset as highest yielding ligand family (see Figure S\textsuperscript{41}).

![Figure 2. Multivariate linear regression model to predict yield for ligands A1–14, A16–19, A24–26, A30–31 and A33 with depiction of parameters within the multivariate model.](image-url)
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 \textbf{A1–14, A16–19, A24–26, A30–31 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), yielding good scores for all cases consistent with a well-validated model.\textsuperscript{25-27, 68} 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 2b). The steric descriptor \(QV_{\text{tot, min}}\text{Boltz}^\ddagger\) describes the lowest quadrant total volume. 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 \(E_{\text{SOMO},r_c}\text{Boltz}^\ddagger; V_{\text{tot}}(z+)\text{burminconf}^\ddagger\) could relate to the \(\sigma\)-donor ability of the phosphine (the SOMO energy of the radical cation is correlated to the nucleophilicity of a phosphine), 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 \(\sigma\)-donation and steric requirements for the coordination/decoordination to/from palladium. The average occupancy of the P–C bonds \(\text{Occ}(p–c)\text{avgBoltz}^\ddagger\) is a probe of the overall electronic state at phosphorus (the occupancy is most strongly correlated with the \textit{HOMO-LUMO} gap). Together with \(E_{\text{SOMO},r_c}\text{Boltz}^\ddagger\), this descriptor captures the electron-richness/donation of the ligand, where in general less electron-rich ligands (smaller values for \(\text{Occ}(p–c)\text{avgBoltz}^\ddagger\)) lead to increased yields.

Considering the multivariate model, the yield of the cyanation reaction heavily depends on the stereoelectronic 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 \(\sigma\)-bonding interaction, while being bulky enough to favor dissociation of at least one phosphine ligand. When the ligand steric increase, the \(\sigma\)-bonding interaction to the metal is hindered and the \(\pi\)-acidity compensates to weakly interact with the metal, as can be seen for the diterbutylbiaryl phosphines and the simple alkyl/aryl phosphines. This hypothesis holds true for the adamantyl phosphines \textbf{A13–A15} and explains the low yield obtained with phosphites and phosphoramidites \textbf{C6–8}, that are weak \(\sigma\)-donors, but strong \(\pi\)-acceptors. The importance of ligand lability also explains the low yields observed for non-phosphinic ligands \textbf{C1–5}, that usually form strong metal–ligand bonds and do not dissociate easily.

**Analysis of the bisphosphines**

In an analogous approach to the one applied for the monophosphine set \textbf{A}, a series of structurally similar ligands was chosen to analyze the effect of stericities and electronics on a subclass of the bisphosphine set \textbf{B}. The XantPhos-derivatives (\textbf{B1–17}) were particularly interesting to investigate as they represent over one third of all ligands in group \textbf{B} and cover a broad range of yields \((0–93\%)\). In a first attempt, univariate correlations with the ligands in \textit{cis}-\textit{PdCl}_2 were explored, but the \(R^2\) values of the univariate correlation matrix did not exceed 0.54 (see Figure S42). Inability to model \textit{tBu-XantPhos} \textbf{B17} as a \textit{cis}-complex and crystallographic evidence of XantPhos-type square-planar palladium complexes in \textit{trans} configuration,\textsuperscript{69-71} inspired the hypothesis that parametrizing ligands as \textit{trans}-complexes might be required. Indeed, treating ligands \textbf{B4–5, B10, B12–13} and \textbf{B15–17}, all affording less than 21\% yield, as \textit{trans}-\textit{PdCl}_2 complexes improved univariate correlations significantly (see Figure S43). In particular, the inverse correlation with the longest palladium–chlorine bond length \(d_{\text{Pd-Cl}}^\text{max}\) (see Figure 3a) displayed a high coefficient of determination \((R^2 = 0.77)\). This descriptor possibly represents the \textit{cis} or \textit{trans}-influence of the bidentate ligand,\textsuperscript{71-73} a measure of the lability of ligands that are \textit{cis} or \textit{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. A sharp reactivity cliff could be found with the largest P–C antibonding energy of the ligand ($E\sigma^*(P-C)_{max}$) at a threshold value of 0.237 Hartree, allowing us to bin the outcomes accurately. As previously discussed, $E\sigma^*(P-C)$ 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 previously 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, a more detailed analysis through multivariate regression was performed using the ligand classified as active following the threshold analysis. The produced model includes all dicyclohexyl and diphenyl-derivatives (B1–14 and B16), but omits B4, B15 and B17 as low-yielding strongly trans-chelating ligands. The model features the electronic descriptors $d(Pd-Cl)_{max}$ and $E\sigma^*(P-C)_{min}$, 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.
Figure 4. (a) Threshold analysis of the bisphosphine dataset B with \( E\sigma^*_{(P-C)_{\text{max}}} \), including computed cis and trans complexes. (b) Multivariate linear regression model to predict yield for bisphosphine ligands B1–3, B5–14, B16, B18–25, B28–30, B33–34, B36–40 and B45. (c) Depiction of parameters within the multivariate model.

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 4). After performing a classification with the same parameter used for the XantPhos ligand subset, the threshold value for \( E\sigma^*_{(P-C)_{\text{max}}} \) remained at 0.237 Hartree (Figure 4a). 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, respectively). 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.

Using the insights from the threshold analysis, the %yield response was evaluated via multivariate regression analysis (Figure 4b). Apart from ligands B1–3, B5–14 and B16 (vide infra), the model includes the biphienyl and binaphthyl derivatives B18–23, the variable chain length bisphosphines B33–34, B36–40 and B45, as well as B27–30, covering 32 of the 45 ligands in set B. The obtained model includes the electronic parameters \( d_{(Pd-Cl)_{\text{avg}}} \), \( E\sigma^*_{(P-C)_{\text{max}}} \), \( NBO_{\text{LP}(P)s^{\text{min}}} \) and \( \text{Occ}(P-C)_{\text{avg}} \), as well as the steric descriptor \( l_{P-\text{trans}}^{\text{min}} \). The first electronic term, the average palladium–chlorine 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 endorsed on the one hand by the correlation with \( NBO_{\text{LP}(P)s^{\text{min}}} \), 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 \(\sigma\)-donation. Here, an increase in yield is promoted by having a strong \(\sigma\)-donating phosphine. In contrast, \(EO^*(P-C)_{\text{max}}\), the largest \(P-C\) antibonding energy of the ligand, is responsible for an increase in yield with higher energies and hence, lower \(\pi\) acidity. The overall electron-richness of the phosphine shows a detrimental effect on yield as indicated by the negative coefficient on \(OCC(P-R)_{\text{av}}\), the average occupancy of the phosphorus non-framework carbon atom \(P\)-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 \(L_{\text{P-frame}}\), the minimum Sterimol length on the phosphorus framework carbon bond, describes the fine balance of stericls required for efficient catalysis. Yield increases with an increase of the framework size, following the same trend observed with the monophosphine set \(A\), where increased bulk likely facilitates de-coordination.

Taking into account 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 \(\sigma\)-bonding, \(\pi\)-bonding and steric interactions, where strong bonding 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 \(dBA_{\text{Cl}}\). Likely owing to the possibility of facilitating \(cis\)-\(trans\) isomerism of the square-planar complexes or opening a coordination site for incoming reactants.\(^{70,79}\) This hypothesis would explain the low yields observed with \(Cy\)-XantPhos \(B15\), \(tBu\)-XantPhos \(B17\) and PNP pincer ligand \(C10\) that form stable \(trans\) square planar complexes with strong phosphorus–palladium bonds.\(^{69,80}\) The hypothesis also holds true for 20F-dppe \(B41\) and the bisphosphate \(C9\), that are weak \(\sigma\)-donors, but strong \(\pi\)-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 anerobic oxidation of dppp, commonly observed under similar reaction conditions,\(^{81-84}\) that would yield a phosphine oxide that is more labile than its parent compound.\(^{85-86}\) 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 \(\sigma\)-donation abilities favored), while maintaining the ability to decoordinate easily hence it is disfavored by strong \(\pi\)-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 4). In this arena, structurally-responsive ligands (SRL) like Buchwald dialkyl biaryl3 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 3).\(^{76-77}\)

**Scheme 3.** Structurally-responsive ligand behaviour for Buchwald dialkyl biaryls and XantPhos-type ligands.

**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 to a broad range of aryl boronic acids with electron donating and withdrawing functional groups.

Scheme 4. 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%, respectively). 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–1j and 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, which usually prefer electron-rich substrates.

Scheme 4. Scope of the aryl nitriles 2 obtained by the cyanation of aryl boronic acids 1 with the optimized reaction conditions.

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$_3$PO$_4$ required to activate the Pd G3 precatalyst. 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 presence of oxidants such as nitrates. These byproducts, 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 SI 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-bromophenylbenzonitrile 2p was only observed in trace amounts. GC-Mass spectrometric analysis of the crude reaction 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 80% NMR yields, respectively), polyfluorinated boronic acids 1s–1t proved to be difficult substrates, as their incompatibility with the basic environment is well-documented in the literature.92–94 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 2-thiophenecarbonitrile 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.95–96

Conclusions

In summary, we 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 bispaphines as ideal ligands. Multivariate linear regression analysis allowed to determine σ-donation, π-acidity and sterics of the ligands to be essential in promoting high reaction yields. In the monophosphine group A, 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 bispaphine group B, the yield depends on the ability of the bidentate ligands to dissociate at least with one phosphine, as described by the detrimental effects of σ-donation and 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.

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Author Contributions

J.D.J.S., 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 bispaphines and modelling of the data. S.G. performed calculations on bispaphines. T.G. performed calculations on the monophosphines. C.S. synthesized XantPhos-type ligands. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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