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Parameterization of phosphine ligands demonstrates enhancement of nickel catalysis via remote steric effects

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The field of Ni-catalysed cross-coupling has seen rapid recent growth because of the low cost of Ni, its earth abundance, and its ability to promote unique cross-coupling reactions. Whereas advances in the related field of Pd-catalysed cross-coupling have been driven by ligand design, the development of ligands specifically for Ni has received minimal attention. Here, we disclose a class of phosphines that enable the Ni-catalysed C*sp*^{3} Suzuki coupling of acetals with boronic acids to generate benzylic ethers, a reaction that failed with known ligands for Ni and designer phosphines for Pd. Using parameters to quantify phosphine steric and electronic properties together with regression statistical analysis, we identify a model for ligand success. The study suggests that effective phosphines feature remote steric hindrance, a concept that could guide future ligand design tailored to Ni. Our analysis also reveals that two classic descriptors for ligand steric environment—cone angle and % buried volume—are not equivalent, despite their treatment in the literature.

Over the past 50 years, Pd-catalysed cross-coupling has evolved to become one of the most useful strategies for carbon–carbon (C–C) and C–heteroatom bond formation[1]. The development of new ligands for Pd has been arguably the most important contributor to the advancement of these methods, enabling reactions with a broad range of substrates under mild and efficient conditions[2–4]. By contrast, the field of nickel-catalysed cross-coupling has witnessed tremendous activity over the past two decades[5], but minimal effort has been dedicated to the identification of new ligand sets (Fig. 1a)[6–9]. Furthermore, phosphines developed for Pd catalysis have generally proven ineffective for Ni (refs 10–12). According to the example set by Pd, the design of new ligands for Ni should facilitate the refinement of existing methods and the identification of new chemical transformations. Here, we report the development of a new class of phosphines and demonstrate that these bench-stable ligands facilitate a Ni-catalysed C*sp*^{3} Suzuki coupling reaction that failed with known ligand architectures for Ni and Pd. Quantitative molecular parameterization of these ligands and multivariate correlation with reaction outcome are conducted[13,14]. These studies reveal that two of the most frequently used parameters to describe ligand steric effects—cone angle and buried volume—are not equivalent, despite their reported treatment in the literature[15,16]. Indeed, it is precisely their difference that provides an intuitive as well as quantitative rationale for their success and for the failure of ligands developed for Pd. We expect that the new phosphines in this study will find application in other Ni-catalysed coupling reactions. Moreover, the insight gained from molecular parameterization should serve as a general design principle for the identification of new ligands tailored for Ni.

The field of Ni catalysis has recently witnessed rapid growth owing to the base metal's low cost and unique properties compared to its precious-metal sibling, Pd. One of the most significant contributions of Ni catalysis to cross-coupling methodology has been enabling the use of substrates bearing abundant and relatively inert C*sp*^{2}–O and C*sp*^{3}–O bonds as electrophilic coupling partners[17]. In this context, our group reported Ni-catalysed Suzuki couplings of *N*,*O*-acetals and *O*,*O*-acetals that deliver 2-arylated heterocycles using triphenylphosphine (PPh_3) as a ligand[18,19]. A mechanistic study suggested a pathway involving boroxine-assisted ionization of the acetals followed by Ni-catalysed coupling of the resulting iminium or oxocarbenium ions[20]. Accordingly, we were able to develop an asymmetric variant of the *N*,*O*-acetal coupling using a chiral phosphonite ligand for Ni (ref. 21). We recently considered whether this strategy could be expanded to offer a general C*sp*^{3}–C bond-forming approach to ether synthesis from a broad range of readily available and stable acyclic and cyclic acetals in combination with boronic acids (Fig. 1b). This reaction would offer an expedient synthesis of benzylic ethers—highly valuable pharmacophores in medicinal chemistry[22]—which are most commonly constructed by C–O bond formation.

The coupling of benzaldehyde dimethyl acetal **1** with *para*-fluorophenyl boroxine was chosen as the model system for optimization (Fig. 2a). This coupling was anticipated to be more challenging than our previously described Suzuki coupling of chromene acetals, because the C*sp*^{3}–O bond of chromene acetals experiences significant bond weakening due to conjugation, and addition of Ni to the benzopyrylium delivers a stabilized π-allyl intermediate[20], both not possible with simple acetals. Indeed, application of the previously identified conditions using PPh_3 **L1** as ligand only yielded trace ether **2** at elevated temperature. By contrast, use of tricyclohexylphosphine (PCy_3, **L2**), one of the most common phosphines used for Ni-catalysed cross-coupling[5,17], afforded modest amounts of product (29% yield). More hindered trialkylphosphines (*tert*-butylphosphine, P^tBu_3, **L3**) were ineffective, as were *N*-heterocyclic carbenes (**L4**). Alkyl arylphosphines, which possess intermediate steric hindrance and electronic character to trialkylphosphines and triarylphosphines, were also evaluated. Unsubstituted alkyl diarylphosphines (cyclohexyl diphenylphosphine, $PCyPh_2$ **L9** and cyclopentyl diphenylphosphine, $PCypPh_2$ **L11**) were less effective than **L2**. However, PCy_2Ph (**L5**) delivered similar yields to PCy_3, as did the less hindered cyclopentyl variant $PCyp_2Ph$ (**L8**). More decorated versions of these ligand

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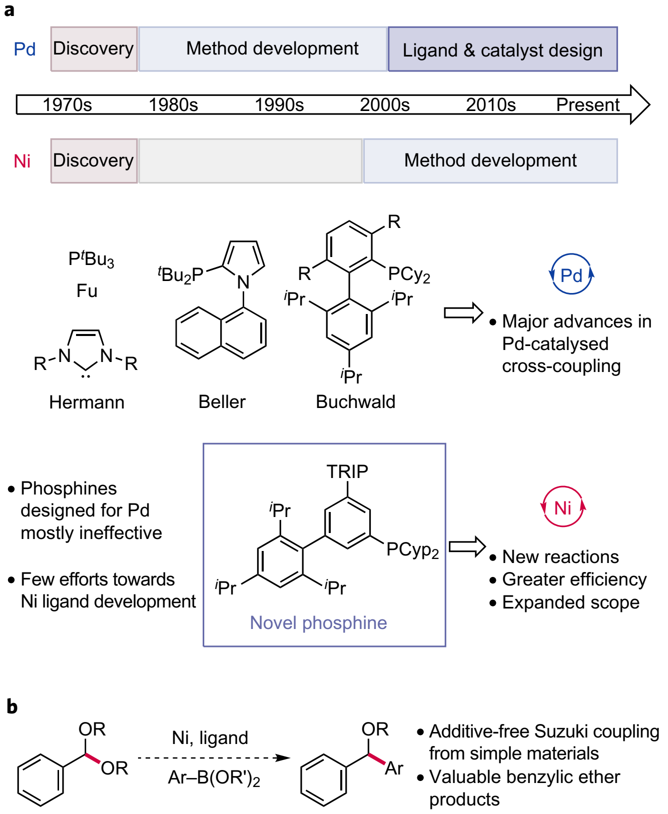


Figure 1 | Design of new ligands for Ni catalysis enables Suzuki coupling of benzylic acetals. **a**, Ligand development in Pd versus Ni-catalysed cross-coupling. Ligands engineered for Pd catalysis have facilitated many advances in cross-coupling, including the discovery of altogether new transformations and the refinement of existing methods such that they can be used for large-scale synthesis. By contrast, minimal effort has been directed at ligand design for Ni-catalysed cross-coupling, despite the opportunity it presents for discovering novel reactions and for improving the efficiency of existing methods. **b**, Ligand design for Suzuki coupling of acetals. The development of a Ni-catalysed Suzuki coupling of acetals with readily available boronic acids would facilitate the preparation of valuable ether products by C–C bond formation. Application of known ligands for Ni and re-purposing ligands designed for Pd to this transformation were both unsuccessful in this regard, prompting the development and study of a new phosphine ligand class for Ni.

architectures have been pioneered by the Buchwald laboratory for Pd-catalysed couplings[2]. Unfortunately, members of this class, such as JohnPhos **L6** and XPhos **L7**, provided no detectable product. The low reactivity observed with ligands developed for Pd is not unique to this example and highlights the limitations of these ligands when used with Ni (refs 10–12). Because Ni is smaller and more nucleophilic than Pd, we questioned whether a novel ligand framework designed specifically for this base metal could overcome the limitations of current ligands and achieve efficient cross-coupling. Furthermore, we sought to obtain a rationale for the effect of phosphine structure on reactivity to facilitate the development of other Ni-catalysed couplings and the discovery of additional ligand frameworks for Ni.

We focused our efforts on modification of the aryl alkylphosphine architecture, because the parent members of this class provided modest reactivity and, unlike trialkylphosphines, this ligand scaffold is readily modifiable and tunable. A synthetic sequence that allowed facile access to these frameworks from readily available starting materials was developed (Supplementary Section C). Notably, many of the new phosphines shown in Fig. 2a were isolated on a gram scale as air-stable solids that could be stored on the bench for over a month without oxidation or decomposition.

We found that, within the alkyl diarylphosphine ((alkyl)PAr$_2$) platform, 2-substitution on the aryl groups was detrimental to reactivity (**L12**), consistent with earlier observations using Buchwald ligands **L6** and **L7**. Ligands with electron-withdrawing groups at the 3,5-positions were also ineffective (**L15**). In contrast, ligands bearing bulky, electron-donating substituents (^{t}Bu) at the 3,5-positions (**L13**, **L16**) afforded improved reactivity over the parent ligands (**L9**, **L10**), providing 67 and 68% yield of the desired ether product, respectively. We questioned whether inclusion of larger substituents at the 3,5-positions would further improve ligand performance. The 2,4,6-tri-*iso*propylphenyl (TRIP) group has proven of high utility in ligand and catalyst design as a very bulky substituent. For reasons of synthetic accessibility, we investigated modification of the (alkyl)$_2$PAr framework with this substituent. Gratifyingly, the catalyst system using **L17** demonstrated further improvement, delivering **2** in 78% yield.

The superior yields with **L16** and **L17** could be due to greater catalyst stability, improved rates of reaction, or both. To probe this question, NMR timepoint experiments were conducted to qualitatively assess reaction progress with various ligands (Fig. 2b). Ligands **L16** and **L17** exhibited greater rates than **L2**, thus suggesting these ligands generate more active Ni catalysts. Furthermore, these timepoint studies illustrate that the catalyst system with **L17** affords superior yields to **L16**, despite having a lower initial rate and an induction period.

Next, we sought to understand what structural features of the new ligands are responsible for their significantly improved rate and catalyst stability. In particular, we sought to quantify the steric and electronic properties of these ligands using numerical parameters and search for statistical correlations with reaction yield. The electronic properties of the ligands were evaluated using the computationally derived minimum electrostatic potential (V_{min}) parameter, which correlates with the Tolman electronic parameter[23]. No strong correlation with yield was observed using V_{min} alone ($r^2 = 0.18$, Supplementary Fig. 2); notably, **L16** and **L17** have only slightly greater V_{min} values than the parent scaffolds **L6** and **L4**, respectively. The steric properties of the ligands were also quantified and analysed. To achieve internal consistency, all steric parameters were computed from molecular mechanics models as opposed to using literature values (Supplementary Section H). The first steric parameter examined was Tolman's cone angle metric[15,24]. Although the cone angle correlated strongly with yield for a range of ligands (circles in Fig. 3a), JohnPhos, XPhos, P^{t}Bu$_3$ and **L12** were notable outliers (triangles). Another parameter often used to quantify ligand steric effects is buried volume ($\%V_{\mathrm{bur}}$)[16,25]. A qualitative trend readily became apparent with this parameter: ligands with large buried volumes are ineffective. The plot of $\%V_{\mathrm{bur}}$ in Fig. 3a illustrates that a ligand possessing a high buried volume is inactive, regardless of its cone angle (for example, JohnPhos, **L12**). Notably, cone angle and $\%V_{\mathrm{bur}}$ have been considered as equivalent measures of ligand steric size and used interchangeably in the literature[16]. The divergence in the parameter–reactivity relationships shown in Fig. 3a provides a striking example showing how these two metrics are far from equivalent (Fig. 3b). We sought to understand the origin of this discrepancy and how it translates to a structure-based insight into ligand effectiveness.

The difference between these two steric parameters can be appreciated through an understanding of the distinct methods each uses to describe ligand size. The buried volume metric emphasizes steric hindrance proximal to the metal by measuring the volume occupied by the ligand in a sphere of defined radius ($r = 3.5$ Å, Fig. 3c). By contrast, the cone angle parameter measures a cone that encloses all groups of the ligand, regardless of how far they are from the metal, and is therefore sensitive to ligand size, even at a

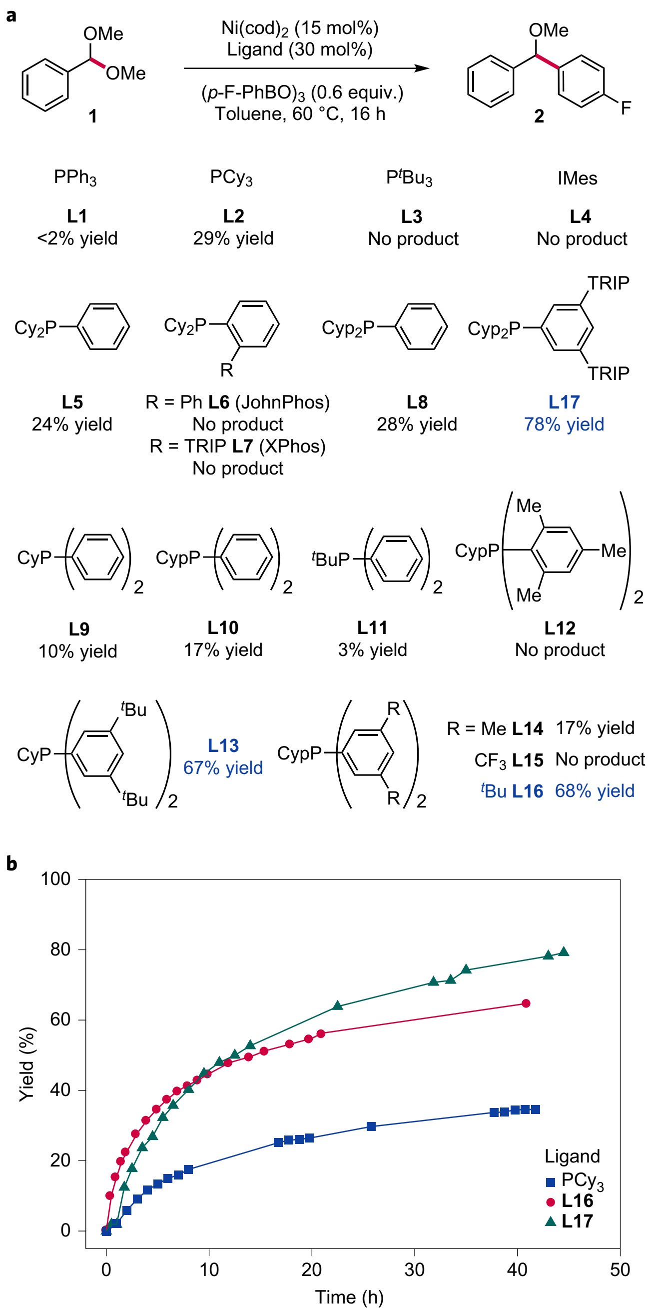


Figure 2 | Ligand evaluation and timepoint studies. a, Screen of existing and novel phosphines for Ni. Ligand evaluation reveals that phosphines bearing tertiary alkyl groups or *ortho*-substituted aryl groups are completely ineffective. However, dialkylaryl [(alkyl)$_2$PAr] and alkyldiaryl [(alkyl)PAr$_2$] phosphines with secondary alkyl substituents and 3,5-substituted aryl groups are highly effective. IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazolium. Yields determined by ^{19}F NMR with 2-fluorobiphenyl as a quantitative internal standard. **b**, Timepoint studies comparing the reaction profile with L16, L17 and PCy$_3$ (L2). Ligands L16 and L17 afford highly active Ni catalysts in the Suzuki coupling; ligand L17 delivers the highest overall yields, despite a slower initial rate of reaction. Reactions were conducted at 60 °C in toluene (0.06 M), 15 mol% Ni(cod)$_2$ and 30 mol% of ligand. cod = 1,5-cyclooctadiene.

distance. Because most ligands have operated in the first coordination sphere, a correlation between the two parameters has been observed; however, this correlation is not required by definition. Taken together, ligands with small buried volume and large cone angle are the ones that feature remote steric hindrance; they are relatively unencumbered near the metal binding site but have large groups distant from the metal. Given the smaller size of Ni relative to Pd and the shorter Ni–P bond distance (2.05 versus 2.28 Å), it makes intuitive sense that sterically hindered phosphines designed for Pd catalysis would crowd a Ni centre, preventing critical substrate or even ligand-binding events. In contrast, new ligands **L16** and **L17** probably permit coordination of reaction components to Ni while still discouraging the binding of multiple ligand equivalents and preventing bimetallic deactivation mechanisms[26]. Additional studies are currently ongoing to investigate the specific influence ligands **L16** and **L17** impart on catalyst structure and activity.

Going further, a quantitative model to relate the cone angle and $\%V_{\mathrm{bur}}$ with yield was developed to explain the outliers and provide quantitative support for the remote steric effect hypothesis (Supplementary Section G). A positive correlation with cone angle was observed, as well as an inverse correlation with the buried volume (Fig. 3d). Taken together, these two terms are a mathematical representation of the remote steric effect concept. The function can be visualized by plotting predicted versus measured yield (Fig. 3d). A slope approaching one and a small intercept indicate the model is accurate, while an r^2 value of 0.96 demonstrates the model's precision. Notably, the model correctly accounts for the entire scope of ligands tested in the study, including ligands with high buried volume (JohnPhos, P^{t}Bu$_3$), whereas they fell as outliers in the simple yield versus cone angle correlation (Fig. 3a). Leave-one-out cross-validation of the model was also performed. A Q^2 value of 0.88 indicates that the model has potential predictive ability on a new data set, a feature made more attractive given that all of the ligand parameters are generated computationally rather than obtained from experiment or literature. Indeed, a preliminary evaluation suggests that the model can predict the performance of ligands (Fig. 3d, squares) across a range of structures, including two ligands possessing substituents not present in the training set and a third ligand predicted and found to be active despite its bearing a *tert*-butyl substituent that rendered all ligands in the training set inactive.

Having arrived at an enabling ligand, the scope of boroxine nucleophiles was then evaluated (Table 1). Both electron-deficient (**2**,**3**) and electron-neutral (**5**) phenylboroxines afforded ethers in good to excellent yields, whereas electron-rich phenylboroxines (**4**) delivered modest reaction efficiency, presumably due to their attenuated Lewis acidity[20]. Carbonyl-functionalized (**6**) and sterically hindered (**8**) boroxines are competent coupling partners. Furthermore, ligand **L17** induces good reaction efficiency with heterocyclic boroxines (**9**), as long as the heterocycle is not strongly Lewis basic. Acetal scope investigations also revealed tolerance for electronic and steric variation. *Ortho*-substitution on the benzaldehyde was well tolerated under the reaction conditions (**10**). Both electron-rich (**11**) and electron-neutral (**12**) acetals were also compatible; the former affords a synthetic alternative to the limitation of using electron-rich aryl boroxines described above. Unfortunately, electron-deficient acetals did not undergo coupling. This result, taken together with the ineffectiveness of electron-rich boroxines, is consistent with a mechanism involving boronic acid-assisted ionization of the acetal followed by oxidative addition to the resulting oxocarbenium intermediate[20]. Notably, no over-arylation of the ether products to give triarylalkanes is observed, even though Jarvo and Shi have reported Ni-catalysed couplings of benzylic ethers related to the products in Table 1 (refs 27,28).

More complex substrates, including exo- and endocyclic, bidentate and hindered acetals, also underwent coupling to provide several important structural motifs (Table 2). Products **17** and **19** are of particular interest because they represent the structural cores of important pharmaceutical compounds[29]. Notably, phthalan

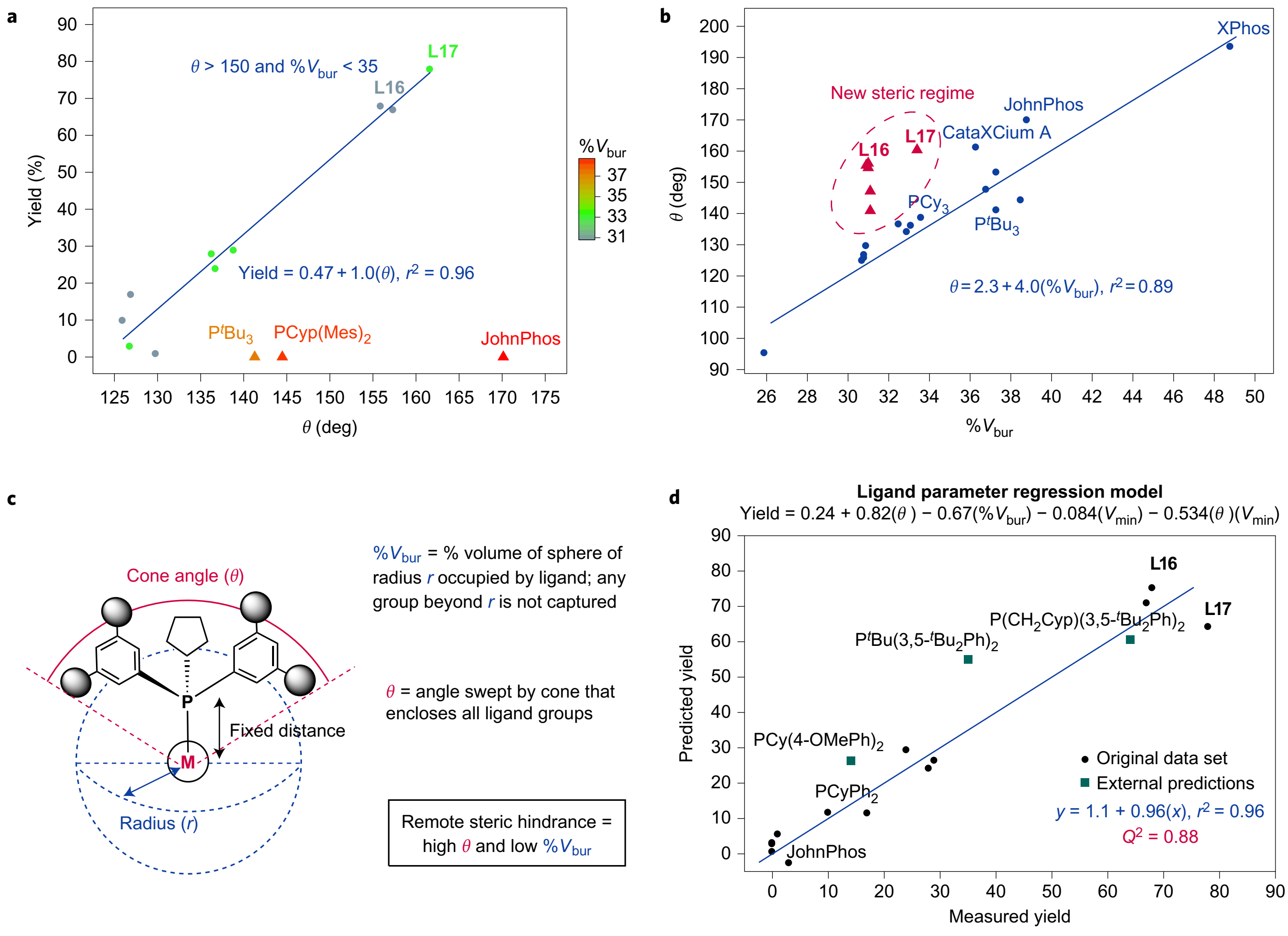
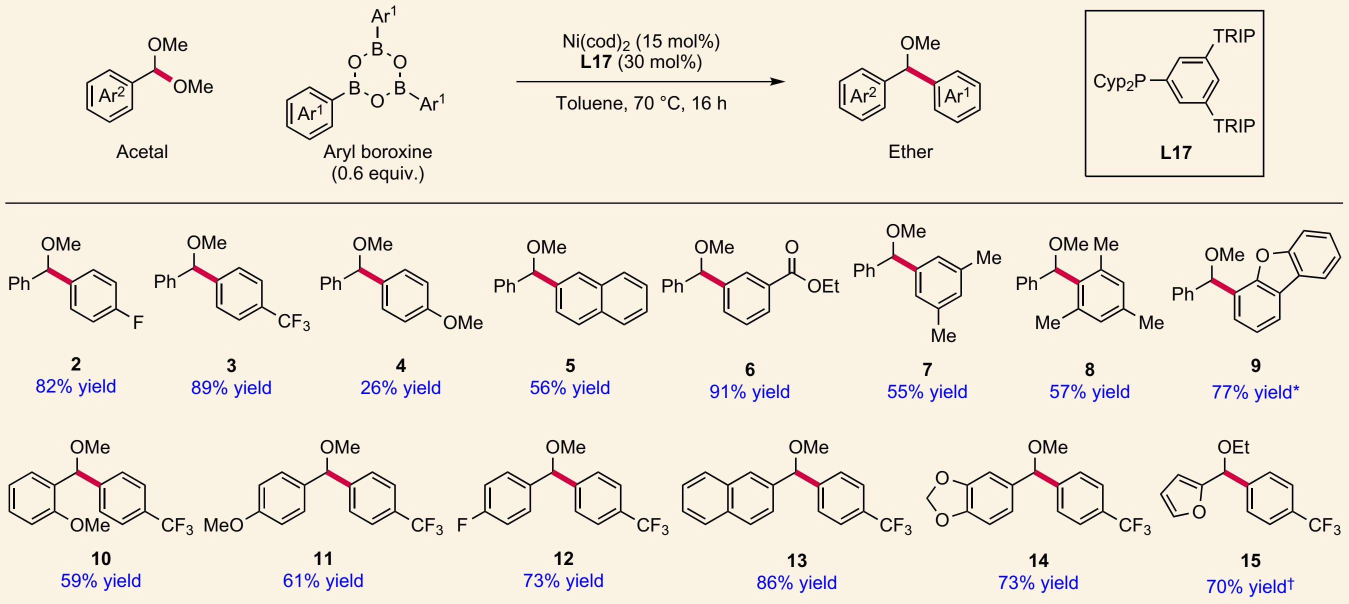


Figure 3 | Steric parameterization and analysis. **a**, Plot of yield versus cone angle (θ) and buried volume (%V_{bur}). A comparison of the ligand steric parameters against reaction yield reveals that larger cone angle correlates with higher yield (circles), with the exception of ligands featuring high buried volume (triangles). The regression equation only includes the circle data points. **b**, Plot of cone angle versus buried volume. Cone angle and buried volume have previously been treated as equivalent measures of ligand steric environment, as illustrated by a 1:1 mapping of the two parameters (circle data points). The regression equation only includes circle data points. The new phosphines prepared in this study (triangles) fall outside this 1:1 mapping, highlighting that these two terms are not equivalent, by definition. **c**, Definition of cone angle and buried volume. Both measure steric encumbrance but with different distance dependencies. Buried volume only accounts for steric hindrance proximal to the metal whereas cone angle is sensitive to ligand size at a distance. A ligand with a large cone angle and low %V_{bur}, such as those most successful in this new method, therefore possesses remote steric hindrance. **d**, Plot of predicted yield versus actual yield. A quantitative model to relate cone angle, buried volume and V_{min} to yield was obtained by regression analysis. This model accounts for the entire scope of ligands tested in the study and features a mathematical representation of the remote steric effect concept. We show that the model can predict the performance of ligands (green squares) that feature unique structural motifs to those included in the ligand training set.

and dioxolane acetals 18 and 20, which were completely unreactive with PCy_3, undergo C–C bond formation using L17 to afford α-arylated ethers 19 and 21 in good yield. The products 21 and 23 possess an alcohol tether capable of undergoing further functionalization, including serving as a directing group for additional Ni-catalysed coupling to give bioactive triarylmethane products[30,31]. Acetal 22 (1.3:1 d.r.) reacts to generate 23 in a 2:1 mixture of regioisomers, with the major regioisomer (3.8:1 d.r.) derived from functionalization of the less substituted C–O bond. Compared with the five-membered cyclic acetals 20 and 22, dioxane acetal 24 was less reactive. Perhaps most notably, acetals derived from sterically hindered alcohols (22, 26, 30) deliver products in excellent yield that could not be easily obtained through most C–O bond-forming methods[32]. Although acid-catalysed approaches to these products exist, they are typically limited to methyl ether formation from electron-rich or neutral benzhydrols and require strong acid and forcing conditions[33]. Furthermore, our laboratory previously described a reductive cross-coupling method for the synthesis of this same product class from acetals and aryl iodides using a stoichiometric reductant and a potent Lewis acid[34]. This reductive approach failed with substituted acetals such as 22, 26, 28 and 30, highlighting a major strategic advantage of this new method.

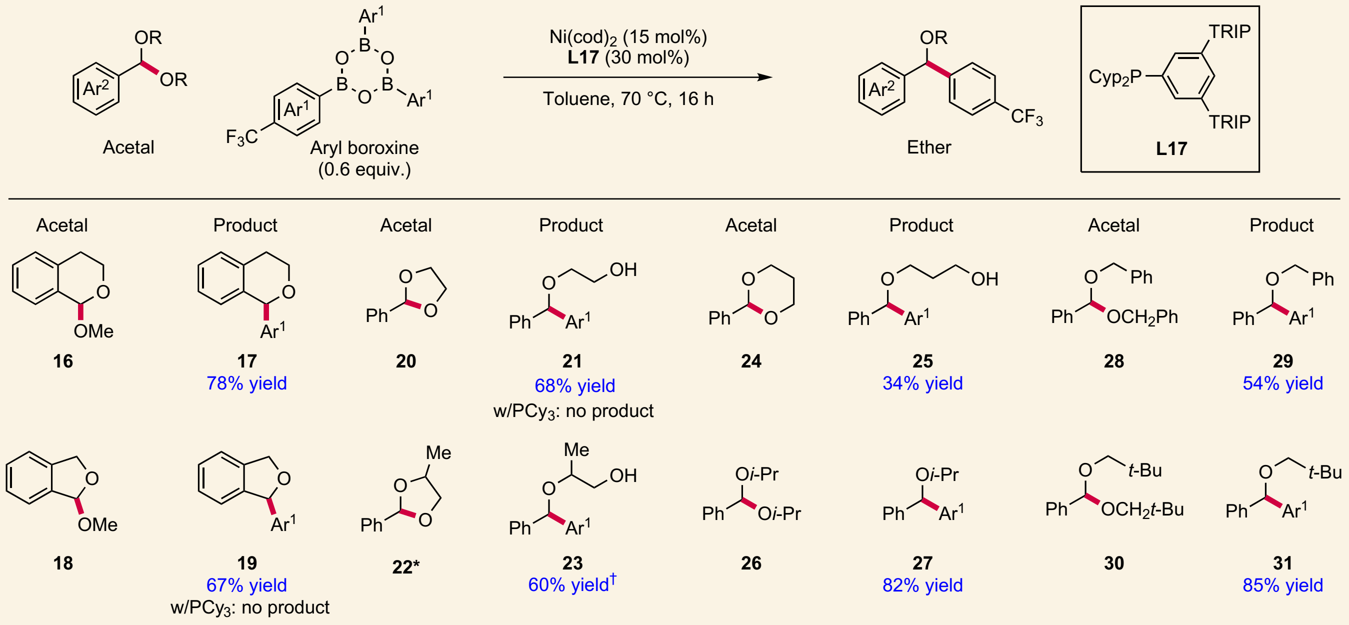
In conclusion, we have developed a novel class of aryl alkylphosphines containing bulky groups at the 3,5-positions (L17) that confer high activity upon Ni catalysts for the Suzuki coupling of benzylic acetals. Parameterization and modelling studies reveal that the effectiveness of these ligands is a function of remote steric hindrance, a structural concept relatively unexplored in ligand design. We reveal a divergence between the cone angle and buried volume (%V_{bur}) parameters, two measures of steric size previously considered to be equivalent. Whereas %V_{bur} only describes steric hindrance in the metal's first coordination sphere, cone angle captures it beyond the immediate proximity of the metal. We show that the two can be used in conjunction to develop a quantitative model for predicting ligand reactivity. We believe this new ligand architecture and the concept of remote

Table 1 | Scope investigation.



A range of aryl boroxines undergo cross-coupling with dimethyl acetals derived from benzaldehydes. Yields shown are isolated yields. *Run at 60 °C. †2-furan diethyl acetal used.

Table 2 | Scope investigation with more complex acetal substrates.



Several exocyclic and endocyclic acetals undergo C–C bond formation to afford valuable cyclic and acyclic ethers. Access to sterically hindered ethers is also possible using this method. In the cases examined, the new phosphine framework is exclusively effective. PCy$_3$, a ligand that delivered low but measurable yield in the model reaction, is completely inactive, highlighting the impact of ligand development on reaction discovery. Yields shown are isolated yields. *1.3:1 mixture of diastereomers. †Run at 85 °C; isolated as a 2:1 mixture of regioisomers (major regioisomer shown).

steric hindrance will lead to significant advances in both Ni catalysis and ligand design.

Data availability. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as CCDC 1520891 (**S-1**) and can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/getstructures. Procedures, code and data for statistical analysis are available in the Supplementary Information at http://www.nature.com/nchem.

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Author contributions

K.W. and A.G.D. conceived the work. K.W. performed and analysed the experiments and calculations. K.W. and A.G.D. designed the experiments, analysed the data and co-wrote the paper.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to A.G.D.

Competing financial interests

The authors declare no competing financial interests.