Scaling Relations in Homogeneous Catalysis: Analyzing the Buchwald–Hartwig Amination Reaction

Anand, Megha; Nørskov, Jens K.

Published in:
ACS Catalysis

Link to article, DOI:
[10.1021/acscatal.9b04323](https://doi.org/10.1021/acscatal.9b04323)

Publication date:
2020

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):
Anand, M., & Nørskov, J. K. (2020). Scaling Relations in Homogeneous Catalysis: Analyzing the Buchwald–Hartwig Amination Reaction. *ACS Catalysis*, 10, 336-345. <https://doi.org/10.1021/acscatal.9b04323>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Scaling Relations in Homogeneous Catalysis: Analyzing the Buchwald–Hartwig Amination Reaction

Megha Anand^{†,‡,§} and Jens K. Nørskov^{*,†,‡,§}

[†]Department of Physics, Technical University of Denmark, 2800 Kongens Lyngby, Denmark

[‡]Department of Chemical Engineering, SUNCAT Center for Surface Science and Catalysis, Stanford University, 443 Via Ortega, Stanford, California 94035, United States

[§]SUNCAT Center for Surface Science and Catalysis, SLAC National Laboratory, 2575 Sand Hill Road, Menlo Park, California 94025, United States

ABSTRACT: Scaling relations are widely used to study surface reactions. However, the exploration of its utility in homogeneous catalysis is currently far less reported. In this work, we have investigated the transferability of the concept of scaling relations to a homogeneous catalysis reaction known as the Buchwald–Hartwig amination (BHA) reaction. The reaction of PhBr with MeNH₂ using 37 different Pd–L complexes (L = phosphine ligand) is studied, and scaling relations are established among the reaction intermediates and transition states. Using the scaling relations, we construct volcano plots, which is the plot of the log(rate) vs the descriptor intermediate energy. The insights from the volcano plots agree well with the experimental trends from the literature and give direction toward better catalyst design.

KEYWORDS: homogeneous catalysis, heterogeneous catalysis, Buchwald–Hartwig amination, volcano plots, scaling relations, phosphine ligands

INTRODUCTION

Scaling relations are a well-known concept in heterogeneous catalysis. It suggests that the energies of reaction intermediates binding to the catalyst are dependent on each other.¹ This implies existence of an empirical mathematical relationship between the energies of intermediates and transition states of a reaction or a class of reactions over a range of different catalysts. These mathematical relations have been identified for a large number of heterogeneous and electrochemical catalytic reactions.^{2–5} It is, thus, possible to express the energies of all the reaction intermediates and transition states in terms of the energy of one (or a few) particular intermediate(s), often called the descriptor(s) of the reaction (or a class of reactions).

Once the scaling relations for all the intermediates and transition states of the reaction are identified, rate of the reaction can be expressed as a function of the descriptor energy.^{6–10} This allows the projection of the many energies describing a catalytic reaction in terms of a single (or a few) descriptors, and the reaction rate expressed as a function of a single (or a few) descriptor energy(ies) results in a volcano-like relationship as illustrated in Figure 1. The top of volcano defines the region of optimal catalyst giving the highest possible reaction rate.⁸ The optimal descriptor value at the volcano top is relatable to the stereoelectronic properties of a

Figure 1. Linear free energy scaling relation between an intermediate (or transition state) *x* and *y* for a hypothetical reaction involving these two species using different catalysts (shown using colored dots). Combining scaling relations for all reaction species results in volcano plot, shown in the right. The intermediate *y* is assumed to be the descriptor here.

“perfect” catalyst for the reaction and assist in a priori, in silico discovery of newer catalysts.¹¹

The volcano curves are used routinely for the surface reactions.¹² They make it easier to understand the catalytic trends in the terms of one or few descriptors rather than

separately exploring the mechanism for each catalyst (or the variable component in the reaction), and they have been used in a number of cases to help design new heterogeneous catalysts.^{13–16} However, these concepts were not utilized to deconstruct multicomponent homogeneous catalytic reactions until recently.^{17–20} Extending such ideas to homogeneous catalysis may provide a new, systematic path to discovery of molecular catalysts using computational tools by reducing the dimensionality of primarily multistep and multicomponent catalytic reactions.^{21–23} In this study, we investigate scaling relations and volcano plots to study an important class of C–N bond forming homogeneous reactions known as the Buchwald–Hartwig amination (BHA) reaction. We derive insights from our computed data and connect it to the experimental observations from BHA reaction literature.

The ubiquity of amines in pharmaceuticals, agrochemicals, pigments, electronic materials,²⁴ etc., catapulted the development of BHA, and soon it became the preferred method for synthesizing amines both in industry and academia.^{25–29} As shown in Scheme 1, BHA involves multiple components such

Scheme 1. General Scheme for Palladium-Catalyzed Buchwald–Hartwig Amination

as (a) electrophiles: aryl halides, tosylates, mesylates, triflates, etc., (b) nucleophiles with an NH group such as primary or secondary anilines, amides, NH heterocycles; (c) palladium catalysts with phosphine ligands L (vide infra), and (d) bases such as NaOtBu, Cs₂CO₃, and K₃PO₄ whose role will be discussed later. BHA reactions are typically performed in solvents such as toluene, THF, etc., similar to most homogeneous reactions. The choice of the ligand, base, and solvent are dependent on the nature of the substrates and the groups R₁, R₂, R₃ attached to the coupling partners. Different strategies are used to arrive at the best combination of reagents that include the ligands, base, and solvent for a given set of substrates. One such strategy is to vary the phosphine ligands L that can be decorated with different substituents, allowing systematic tuning of the electronic and steric properties of the catalyst L_nPd.

The literature abounds with diverse bulky phosphine ligands that have been used for BHA reaction. For our analysis, we chose 37 phosphine ligands based on how often it was employed in the catalytic reactions. Whether linear scaling relations between the energies of the reaction intermediates of BHA can be established upon varying the phosphine ligands on palladium is the key motivation of our study. We use relatively simpler substrates, PhBr and MeNH₂, in combination with sodium *tert*-butoxide as the base while varying the ligands. We hope to use the data from existing literature to develop generalizable concepts of catalysis similar to heterogeneous reactions that can be used for better catalyst prediction. This work is a small step toward our vision.

RESULTS AND DISCUSSION

The series of reactions considered for making scaling relations are assumed to have similar reaction mechanisms. To the best of our knowledge, the literature concurs in regards with the key mechanistic steps in the BHA reaction as shown in Scheme 2.

Scheme 2. General Reaction Mechanism of Buchwald–Hartwig Amination

The catalytic cycle starts with a preformed catalyst **C** of the form L_nPd (*n* = 1–2) where L denotes the phosphine ligand. Often a palladium salt such as Pd(dba)₂ or Pd(OAc)₂ is mixed with the ligand L to form the active catalyst L_nPd in situ. Soon it was realized that using a preformed catalysts such as Pd(PtBu₃)₂ results in significant increase in the reactivity, and therefore the catalytic cycle in Scheme 2 starts with L_nPd.³⁰ The first step is the catalyst (**C**)–substrate (**S**) combination resulting in intermediate **r_{OA}** (reverse of oxidative addition). Binding of PhBr to C weakens the Ph–Br bond which results in the oxidative addition of PhBr on L_nPd. In this step the formal oxidation state of the metal Pd increases from Pd(0) to Pd(II) as evident from the structure of intermediate **f_{OA}** (forward of oxidative addition). The third step involves the formation of a tetracoordinated Pd–complex (**I**) with the methylamine (NH₂Me) occupying the fourth coordinating site. The base, NaOtBu, then assists in removing bromine from the metal center and simultaneously abstracting the amidic hydrogen to form NaBr and HOTu. This leads to the formation of a Pd–N covalent bond in intermediate **r_{RE}** (reverse of reductive elimination). The next step is the key reductive elimination step where the C–N bond is formed between the phenyl and the NHMe group via the transition state **TS_{RE}**. The palladium reverts to its initial oxidation state of Pd(0) from Pd(II) in the intermediate **f_{RE}** (forward of reductive elimination). The final step is the catalyst–product separation where catalyst L_nPd is regenerated and the product is released (see section 1 of SI for the complete catalytic cycle with optimized geometries for each of the ligands). The model reaction, thus, can be written as shown in Scheme 3.

The active catalyst is believed to be the monoligated palladium phosphine complex, Pd–L (*n* = 1) for most of the practical ligands used in BHA.^{31–36} The palladium atom would be inaccessible for the incoming substrate (PhBr) in the

Scheme 3. Model Buchwald–Hartwig Amination Reaction Studied in This Work^a

^aThe free energy for the reaction is in kcal/mol.

bisligated L–Pd–L ($n = 2$) complex (see section 2 in SI for more details). Figure 2 shows the chemical structures of such 37 distinct phosphine ligands categorized as mono- and biphosphine ligands with one or two phosphorus atom(s)

capable of coordinating to the palladium. The ligands, PPh₃, P(*o*-tolyl)₃, P(furyl)₃, P(Cy)₃, nBuPAD₂, PtBu₃, DTBNpP, and TNpP, are monophosphine ligands with three bulky alkyl or aryl (or both) groups attached to the phosphorus atom.^{37,38}

The other set of monophosphine ligands comprising DavePhos, XPhos, JohnPhos, CyJohnPhos, RuPhos, SPhos, BrettPhos, tBuXPhos, tBuBrettPhos, Me₄tBuXPhos, and JackiePhos have the dialkylbiaryl phosphine framework is common.³⁰ BippyPhos³⁹ and MorDalPhos³³ do not have the biaryl framework but have similar skeletal structure with pyrazole and morpholine units in place of phenyl rings. NHC–IPr is a N-heterocyclic carbene based ligand with bulky groups

Mono-phosphine Ligands

Bi-phosphine Ligands

Figure 2. Chemical structures of mono- and biphosphine ligands considered in this study.

Figure 3. Free energy profile of BHA reaction using 37 different ligands.

on the nitrogen atoms and is often used as the phosphine mimic in BHA.⁴⁰ Ligand pDavePhos, though it has the biaryl framework, has the PCy₂ group para to the biphenyl linkage unlike DavePhos. pMorDalPhos links to MorDalPhos in similar fashion. nJackiePhos has structures similar to JackiePhos with the CF₃ groups replaced by fluorine atoms. We included the last three ligands in our analysis to understand the significance of placing the phosphine unit ortho to the biphenyl (or C–N in case of MorDalPhos) linkage and replacing the CF₃ group by fluorine atoms.

The biphosphine ligands such as DPPM, DPPE, and DPPP have two phosphorus atoms connected using (CH₂)_n groups ($n = 1–3$) with natural bite angle (β_n) of 73°, 86°, and 91°, respectively.⁴¹ Wider bite angles increase the effective steric bulk of the ligand, and its implications on the scaling lines will be discussed later. Hartwig introduced ferrocene-based ligands with even wider bite angles such as DPPF (99°),³⁵ DtBuPF,⁴² and DCyPDtBuPF with the latter two being variants of DPPF with different R (alkyl) groups on the phosphorus atom. JosiPhosCyPFtBu has the two phosphine units on the same cyclopentadienyl group of the ferrocene unit.⁴³ Buchwald and

co-workers suggested binaphthyl-based ligands such as BINAP with $\beta_n = 93^\circ$ for C–N coupling.^{26,44} BINAP–NMe₂ and MOP are modifications to BINAP with NMe₂ and OMe groups instead of the second PR₂ in BINAP.⁴⁵ XantPhos ($\beta_n = 108^\circ$) and DPEPhos ($\beta_n = 104^\circ$) have larger bite angles than the remaining biphosphine ligands.^{46,47}

Figure 3 shows the computed free energy diagrams for the BHA reaction using 27 mono- and 10 biphosphine ligands. It is clear already from the fact that the potential energy diagrams are generally parallel to each other that the energies of intermediates and transition states scale with each other. This means that the relative energies of all the intermediates can be elegantly expressed as a linear function of the energy of one intermediate (we choose I, see section 3 in SI for more details), $\Delta G(I)$ as shown in Figures 4 and 5.

We consider the mono- and biphosphine ligands separately, because they have different structural motifs (one P versus two P) resulting in different catalyst structures (mono- versus bidentate Pd–L) and intermediates. The difference in scaling lines can be traced to geometric differences between mono and biphosphine ligands. For instance, the square planar geometric

Figure 4. Relative free energies (ΔG in kcal/mol) of intermediates (a) r_{OA} , (b) TS_{OA} , and (c) f_{OA} expressed in terms of intermediate $\Delta G(I)$ for each of the ligands.

requirement of Pd(II) intermediates is evident from the energy of intermediate f_{OA} in Figure 3 which is more readily satisfied by bis-phosphine ligands than in the case of monophosphine ones. Such structural effects are well-known in heterogeneous catalysis where different surface facets result in slightly different scaling relations. We use simple linear regression method to fit

the energies of different states versus the $\Delta G(I)$ over the sets of mono- and biphosphine ligands. The few outliers are generally the result of unusual steric crowding caused by the larger ligand either resulting in unfavorable interactions with the neighboring groups, thus destabilizing the structure or favorable interactions stabilizing the reaction intermediates

Figure 5. Relative free energies (ΔG in kcal/mol) of intermediates (a) r_{OA} , (b) TS_{OA} , and (c) f_{OA} expressed in terms of intermediate $\Delta G(I)$ for each of the ligands.

with low-coordinated palladium. For instance, the intermediate f_{OA} is greatly stabilized by the strong palladium–aryl interaction in Me₄tBuXPhos which makes it difficult for the incoming amine to bind to the metal to form intermediate I.

The individual points do not all fall perfectly on the linear scaling line. The analysis is therefore meant to reveal the major trends and cannot be expected to provide a very detailed map,

but the experience from heterogeneous catalysis shows that, in general, the scaling lines are more accurate than the individual calculated points.⁴⁸ We now provide a simple kinetic analysis of the reaction. On the basis of the calculated results, we identify three activation energies (E_{ai}) that are likely to control the reaction rate:

Figure 6. Volcano plot for (a) 27 monophosphine and (b) 10 biphosphine ligands.

$$E_{a1} = \max \begin{cases} \Delta G(\text{TS}_{\text{OA}}), & (1a) \\ \Delta G(\text{TS}_{\text{OA}}) - \Delta G(\text{r}_{\text{OA}}) & (1b) \end{cases}$$

$$E_{a2} = \max \begin{cases} \Delta G(\text{TS}_{\text{RE}}) - \Delta G(\text{r}_{\text{RE}}), & (2a) \\ \Delta G(\text{TS}_{\text{RE}}) - \Delta G(\text{I}), & (2b) \\ \Delta G(\text{TS}_{\text{RE}}) - \Delta G(\text{f}_{\text{OA}}) & (2c) \end{cases}$$

$$E_{a3} = \Delta G(\text{P}) - \Delta G(\text{f}_{\text{RE}}) \quad (3)$$

The rate of each of the possible rate-determining steps can be expressed in terms of the activation energy by a simple Arrhenius expression:

$$r_i = A \exp(-E_{ai}/RT)$$

$$\text{or } \log r_i = \log(A) - E_{ai}/RT$$

$$\text{or } \log r_i \propto -E_{ai} \quad (4)$$

such that $-E_{ai}$ can be used as a (logarithmic) measure of the rate of each reaction step. Using the scaling relations, the individual rates are all a function of a single descriptor, and in Figure 6 we show the five rate functions for mono- and biphosphine ligands. For each value of the descriptor, the lowest rate (of the three in eqs 1–3), or equivalently the highest activation energy will be used to determine the rate net forward rate,

$$\log r \propto -\max(E_{a1}, E_{a2}, E_{a3}) \quad (5)$$

Such a procedure, known as a Sabatier analysis,⁸ provides an exact upper bound to the actual rate; it neglects concentration variations between the different intermediates, for example by assuming that they are all equal to the reactant concentration. In reality they can be lower. The net rate is shown in solid lines in Figure 6 (see section 3 in SI for more details).

Our analysis suggests that the conversion of I to TS_{RE} is the rate-determining step for most of the ligands. The mono-

phosphine ligands: $\text{Me}_4\text{tBuXPhos}$, tBuBrettPhos , tBuXPhos , and BippyPhos are closest to the top of the volcano. For these four ligands, the C–N bond forming step (r_{RE} to TS_{RE}) becomes the rate-determining step. The rate can be further improved by focusing on modifying the best ligand, $\text{Me}_4\text{tBuXPhos}$, in a way such that the barrier for the r_{RE} to TS_{RE} step is lowered. One strategy would be making the palladium more electron deficient which will move the points more toward the right along the dark blue line 2(a) in Figure 6(a). Note that as electron-rich metal center facilitates oxidative addition and vice versa for the reductive elimination step. Thus, an optimal electron density at the metal center, hence the optimal rate, would be obtained at the intersection of the line 2(a) and 1(a).

The experimental reports on BHA reactions consist of various different combinations of reactants for each of the 37 ligands considered in this work. Therefore, it is not possible to make one to one comparison of the computed results with the available experimental literature. In a few selected works where methylamine is employed as the nucleophile, the electrophile used is not exactly phenyl bromide (as computed) and vice versa.⁴⁹ However, the general trends of ligand behavior from the volcano plots can be connected with the experimental observations for primary amines and aryl bromides (or aryl halides).

For example, the earliest monophosphine ligands (referred to as first-generation BHA ligands), $\text{P}(o\text{-tolyl})_3$ and PPh_3 , worked poorly for the primary amines.^{35,50} These two ligands are also among the ligands with the lowest reaction rate as shown in the Figure 6a. The second-generation BHA ligands consisted of biphosphine ligands (Figure 6b) which follow different scaling lines compared to the monophosphine ligands because they mostly bind to palladium in bicoordinate fashion. We find that the electron-rich biphosphines with a bite angle of 90° are more active toward the aminated product in concordance with the experimental findings for similar substrates.^{51,52} Among the ligands with $\approx 90^\circ$ bite angle, the DtBuPF with tertiary butyl groups on both the phosphorus

atoms is located near the volcano top and gives the highest rate.⁴² The electron richness of ligands facilitates the oxidative addition step while the steric bulk makes reductive elimination easier.

Soon after the discovery of second-generation ligands, it was realized that the bidentate binding is not necessary, because the bulky monophosphine ligand PtBu₃ was found to be a remarkably active ligand. As evident in the Figure 6, PtBu₃ and similar ligands such as DTBNpP and TNpP have rates higher than that of first-generation ligands. Several other bulky electron-rich monophosphine ligands such as JohnPhos, XPhos, SPhos, RuPhos, BrettPhos, tBuBrettPhos, etc., were discovered since the discovery of PtBu₃. These are the third-generation BHA ligands and perform better than the first generation ligands (Figure 6a) in excellent agreement with the experimental findings.³⁰ The third generation ligands are hemilabile because the phosphorus coordinates strongly to the palladium while the nonphosphorus-containing phenyl group of the biaryl substituent interacts weakly with the metal center. Hemilability makes it easier to donate/withdraw electrons depending upon the reaction step in the catalytic cycle (for example, favor OA/RE by donating/withdrawing electrons to/from the metal center via aryl–palladium interaction).

The ligands Me₄tBuXPhos, tBuBrettPhos, tBuXPhos, and BippyPhos have bulkier substituents on the aryl rings of the biaryl substituent on phosphorus. This restricts the free rotation of (1) the nonphosphorus-containing phenyl group along the biphenyl linkage and (2) the biaryl substituent along the P–C bond. As a result of the steric congestion due to bulky groups, the nonphosphorus-containing phenyl group is well-placed over the fourth coordination site on palladium, facilitating palladium–aryl interaction. In fact, the ligands BrettPhos and tBuBrettPhos have experimentally been found to be highly selective and active for the monoarylation of methylamine, though with aryl chlorides.³⁴ BippyPhos, close to the tBuBrettPhos in the volcano plot, is also known to be active for methylamine and capable of similar Pd–heteroaryl interactions.^{39,53} Lastly, the distinction between the para- and ortho-substituted biphenyl rings in pDavePhos and DavePhos (or pMorDalPhos and MorDalPhos) is apparent in the plot, and therefore it is not surprising that the most experimentally used third-generation ligands have the phosphine group ortho to the biphenyl linkage.

CONCLUSION

We have shown that volcano plots derived using the scaling relations can be used to understand reactivity trends across different ligands in C–N coupling reaction, namely the Buchwald–Hartwig amination reactions. The computed results largely reproduce the experimental trends, though making one-to-one comparisons is difficult due to the lack of experiments for the exact set of reactants. In this work, the ligands are varied, though one can use a volcano plot for any other variable(s) in catalytic reactions. Undoubtedly, the scaling relations and volcano plots hold promise for homogeneous catalytic reactions parallel to the surface reactions.⁵⁴ With modern computational tools, it will soon be possible to construct multidimensional volcano surfaces for attaining the optimal set of reagents for a synthetic conversion.

COMPUTATIONAL METHODS

All structures are optimized using the Gaussian 16 suite of programs at B3LYP/6-31+G** (LANL2TZ(f) for Pd, Fe, SDD for Br) level of theory with the inclusion of Grimme's D3 dispersion correction.^{55,56} The transition states are characterized by one and only one imaginary frequency. We performed intrinsic reaction coordinate (IRC) computations on all the transition states to ensure that they correspond to the correct reaction step. To include the effect of solvent, the gas-phase-optimized geometries were subjected to single point computations at B3LYP/6-311+G** (LANL2TZ(f) for Pd, Fe, SDD for Br) level of theory using Truhlar's SMD implicit solvation model⁵⁷ and toluene as the solvent [$\epsilon = 2.38$]. The free energy corrections from the gas-phase frequency computations are added to the condensed phase single point energies to account for the entropic effects. The relative free energies of all intermediates and the transition states are calculated with respect to infinitely separated reactants comprising L_nPd, MeNH₂, PhBr, and NaOtBu under similar conditions. Unless otherwise stated, all the energies reported in the discussion are relative free energies at 300 K in kilocalories per mol.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jkno@dtu.dk.

ORCID

Megha Anand: 0000-0003-2707-3587

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. The authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Villum Foundation V-SUSTAIN grant 9455 to the Villum Center for the Science of Sustainable Fuels and Chemicals and the Department of Energy, Basic Energy Sciences through the SUNCAT Center for Interface Science and Catalysis. M.A. gratefully acknowledges Dr. Aayush R. Singh from the Stanford University for many helpful discussions.

REFERENCES

- (1) Abild-Pedersen, F.; Greeley, J.; Studt, F.; Rossmeisl, J.; Munter, T. R.; Moses, P. G.; Skúlason, E.; Bligaard, T.; Nørskov, J. K. Scaling Properties of Adsorption Energies for Hydrogen-containing Molecules on Transition-Metal Surfaces. *Phys. Rev. Lett.* **2007**, *99*, 4–7.
- (2) Van Santen, R. A.; Neurock, M.; Shetty, S. G. Reactivity Theory of Transition-Metal Surfaces: A Bronsted-Evans-Polanyi Linear Activation Energy-Free-Energy Analysis. *Chem. Rev.* **2010**, *110*, 2005–2048.

- (3) Montemore, M. M.; Medlin, J. W. Scaling Relations Between Adsorption Energies for Computational Screening and Design of Catalysts. *Catal. Sci. Technol.* **2014**, *4*, 3748–3761.
- (4) Jørgensen, M.; Grönbeck, H. Scaling Relations and Kinetic Monte Carlo Simulations to Bridge the Materials Gap in Heterogeneous Catalysis. *ACS Catal.* **2017**, *7*, 5054–5061.
- (5) Andersen, M.; Levchenko, S. V.; Scheffler, M.; Reuter, K. Beyond Scaling Relations for the Description of Catalytic Materials. *ACS Catal.* **2019**, *9*, 2752–2759.
- (6) Cheng, J.; Hu, P.; Ellis, P.; French, S.; Kelly, G.; Lok, C. M. Brønsted-Evans-Polanyi Relation of Multistep Reactions and Volcano Curve in Heterogeneous Catalysis. *J. Phys. Chem. C* **2008**, *112*, 1308–1311.
- (7) Calle-Vallejo, F.; Loffreda, D.; Koper, M. T. M.; Sautet, P. Introducing Structural Sensitivity into Adsorption–Energy Scaling Relations by Means of Coordination Numbers. *Nat. Chem.* **2015**, *7*, 403–410.
- (8) Medford, A. J.; Vojvodic, A.; Hummelshøj, J. S.; Voss, J.; Abild-Pedersen, F.; Studt, F.; Bligaard, T.; Nilsson, A.; Nørskov, J. K. From the Sabatier Principle to a Predictive Theory of Transition-Metal Heterogeneous Catalysis. *J. Catal.* **2015**, *328*, 36–42.
- (9) Bligaard, T.; Nørskov, J. K.; Dahl, S.; Matthiesen, J.; Christensen, C. H.; Sehested, J. The Brønsted-Evans-Polanyi relation and the volcano curve in heterogeneous catalysis. *J. Catal.* **2004**, *224*, 206–217.
- (10) Seh, Z. W.; Kibsgaard, J.; Dickens, C. F.; Chorkendorff, I.; Nørskov, J. K.; Jaramillo, T. F. Combining Theory and Experiment in Electrocatalysis: Insights into Materials Design. *Science* **2017**, *355*, eaad4998.
- (11) Nørskov, J. K.; Bligaard, T.; Rossmeisl, J.; Christensen, C. H. Towards the Computational Design of Solid Catalysts. *Nat. Chem.* **2009**, *1*, 37–46.
- (12) Greeley, J. Theoretical Heterogeneous Catalysis: Scaling Relationships and Computational Catalyst Design. *Annu. Rev. Chem. Biomol. Eng.* **2016**, *7*, 605–635.
- (13) Nørskov, J. K.; Abild-Pedersen, F.; Studt, F.; Bligaard, T. Density Functional Theory in Surface Chemistry and Catalysis. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 937–943.
- (14) Curtarolo, S.; Hart, G. L. W.; Nardelli, M. B.; Mingo, N.; Sanvito, S.; Levy, O. The High-throughput Highway to Computational Materials Design. *Nat. Mater.* **2013**, *12*, 191–201.
- (15) Diaz-Morales, O.; Ledezma-Yanez, I.; Koper, M. T. M.; Calle-Vallejo, F. Guidelines for the Rational Design of Ni-based Double Hydroxide Electrocatalysts for the Oxygen Evolution Reaction. *ACS Catal.* **2015**, *5*, 5380–5387.
- (16) Metiu, H.; Agarwal, V.; Kristoffersen, H. H. In *Reviews in Computational Chemistry*; Parrill, A. L.; Lipkowitz, K. B., Eds.; John Wiley & Sons, Ltd., 2018; pp 171–198.
- (17) Sues, P. E.; Lough, A. J.; Morris, R. H. Stereoelectronic Factors in Iron Catalysis: Synthesis and Characterization of Aryl-Substituted Iron(II) Carbonyl P-N-N-P Complexes and their Use in the Asymmetric Transfer Hydrogenation of Ketones. *Organometallics* **2011**, *30*, 4418–4431.
- (18) Wodrich, M. D.; Sawatlon, B.; Busch, M.; Corminboeuf, C. On the Generality of Molecular Volcano Plots. *ChemCatChem* **2018**, *10*, 1586–1591.
- (19) Wodrich, M. D.; Busch, M.; Corminboeuf, C. Accessing and Predicting the Kinetic Profiles of Homogeneous Catalysts from Volcano Plots. *Chem. Sci.* **2016**, *7*, 5723–5735.
- (20) Busch, M.; Wodrich, M. D.; Corminboeuf, C. Linear Scaling Relationships and Volcano Plots in Homogeneous Catalysis – Revisiting the Suzuki Reaction. *Chem. Sci.* **2015**, *6*, 6754–6761.
- (21) Busch, M.; Wodrich, M. D.; Corminboeuf, C. A Generalized Picture of C-C Cross-Coupling. *ACS Catal.* **2017**, *7*, 5643–5653.
- (22) Busch, M.; Wodrich, M. D.; Corminboeuf, C. Improving the Thermodynamic Profiles of Prospective Suzuki–Miyaura Cross-Coupling Catalysts by Altering the Electrophilic Coupling Component. *ChemCatChem* **2018**, *10*, 1592–1597.
- (23) Sawatlon, B.; Wodrich, M. D.; Meyer, B.; Fabrizio, A.; Corminboeuf, C. Data Mining the C–C Cross-Coupling Genome. *ChemCatChem* **2019**, *11*, 4096–4107.
- (24) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald–Hartwig Reaction: An Overview. *J. Organomet. Chem.* **2018**, *861*, 17–104.
- (25) Frost, C. G.; Mendonça, P. Recent Developments in Aromatic Heteroatom Coupling Reactions. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 2615.
- (26) Wolfe, J. P.; Wagaw, S.; Marcoux, J. -f.; Buchwald, S. L. Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation. *Acc. Chem. Res.* **1998**, *31*, 805–818.
- (27) Hartwig, J. F. Carbon–Heteroatom Bond Formation Catalysed by Organometallic Complexes. *Nature* **2008**, *455*, 314–322.
- (28) Surry, D. S.; Buchwald, S. L. Biaryl Phosphine Ligands in Palladium-Catalyzed Amination. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.
- (29) Gildner, P. G.; Colacot, T. J. Reactions of the 21st Century: Two Decades of Innovative Catalyst Design for Palladium-Catalyzed Cross-Couplings. *Organometallics* **2015**, *34*, 5497–5508.
- (30) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide. *Chem. Sci.* **2011**, *2*, 27–50.
- (31) Arrechea, P. L.; Buchwald, S. L. Biaryl Phosphine Based Pd(II) Amido Complexes: The Effect of Ligand Structure on Reductive Elimination. *J. Am. Chem. Soc.* **2016**, *138*, 12486–12493.
- (32) Su, M.; Buchwald, S. L. A Bulky Biaryl Phosphine Ligand Allows for Palladium-Catalyzed Amidation of Five-Membered Heterocycles as Electrophiles. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710–4713.
- (33) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. A P, N-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl Chlorides, Chemoselective Arylations, and Room Temperature Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071–4074.
- (34) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines using Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.
- (35) Driver, M. S.; Hartwig, J. F. A Second-Generation Catalyst for Aryl Halide Amination: Mixed Secondary Amines from Aryl Halides and Primary Amines Catalyzed by (DPPF)PdCl₂. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
- (36) Louie, J.; Hartwig, J. F. Transition Metals in the Synthesis of Complex Organic Molecules. *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599.
- (37) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.
- (38) Hill, L. L.; Moore, L. R.; Huang, R.; Craciun, R.; Vincent, A. J.; Dixon, D. A.; Chou, J.; Woltermann, C. J.; Shaughnessy, K. H. Bulky Alkylphosphines with Neopentyl Substituents as Ligands in the Amination of Aryl Bromides and Chlorides. *J. Org. Chem.* **2006**, *71*, 5117–5125.
- (39) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. BippyPhos: A Single Ligand with Unprecedented Scope in the Buchwald–Hartwig Amination of (Hetero)aryl Chlorides. *Chem. - Eur. J.* **2013**, *19*, 16760–16771.
- (40) Marion, N.; Nolan, S. P. Well-Defined N-Heterocyclic Carbenes-Palladium(II) Precatalysts for Cross-Coupling Reactions. *Acc. Chem. Res.* **2008**, *41*, 1440–1449.
- (41) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. Bite Angle Effects of Diphosphines in C–C and C–X Bond Forming Cross Coupling reactions. *Chem. Soc. Rev.* **2009**, *38*, 1099–1118.
- (42) Hamann, B. C.; Hartwig, J. F. Sterically Hindered Chelating Alkyl Phosphines provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370.

- (43) Shen, Q.; Hartwig, J. F. [(CyPF-tBu)PdCl₂]: An Air-Stable, One-Component, Highly Efficient Catalyst for Amination of Heteroaryl and Aryl Halides. *Org. Lett.* **2008**, *10*, 4109–4112.
- (44) Harris, M. C.; Geis, O.; Buchwald, S. L. Sequential N-Arylation of Primary Amines as A Route to Alkyl diarylamines. *J. Org. Chem.* **1999**, *64*, 6019–6022.
- (45) Vyskocil, S.; Smrcina, M.; Kocovsky, P. Synthesis of 2-Amino-2-Diphenylphosphino-1, 1-Binaphthyl (MAP) and its Accelerating Effect on the Pd(0)-Catalyzed N-Arylation. *Tetrahedron Lett.* **1998**, *39*, 9289–9292.
- (46) Guari, Y.; Van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. An Efficient, Palladium-Catalysed, Amination of Aryl Bromides. *Tetrahedron Lett.* **1999**, *40*, 3789–3790.
- (47) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. A Highly Active Palladium Catalyst System for the Arylation of Anilines. *Tetrahedron Lett.* **1998**, *39*, 5327–5330.
- (48) Medford, A. J.; Wellendorff, J.; Vojvodic, A.; Studt, F.; Abild-Pedersen, F.; Jacobsen, K. W.; Bligaard, T.; Nørskov, J. K. Assessing the Reliability of Calculated Catalytic Ammonia Synthesis Rates. *Science (Washington, DC, U. S.)* **2014**, *345*, 197–200.
- (49) Alsabeh, P. G.; Lundgren, R. J.; Longobardi, L. E.; Stradiotto, M. Palladium-Catalyzed Synthesis of Indoles via Ammonia Cross-Coupling-Alkyne Cyclization. *Chem. Commun.* **2011**, *47*, 6936–6938.
- (50) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. Room-Temperature Palladium-Catalyzed Amination of Aryl Bromides and Chlorides and Extended Scope of Aromatic C–N Bond Formation with a Commercial Ligand. *J. Org. Chem.* **1999**, *64*, 5575–5580.
- (51) Hamann, B. C.; Hartwig, J. F. Systematic Variation of Bidentate Ligands Used in Aryl Halide Amination. Unexpected Effects of Steric, Electronic, and Geometric Perturbations. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.
- (52) Wolfe, J. P.; Wagaw, S.; Buchwald, S. An Improved Catalyst System for Aromatic Carbon-Nitrogen Bond Formation: The Possible Involvement of Bis(phosphine) Palladium Complexes as Key Intermediates. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
- (53) Lavery, C. B.; Rotta-Loria, N. L.; McDonald, R.; Stradiotto, M. Pd₂dba₃/Bipphos: A Robust Catalyst System for the Hydroxylation of Aryl Halides with Broad Substrate Scope. *Adv. Synth. Catal.* **2013**, *355*, 981–987.
- (54) Falivene, L.; Kozlov, S. M.; Cavallo, L. Constructing Bridges Between Computational Tools in Heterogeneous and Homogeneous Catalysis. *ACS Catal.* **2018**, *8*, 5637.
- (55) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16, Revision A.03*; Gaussian, Inc., Wallingford, CT, 2016.
- (56) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate *ab-initio* Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104–154123.
- (57) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.