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Research Article

Pd-Catalyzed Cross-Coupling of Hindered, Electron-Deficient Anilines with Bulky (Hetero)aryl Halides Using Biaryl Phosphorinane Ligands

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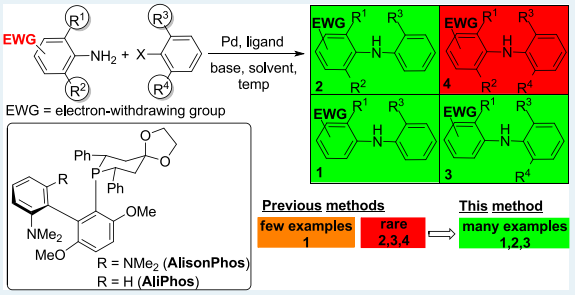
ABSTRACT: Biaryl phosphorinane ligands derived from addition of biaryl primary phosphines to *trans,trans*-dibenzylideneacetone (AlisonPhos and AliPhos) form highly active ligands for Pd-catalyzed coupling of hindered, electron-deficient anilines with hindered (hetero)aryl halides, a challenging class of C−N cross-coupling reaction with few precedents. Broad substrate scope and functional group tolerance were observed under the reaction conditions. Computational studies suggest that ligands containing phenyl substituents provide greater activity through more favorable aniline binding in the catalytic cycle in comparison to alkyl-substituted phosphorinanes. A general and high-yielding procedure for the synthesis of biaryl phosphorinanes by phospha-Michael addition of primary biarylphosphines to 1,4-dien-3-ones in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), under relatively mild conditions (23−110 °C), is also described. HFIP as the solvent significantly accelerates the phospha-Michael addition, allowing the preparation of previously inaccessible ligands and higher yields overall.



KEYWORDS: *amination, phosphine ligands, cross-coupling, palladium, phospha-Michael addition*

INTRODUCTION

With the aid of the development of phosphine ligands, Pd-catalyzed C−X (X = C, N, O) coupling reactions have become an indispensable synthetic tool for both academic and industrial laboratories.[1] The development of new ligand scaffolds is necessary to extend the scope of these reactions to increasingly challenging substrate combinations, such as coupling of *hindered, electron-deficient* anilines with *hindered* aryl halides ArX (X = Cl, Br). Electron-deficient anilines are poorer nucleophiles than electron-rich and -neutral anilines and are more difficult to couple with ArX.[2,3] Sterically hindered anilines are also challenging to couple, particularly with *ortho*-substituted aryl halides.[3c,4] Thus, it is not surprising that no general method is known for coupling hindered, electron-deficient anilines with hindered ArX compounds (Figure 1A).[5] Currently, there are few isolated examples where *ortho*-substituted, electron-poor anilines couple with *ortho*-substituted ArX.[4,6] Two examples were reported by Shaughnessy[4b] and one each by Buchwald[2d] and Organ.[2e] Reactions of *ortho*-substituted ArX with *ortho,ortho′*-disubstituted electron-poor anilines are even less prevalent.[7] Also rare are reactions of *ortho,ortho′*-disubstituted ArX with *ortho*-substituted, electron-poor anilines.[8] This class of C−N couplings is also not well precedented with Ni- and Cu-catalyzed methods.[6d,9]

Recently, we reported that biaryl phosphorinanes are highly effective ligands for Pd-catalyzed C−N and C−O cross-coupling reactions.[10,11] One of these ligands, VincePhos, was used in the multikilogram scale synthesis of dasabuvir, an HCV polymerase inhibitor.[10b] Herein, we report that the newly prepared biaryl phosphorinanes AlisonPhos and AliPhos are highly effective ligands for the Pd-catalyzed coupling of *ortho*- and *ortho,ortho′*-substituted electron-deficient anilines (Hammett parameter (σ) > 0.15) with hindered (hetero)aryl halides (Figure 1B). Many functional groups are tolerated, and the substrate scope and limitations are demonstrated with 100 examples. The ligands AlisonPhos and AliPhos are easily prepared from the phospha-Michael addition of air-stable primary biaryl phosphines with readily available *trans,trans*-dibenzylideneacetone (dba). Computational studies provide insight into the reactivity differences observed between biaryl phosphorinanes derived from dba versus previously described 1,1,5,5-tetraalkylpenta-1,4-dien-3-ones.

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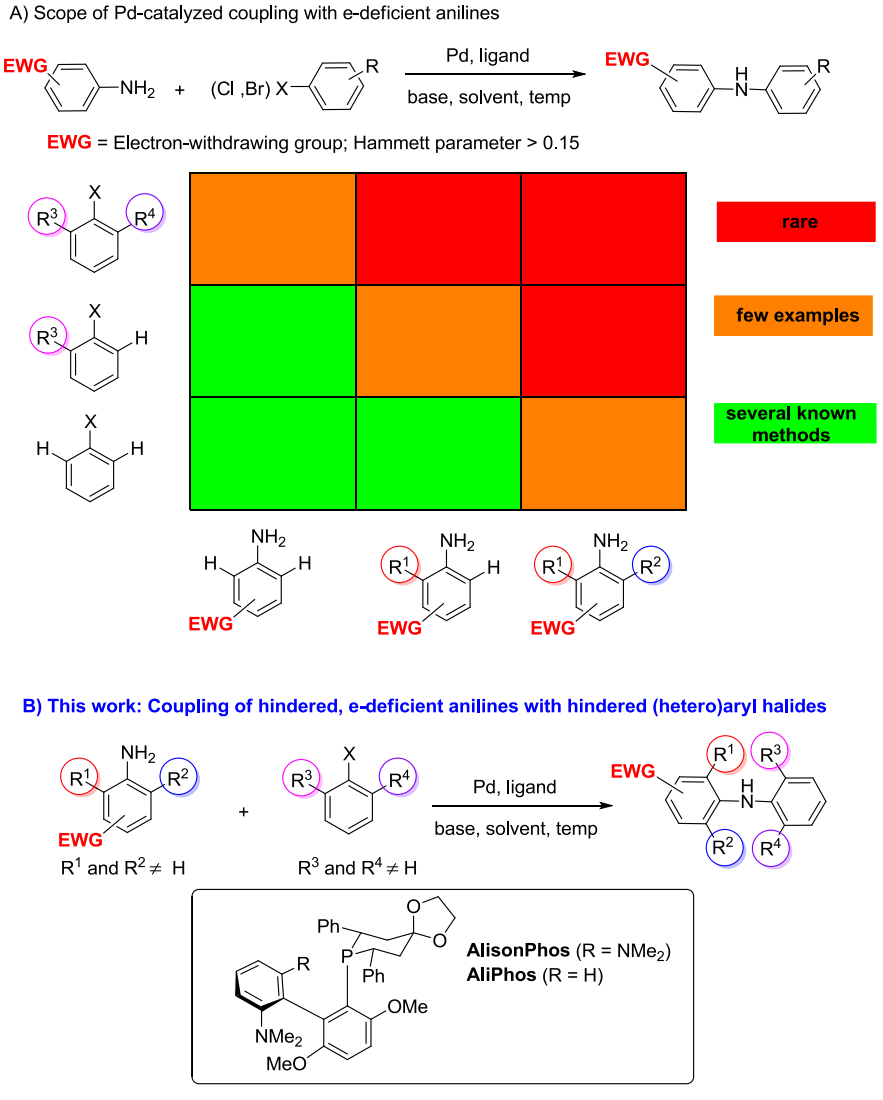
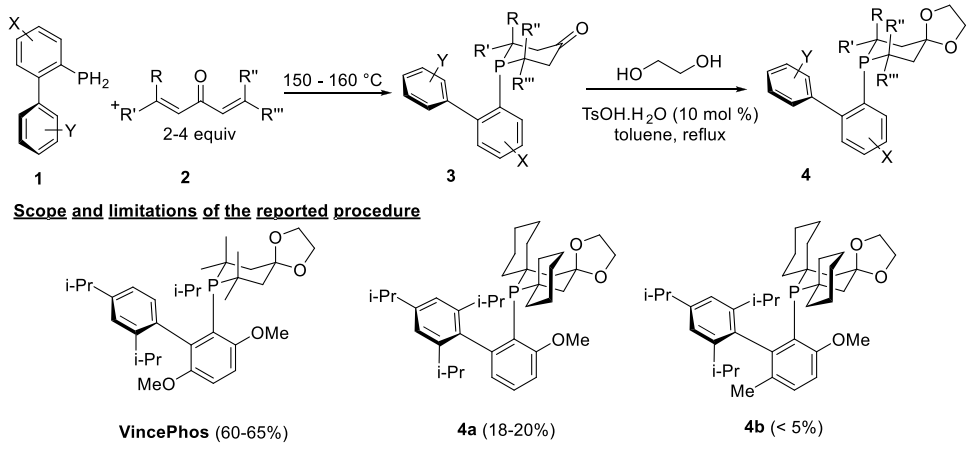


Figure 1. Reactions of hindered, electron-deficient anilines with hindered aryl halides.

Scheme 1. Two-Step Procedure to Prepare Biaryl Phosphorinanes[10a]



RESULTS AND DISCUSSION

We are interested in evaluating biaryl phosphorinanes as ligands for metal-catalyzed reactions.[10] In order to rapidly prepare newer ligands, an improved synthetic procedure was needed. Biaryl phosphorinanes (**4**) were previously synthesized by the phospha-Michael addition of primary biaryl phosphines (**1**) to 1,1,5,5-tetraalkylpenta-1,4-dien-3-ones (**2**) at 150−160 °C, followed by ketalization of the resulting phosphinanones (**3**) with ethylene glycol (Scheme 1).[10a] While many ligands were prepared in good yields using this procedure, increasing the

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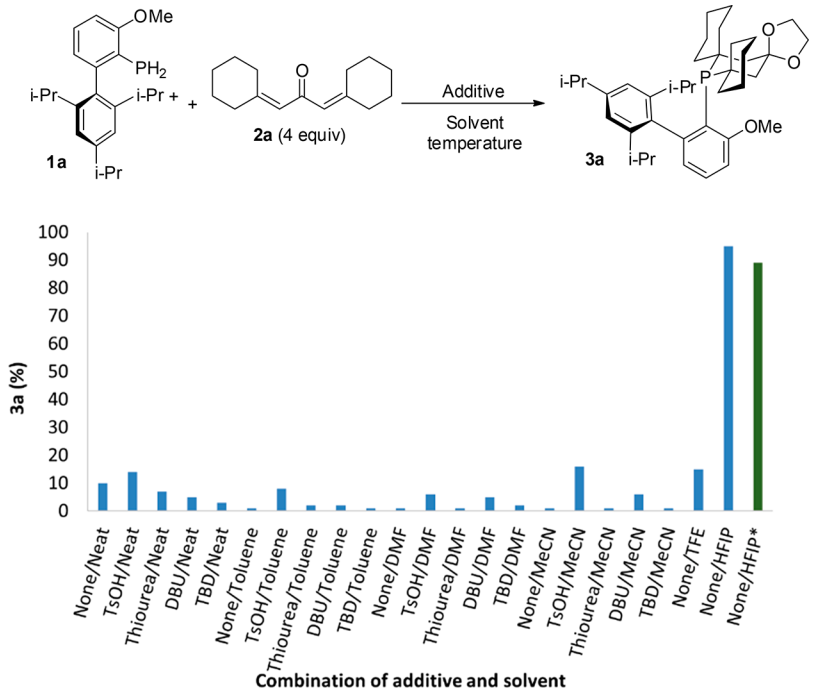

Figure 2. Optimization of reaction conditions for the formation of **3a**. The *x* axis shows the combinations of additives and solvents that were tested. The *y* axis shows the area % of **3a** by HPLC analysis. Definitions: neat, no solvent; TsOH, *p*-toluenesulfonic acid; Thiourea, *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD, triazabicyclodecene; TFE, 2,2,2-trifluoroethanol; HFIP, 1,1,1,3,3,3-hexafluoroisopropanol. Unless noted otherwise, all experiments were conducted with **1a** (1 equiv), **2a** (4 equiv), and additive (0.1 equiv) in the solvent (10 mL/g of **1a**) for 24 h at 150 °C (neat, toluene, DMF) or 110 °C (MeCN, TFE, HFIP). *The reaction corresponding to the green bar was conducted with 1.2 equiv of **2a**.

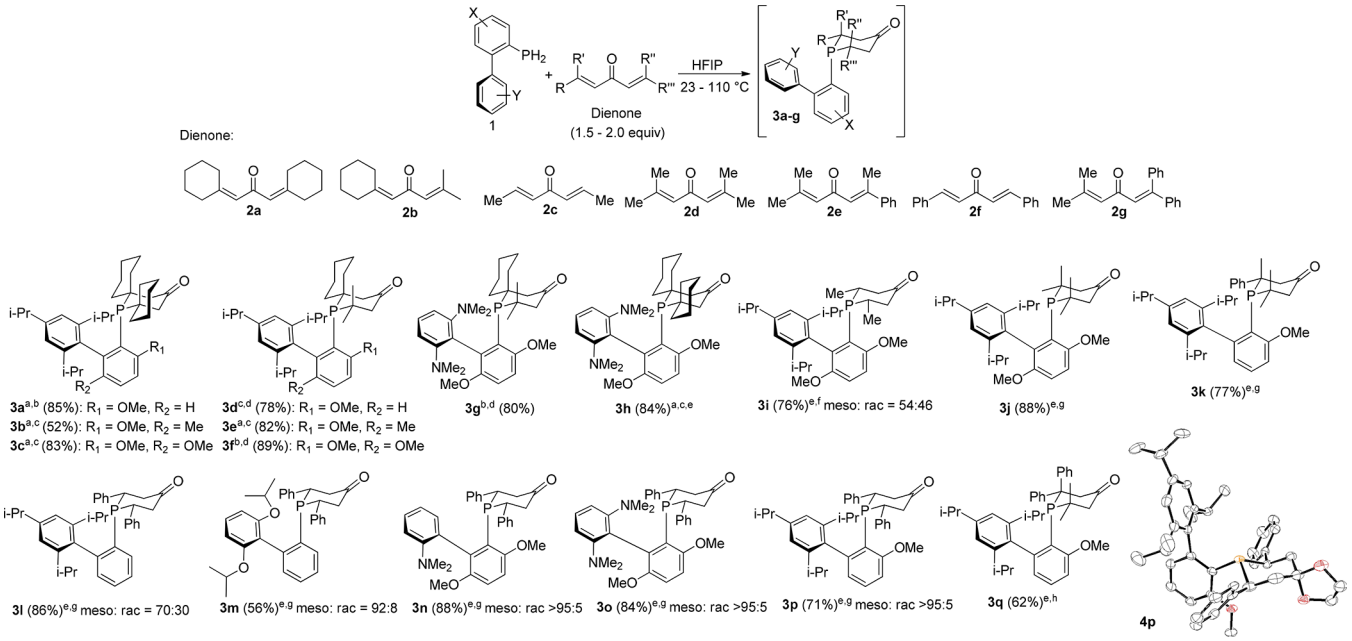

Figure 3. Scope of phospha-Michael addition with **2a**−**g**. The crude yield based on HPLC is shown, unless otherwise noted. Legend: (a) reaction at 110 °C; (b) 1.5 equiv of dienone; (c) 2 equiv of dienone; (d) reaction at 80 °C; (e) isolated yield; (f) reaction at 23 °C, (g) reaction at 50 °C; (h) 2 equiv of **2g**.

steric bulk on **1** and **2** led to diminished yields in the phospha-Michael reaction, even at elevated reaction temperatures. For example, **4a** was isolated in only 18−20% yield and attempts to prepare the more sterically encumbered phosphorinane **4b** failed altogether. Therefore, we sought a more general and higher-yielding procedure to access biaryl phosphorinanes on scale before exploring new cross-coupling reactions.

The effect of solvents (neat, toluene, DMF, acetonitrile) and additives (acid, base, *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea) on the reaction of **1a** with **2a** was evaluated (Figure 2).[10a,11,12] With all combinations, less than 16 area % of **3a** by

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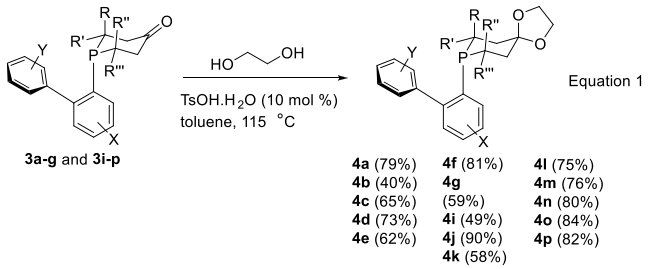
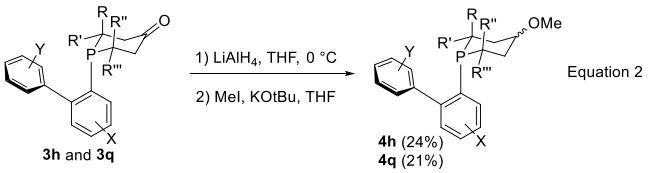
ACS Catal. 2020, 10, 15008−15018

HPLC analysis was formed at 110−150 °C. Fluorinated alcohols, such as 2,2,2-trifluoroethanol (TFE)[13] and HFIP,[13c,14] have been shown to accelerate hetero-Michael additions.[15] While no improvement was observed in TFE, we were pleased to find **3a** was formed in >95 area % in HFIP at 110 °C. Clean conversion to **3a** (89 area %) was retained even when the amount of **2a** was reduced to 1.2 equiv. On the basis of the versatility of the phospha-Michael reaction,[12a] we expect this method to be useful for preparing diversely functionalized phosphorus-containing compounds.

Excited by this simple and high-yielding procedure, we explored the scope of phospha-Michael addition in HFIP (Figure 3). The phosphinanones **3a−q** were observed in excellent yield. The intermediates **3a−g**, derived from additions to **2a**,**b**, were not isolated and were converted directly to the corresponding phosphorinanes **4a−g** (eq 1).[16] Gratifyingly, **4a**,**c**





were isolated in 78 and 65% yields, respectively, over two steps, which is significantly higher than our earlier report of 18−20%.[10a] While we had failed to prepare **4b** previously, it was now isolated in 40% yield.[17]

The phosphinanones **3h−q**, derived from addition to dienones **2c−g**, were isolated in high yield with less than 5% of the uncyclized monoaddition intermediates left at 24 h.[18] A lower reaction temperature (23−50 °C) was suitable for bis-addition to dienones **2c−f**, while the bulkier dienone **2g** required a higher temperature (110 °C) to reach acceptable conversions. The reaction with dienone **2c** formed **3i** in nearly 1:1 dr.[12f] In the reactions with dba (**2f**), the *meso* isomer was the major product formed (**3l−p**), in most cases with >95:5 selectivity.[19] The acid-catalyzed reaction of phenylphosphine ($PhPH_2$) with **2f** was previously studied, and it was determined that the *rac* isomer is the kinetic product while the *meso* isomer is the thermodynamic product.[12f] Under analogous conditions,[20] both *meso* and *rac* isomers were observed in a 3:2 ratio for **3n** and 3:1 for **3o**,**p**. Thus, the thermodynamic products are formed at a much faster rate in HFIP, which results in the higher isolated yield of the major isomer. Only a single diastereomer was observed in the reaction with **2e**. The phosphinanones **3i−p** were converted to phosphorinanes **4i−p** as shown in eq 1. The solid-state structure of **4p** shows the *meso* isomer with the phenyl groups in the equatorial position of the phosphacycle (Figure 3). Ketalization of **3h**,**q** was unsuccessful.[21] Instead, ligands **4h**,**q** were prepared by converting the carbonyl group to methyl ether (eq 2). All primary biaryl phosphines, except that needed to prepare **3m**, are air-stable solids and are conveniently handled on the bench.

Having access to **4a−q** in gram quantities, we evaluated these ligands in the Pd-catalyzed coupling of hindered, electron-deficient anilines with hindered (hetero)aryl halides. The reaction of an *ortho*-substituted aryl bromide (**5**) with an electron-deficient, *ortho*-substituted aniline (**6**) in 1,4-dioxane at 90 °C was chosen as a model reaction to identify an optimal ligand for this challenging class of C−N coupling reactions (Figure 4). Surprisingly, ligands with aryl substituents on the phosphacycle (**4l−q**) formed the coupled product **7** in higher

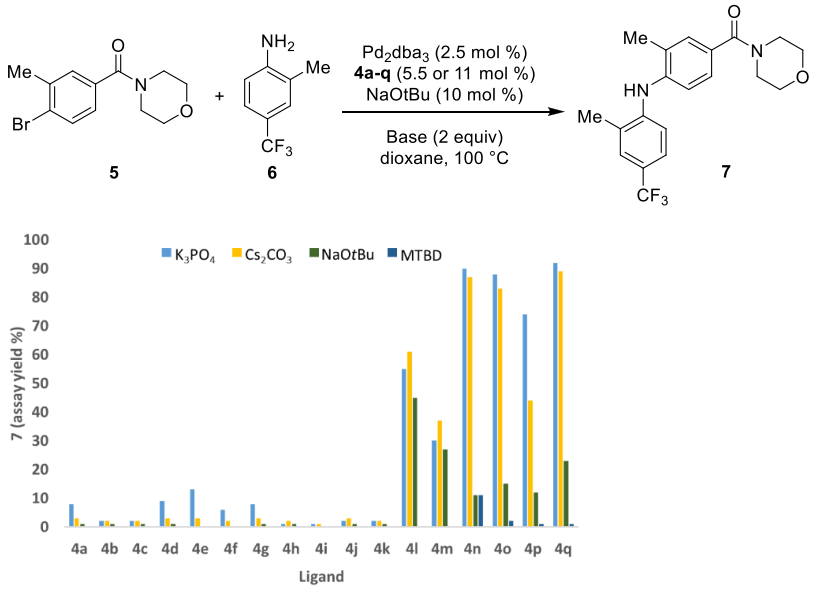


Figure 4. Ligand screening for Pd-catalyzed amination. The *y* axis is the assay yield of **7** in the crude reaction mixture by HPLC analysis using an internal standard, and the *x* axis is the list of ligands. Reactions were conducted with **5** (2.0 μmol), **6** (2.4 μmol), base (4.0 mmol), $Pd_2(dba)_3$ (2.5 mol %), NaO*t*Bu (10 mol %), and **4a−h**,**j** (5.5 mol %) or **4i**,**k−q** (11 mol %) in 1,4-dioxane (60 μL) at 100 °C. $Pd_2(dba)_3$, the ligand, and NaO*t*Bu were prestirred in 1,4-dioxane at 80 °C for 30 min prior to the addition of **5**, **6**, and base.[10a]

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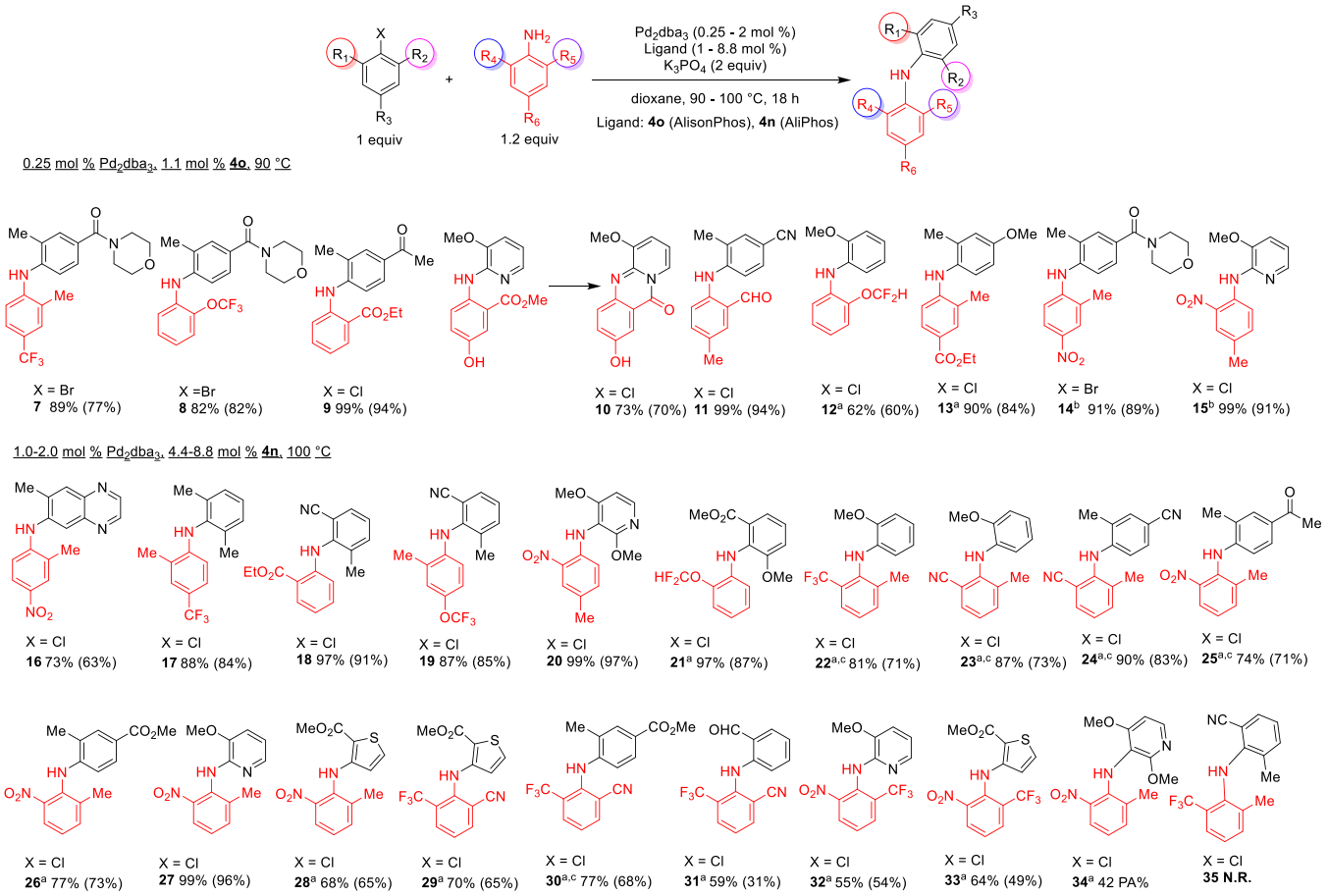

Figure 5. Substrate scope. Unless noted otherwise, all reactions were conducted with (hetero)aryl halide (1 equiv), aniline (1.2 equiv), $Pd_2(dba)_3$ (0.25 mol %), AlisonPhos (1.1 mol %), NaO*t*Bu (1 mol %), and K_3PO_4 (2 equiv) in 1,4-dioxane (0.8 M) at 90 °C for 18 h. $Pd_2(dba)_3$, the ligand, and NaO*t*Bu were prestirred in 1,4-dioxane at 80 °C for 30 min prior to the addition of the substrates. The assay yield of the product in the reaction mixture, determined by HPLC, is reported. The isolated yield is shown in parentheses. Legend: (a) 1.2 equiv of sodium trifluoroacetate was added; (b) AliPhos was used; (c) *t*BuOH was used as the reaction solvent.

yields in comparison to analogous ligands with alkyl substituents. For example, ligands **4g**,**o**, which share a biaryl backbone, produced **7** in 12 and 82% assay yields by HPLC, respectively. Curiously, even the bulky ligand **4q**, expected to be less effective for coupling hindered partners, was superior to the analogues derived from alkyl dienones (**4a**,**d**).

Although a high yield of **7** (>80% assay yield) was observed in the presence of 2.5 mol % of $Pd_2(dba)_3$ with several ligands, conducting the reaction at a lower loading of Pd identified **4o** (AlisonPhos) as the most effective ligand (Table S1). With only 0.25 mol % of $Pd_2(dba)_3$ and 0.5 mol % of AlisonPhos, **7** was observed in 89% assay yield at 90 °C.

Broad substrate scope was observed for coupling of *ortho*-substituted, electron-deficient anilines with *ortho*-substituted electrophiles (**7**−**16**, Figure 5). Aryl bromides (**7**, **8**, and **14**) and chlorides (**9**−**13**) were both suitable electrophiles and formed the coupled products in excellent yields in the presence of only 0.25 mol % of $Pd_2(dba)_3$. Heteroaryl chlorides also formed the coupled products (**10**, **15**, and **16**) in high yields. A variety of commonly encountered functional groups such as amide, CF_3, ester, acetyl, nitrile, aldehyde, $OCHF_2$, and OCF_3 were well tolerated. The reaction displayed excellent selectivity for the N-arylated product in the presence of a hydroxyl group; however, the N-arylated product was found to cyclize to the pyridoquinazolinone (**10**) under the reaction conditions.[22,23]

Initially, the reactions of electron-rich aryl chlorides (**12** and **13**) did not work well under the standard conditions. Electron-rich electrophiles are known to be challenging coupling partners for electron-poor anilines.[2e] Presumably, the electron-rich ArCl forms the less electrophilic oxidative addition intermediate $LPd^{II}(Ar)(Cl)$ in comparison to those formed from electron-poor and -neutral ArCl. Hindered, electron-poor anilines likely do not coordinate effectively to the more electron rich metal center.[2b] We hypothesized that the addition of a chloride scavenger will generate a more electrophilic oxidative addition intermediate and promote coordination of aniline to Pd(II). Indeed, addition of sodium trifluoroacetate (NaTFA)[24] significantly improved the reactions of **12** and **13**.

The reactions of *ortho*-substituted nitro anilines also improved upon modification of the standard reaction conditions. For example, only 75 HPLC peak area % of **14** was observed in the presence of AlisonPhos. We hypothesized that 2-methyl-4-nitroaniline, a highly electron-poor nucleophile, was likely slower to coordinate to the putative oxidative addition complex $(AlisonPhos)Pd^{II}(Ar)(X)$ in comparison to the aforementioned anilines. We reasoned that a less-hindered ligand would promote binding of this aniline to Pd. To our delight, **4n** (AliPhos) enabled the coupling of 2-methyl-4-nitroaniline with a hindered aryl bromide (**14**) and two heteroaryl chlorides (**15** and **16**) in higher yields than were observed with AlisonPhos.

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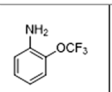
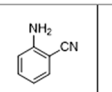
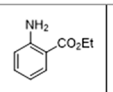
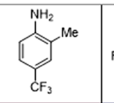
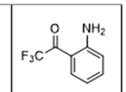
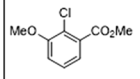
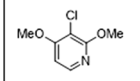
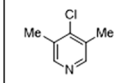
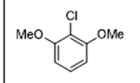
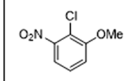
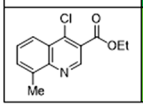
						
	87#	76	94#	68	89#	26
	74	91	95	91	93	51
	23	19	50	16	10	32
	46	90	68	84	82	52
	88	91	94	81	94	46
	60#	60#	79#	33#	66#	43#

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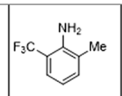
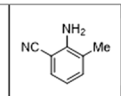
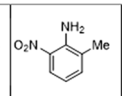
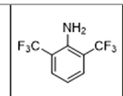
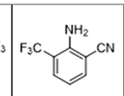
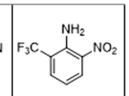
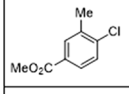
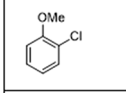
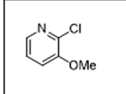
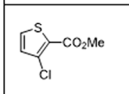
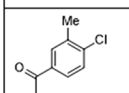
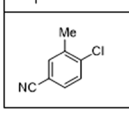
						
	53*	71	92	4	73	40
	67	89*	83*	4	51*	14
	26	86	80	8	30	60
	11	78	67	0	71	46
	68*	86*	80*	0	56*	11
	48	97*	81	0	71	35

Figure 6. High-throughput evaluation ofsubstrate scope for the coupling of (a) *ortho*,*ortho*′-disubstituted ArCl with *ortho*-substituted anilines and (b) *ortho*,*ortho*′-disubstituted anilines with *ortho*-substituted ArCl. All reactions were conducted with (hetero)aryl halide (1 equiv), aniline (1.2 equiv), $Pd_2(dba)_3$ (1.5 mol %), AliPhos (6.6 mol %), NaO*t*Bu (6 mol %), NaTFA (1.2 equiv), and K_3PO_4 (2 equiv) in 1,4-dioxane (0.5 M) at 100 °C for 18 h. $Pd_2(dba)_3$, the ligand, and NaO*t*Bu were prestirred in 1,4-dioxane at 80 °C for 30 min prior to the addition of the substrates. Products were identified by LCMS. The values depicted in each cell are area % values of the desired products in the crude HPLC chromatogram of the reaction. Legend: (#) hydrolyzed product included in yield; (*) reactions were run in *t*BuOH.

AliPhos was also an effective ligand for coupling the more challenging substrate combination, *ortho*,*ortho*′-disubstituted aryl chlorides and *ortho*-substituted anilines, forming **17**−**21** in excellent yields (88−99%), although a higher loading of $Pd_2(dba)_3$ (1.0−1.5 mol %) was required. Impressively, a heteroaryl chloride, 3-chloro-2,4-dimethoxypyridine, could even be coupled with a nitro aniline (**20**).

Next, reactions of *ortho*,*ortho*′-disubstituted, electron-deficient anilines and *ortho*-substituted (hetero)aryl chlorides were evaluated. $Pd_2(dba)_3$ (1.0−1.5 mol %) and AliPhos formed the coupled products in good to excellent yields in reactions with

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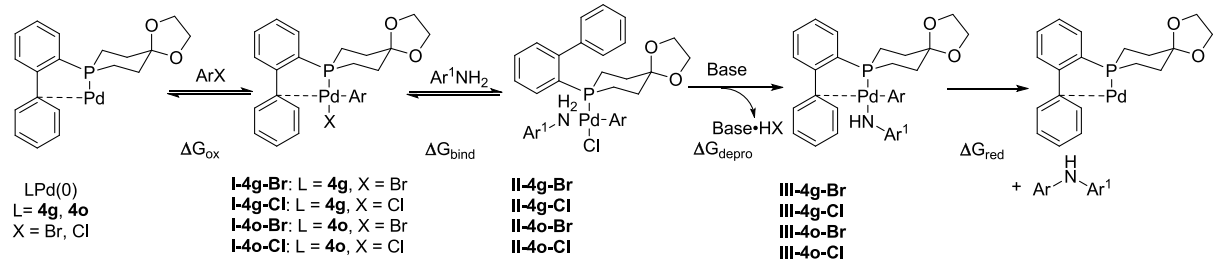
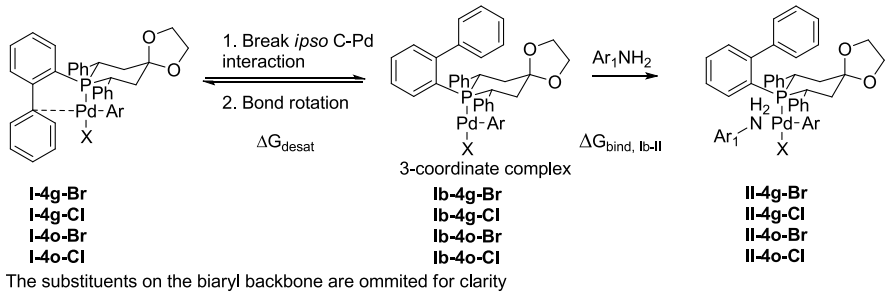
Table 1. Calculated ΔG Values for Catalytic Steps[a]



ligand	X	ΔG_{ox}	ΔG_{bind}	ΔG_{depro}	ΔG_{red}
4g	Cl	−22.8	13.3	−7.5	−10.6
4g	Br	−28.3	13.0	−2.5	−10.6
4o	Cl	−22.1	3.6	−1.5	−7.5
4o	Br	−27.0	2.0	4.2	−7.5

[a]All values given in kcal/mol.

Table 2. Gibbs Free Energy Values for Two-Step Aniline Binding Process[a]



ligand	X	ΔG_{desat}[b]	$\Delta G_{bind,Ib-II}$[c]	ΔG_{bind}[d]
4g	Cl	14.9	−1.7	13.3
4g	Br	13.8	−0.8	13.0
4o	Cl	7.6	−3.9	3.6
4o	Br	7.0	−5.0	2.0

[a]All values given in kcal/mol. [b]Change in Gibbs free energy value for forming a three-coordinate Pd complex from the four-coordinate oxidative addition complex. [c]Change in Gibbs free energy value for aniline binding to the three-coordinate Pd complex. [d]Overall change in Gibbs free energy for aniline binding to the oxidative addition complex.

anilines containing one *ortho*-methyl and one electron-withdrawing *ortho*-substituent (**22**−**28**). In addition to electron-rich (**22** and **23**) and electron-poor aryl chlorides (**24**−**26**), a five-membered heteroaryl chloride was also found to be a suitable electrophile (**28**). To our delight, anilines containing two electron-withdrawing *ortho*-substituents, which are extremely poor nucleophiles, were also effectively coupled in good yield (**29**−**33**). Unfortunately, the reaction of *ortho*,*ortho*′-disubstituted aryl chlorides with *ortho*,*ortho*′-disubstituted anilines remains a limitation (**34** and **35**).

To further explore the utility of our methodology, a "one-pot, multisubstrate screening strategy"[25] was adopted by evaluating two arrays of challenging coupling partners (6 electrophiles × 6 nucleophiles, AliPhos/Pd as catalyst) in a high-throughput experiment (Figure 6a,b).[10a] The products were identified by LCMS, and yields are given in HPLC peak area %. The reactions of *ortho*,*ortho*′-disubstituted aryl chlorides with *ortho*-substituted anilines gave moderate to excellent area % values of the coupled products for most combinations (Figure 6a). A low area % of the coupled products was observed for reactions with 4-chloro-3,5-dimethylpyridine, likely resulting from inhibition by pyridine. In contrast, 51−95 area % of the coupled products was observed for reactions with 3-chloro-2,4-dimethoxypyridine.

Moderate to excellent area % values of the coupled products were also observed for the reactions of *ortho*,*ortho*′-disubstituted anilines with *ortho*-substituted aryl chlorides in most combinations (Figure 6b). Even anilines with two highly electron-withdrawing substituents (CF_3, CN, NO_2) formed the coupled products in synthetically useful yields. Surprisingly, 2,6-bis-(trifluoromethyl)benzenamine was not effectively coupled with any of the electrophiles tested. For electrophiles which were known to be susceptible to hydrodechlorination in the substrate scope, reactions were run in both 1,4-dioxane and *t*BuOH. The reaction with the higher area % of the coupled products is shown.

We were curious about the greater effectiveness of biaryl phosphorinanes derived from aryl dienones in comparison to those derived from alkyl dienones in the C−N coupling reactions described above (Figure 4). The initial rate of reaction with AlisonPhos was independent of the concentration of ArCl and the identity of ArX (X = Cl, Br) but was dependent on the concentration of aniline (Table S2). On the basis of these

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ACS Catal. 2020, 10, 15008−15018

results, transmetalation (i.e., aniline binding and deprotonation) is likely the slowest step in the catalytic cycle.[26]

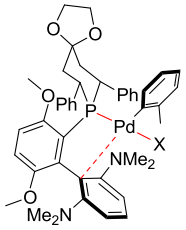
A computational study was undertaken to compare AlisonPhos (**4o**) with **4g**, ligands sharing a common biaryl backbone but having different phosphacycle substitution. Previous reports involving C−N coupling have noted that the formation of the N-bound Pd complex and the energy required to do so are indicative of catalyst performance.[27] With that in mind, the ΔG values were calculated for each step of the catalytic cycle: oxidative addition (ΔG_{ox}), aniline binding (ΔG_{bind}), deprotonation (ΔG_{depro}), and reductive elimination (ΔG_{red}) (Table 1). 1-Bromo-2-methylbenzene, 1-chloro-2-methylbenzene, and aniline **6** were chosen as representative substrate combinations for calculations. Ground state geometries were optimized using DFT (B3LYP-D3/LANL2DZ/6-31G**), with thermal corrections calculated at the same level of theory. Single-point energies were calculated using DFT (B3LYP-D3/LANL2DZ/6-311++G**/COSMO-SMD(dioxane)) and had thermal corrections applied.

The ΔG_{ox} values for forming the oxidative addition complexes **I-4g-Br**, **I-4o-Br** and **I-4g-Cl**, **I-4o-Cl** are comparable, respectively. However, a large difference in ΔG_{bind} is observed. The binding of aniline to **I-4g-Br** is 11 kcal/mol less favorable than to **I-4o-Br**, and binding to **I-4g-Cl** is 10 kcal/mol less favorable than to **I-4o-Cl**.[28] The oxidative addition complexes show endergonic binding to aniline, suggesting relatively low equilibrium concentrations of the aniline-bound Pd complexes; the calculated K_{eq} values are $\sim 10^{-10}$ for **I-4g-Br** and **I-4g-Cl** and $\sim 10^{-3}$ for **I-4o-Br** and **I-4o-Cl** (see the Supporting Information for calculations). Although both deprotonation and reductive elimination steps are thermodynamically favored for **4g**-bound Pd complexes, **4o** forms a superior catalyst. The higher effectiveness of **4o** is likely due to the calculated $\sim 10^{7}$ higher effective concentration of the aniline-bound Pd complexes **II-4o-Br** and **II-4o-Cl** in comparison to **II-4g-Br** and **II-4g-Cl**.

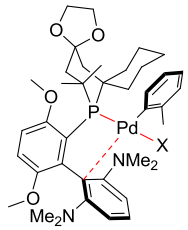
To further understand the difference in ΔG_{bind}, the coordination of aniline to the oxidative addition complex as a two-step process was investigated: first, the formation of a three-coordinate complex from the oxidative addition complex, and second, the binding of aniline to this coordinatively unsaturated complex to form the aniline-bound complex (Table 2). Formation of the three-coordinate complex is less energetically unfavorable for **4o** than for **4g** (ΔG_{desat}). Aniline binding to the three-coordinate complex is favored for **4o** over **4g** ($\Delta G_{bind,\ Ib\text{-}II}$). Further analysis of the oxidative addition complexes shows that the P−Pd bond length is shorter in **I-4o-Br** and **I-4o-Cl** than in **I-4g-Br** and **I-4g-Cl** (Table 3), and the interaction between the *ipso* carbon of the biaryl backbone and Pd is weaker (evidenced by a slightly longer C−Pd distance in **4o**-bound complexes). Contrary to expectation, this suggests that **4o** is more electron-donating than **4g**. The reduced steric bulk of **4o** allows for better coordination of the phosphorus atom to Pd, which produces an apparent increase in electron donation over **4g** (Table S30).[29] These steric and electronic factors stabilize the three-coordinate complex of **4o**, leading to the lower energetic cost for desaturation in comparison to **4g**.

More favorable aniline binding to the **4o**-bound three-coordinate complex over the **4g**-bound complex also results from the decreased steric bulk of **4o**. Steric interactions between the biaryl backbone and phosphorinane substituents of **4g** destabilize both the three-coordinate intermediate (**Ib-4g-Br**) and the aniline-bound complex (**II-4g-Br**). **Ib-4g-Br** shows significant hindrance of the Pd atom that is not present in **Ib-4o-Br**, which likely inhibits aniline coordination (Figure 7). In summary, the more favorable ΔG_{bind} value for **4o** in comparison to that for **4g** arises from (1) increased electron donation from **4o** to the Pd center and (2) decreased steric hindrance in the three-coordinate and aniline-bound Pd complexes of **4o**.

Table 3. Selected Calculated Bond Distances in the Oxidative Addition Complexes (I)[a]



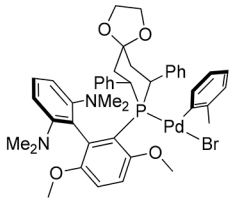
I-4o-X



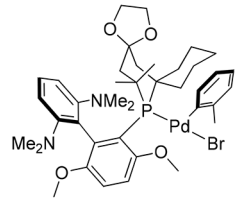
I-4g-X

complex	P−Pd	Pd−X	*ipso* C−Pd
I-4g-Cl	2.42	2.38	2.62
I-4g-Br	2.43	2.56	2.63
I-4o-Cl	2.32	2.38	2.67
I-4o-Br	2.33	2.56	2.67

[a]Distances reported in units of angstroms (Å) taken from optimized geometries.



Ib-4o-Br



Ib-4g-Br

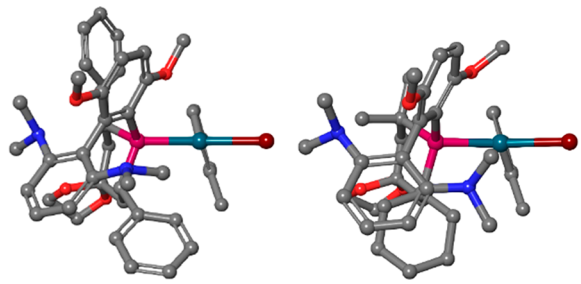


Figure 7. (left) Three-coordinate complex **Ib-4o-Br**, in a view along the Pd−(*o*-tolyl) bond. (right) Three-coordinate complex **Ib-4g-Br**, in a view along the Pd−(*o*-tolyl) bond. Pd atoms are shown in teal. Both the dimethylamino and methoxy subunits of **4g** are in closer proximity to the aniline coordination site in the ground state geometry.

CONCLUSION

In summary, we have developed a general and high-yielding procedure for the synthesis of biaryl phosphorinanes by the double phospha-Michael addition of primary biaryl phosphines to 1,4-dien-3-ones under relatively mild conditions. HFIP was found to be a uniquely effective solvent for the phospha-Michael addition. Unlike previous reports where at least 4 equiv of dienone was required at elevated temperatures (150−160 °C), only 1.2−2.0 equiv of the dienone at 23−110 °C was sufficient. Several phosphorinanes (**4a,c,d,j**), known to be effective for C−

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N and C−O cross-coupling reactions, were isolated in excellent yields on a gram scale. Previously inaccessible, bulky biaryl phosphorinanes, such as **4b**, could also be readily prepared. Our new method provides rapid access to valuable ligands, and several new ligands were prepared on a gram scale.[30]

The biaryl phosphorinanes derived from readily available dba, AlisonPhos (**4o**) and AliPhos (**4n**), are highly effective ligands for Pd-catalyzed couplings of hindered, electron-deficient anilines with hindered (hetero)aryl bromides and chlorides. A broad scope was demonstrated for the following substrate combinations: *ortho*-substituted aryl halides with *ortho*-substituted anilines, *ortho*,*ortho*′-disubstituted aryl halides with *ortho*-substituted anilines, and *ortho*-substituted aryl halides with *ortho*,*ortho*′-disubstituted anilines. Even electron-rich aryl chlorides, typically attenuated electrophiles for coupling with hindered anilines, were found to be suitable coupling partners. Only the coupling of *ortho*,*ortho*′-disubstituted anilines and *ortho*,*ortho*′-disubstituted aryl halides was unsuccessful under the reported conditions.

Computational studies provide insight into the higher effectiveness of biaryl phosphorinanes derived from phospha-Michael addition to aryl dienones (**4o**) in comparison to those from addition to alkyl dienones (**4g**). Coordination of hindered, electron-deficient anilines to the oxidative addition intermediate ((**L**)Pd^{II}(Ar)(X)), prior to deprotonation and reductive elimination, was found to be the key step in enabling the reaction. The aniline coordination proceeds via a two-step process: first, the four-coordinate (**L**)Pd^{II}(Ar)(X) intermediate, containing Pd−P and Pd−C_{ipso} interactions, converts into a three-coordinate (**L**)Pd^{II}(Ar)(X) intermediate that lacks the Pd−C_{ipso} interaction, and second, aniline coordinates to the three-coordinate Pd(II) intermediate. Formation of the three-coordinate complex is less energetically unfavorable for **4o** than for **4g**, and coordination of aniline is more favored to three-coordinate(**4o**)Pd^{II}(Ar)(X) than to (**4g**)Pd^{II}(Ar)(X). The net result is that while coordination of aniline to (**L**)Pd^{II}(Ar)(X) was endergonic for both **4o** and **4g**, coordination to (**4o**)-Pd^{II}(Ar)(X) was calculated to be ∼10 kcal/mol less unfavorable, which supports the higher effectiveness of **4o**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c04280.

Compiled CN experiments (PDF)

Solid-state structures (CIF)

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): All authors are AbbVie employees and may own AbbVie stocks.

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■ REFERENCES

(1) (a) Devendar, P.; Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food Chem.* **2018**, *66*, 8914−8934. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (c) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085. (d) Onoabedje, E. A.; Okoro, U. C. Ligand-Supported Palladium-Catalyzed Cross-Coupling Reactions of (Hetero) Aryl Chlorides. *Synth. Commun.* **2019**, *49*, 2117−2146.

(2) (a) Hartwig, J. F. Electronic Effects on Reductive Elimination to Form Carbon-Carbon and Carbon-Heteroatom Bonds from Palladium(II) Complexes. *Inorg. Chem.* **2007**, *46*, 1936−1947. (b) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational, and Synthetic Investigation. *J. Am. Chem. Soc.* **2007**, *129*, 13001−13007. (c) 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. (d) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. Water-Mediated Catalyst Preactivation: An Efficient Protocol for C-N Cross-Coupling Reactions. *Org. Lett.* **2008**, *10*, 3505−3508. (e) Pompeo, M.; Farmer, J. L.; Froese, R. D. J.; Organ, M. G. Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a Pd-PEPPSI-IPentCl- o-Picoline Catalyst. *Angew. Chem., Int. Ed.* **2014**, *53*, 3223−3226.

(3) (a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. (b) Hartwig, J. F., Shaughnessy, K. H., Shekhar, S., Green, R. A., Palladium-Catalyzed Amination of Aryl Halides. In *Organic Reactions*; Wiley: 2019; pp 853−958. (c) Hoi, K. H.; Çalimsiz, S.; Froese, R. D. J.; Hopkinson, A. C.; Organ, M. G. Amination with Pd NHC Complexes: Rate and Computational Studies Involving Substituted Aniline Substrates. *Chem. - Eur. J.* **2012**, *18*, 145−151.

(4) (a) Hu, H.; Qu, F.; Gerlach, D. L.; Shaughnessy, K. H. Mechanistic Study of the Role of Substrate Steric Effects and Aniline Inhibition on the Bis(trineopentylphosphine)palladium(0)-Catalyzed Arylation of Aniline Derivatives. *ACS Catal.* **2017**, *7*, 2516−2527. (b) Raders, S. M.; Moore, J. N.; Parks, J. K.; Miller, A. D.; Leißing, T. M.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. Trineopentylphosphine: A Conformationally Flexible Ligand for the Coupling of Sterically Demanding Substrates in the Buchwald−Hartwig Amination and Suzuki−Miyaura Reaction. *J. Org. Chem.* **2013**, *78*, 4649−4664.

(5) Electron-rich or -neutral anilines are primarily employed in the known methods for coupling hindered anilines and ArX. See refs 4 and 6 for examples.

(6) (a) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. Pd-Catalyzed Aryl Amination Mediated by Well Defined, N-Heterocyclic Carbene (NHC)−Pd Precatalysts, PEPPSI. *Chem. - Eur. J.* **2008**, *14*, 2443−2452. (b) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. High Turnover Number and Rapid, Room-Temperature Amination of Chloroarenes Using Saturated Carbene Ligands. *Org. Lett.* **2000**, *2*, 1423−1426. (d) Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C−N Cross-Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 4500−4507. (e) Morimoto, Y.; Shimizu, S.; Mokuya, A.; Ototake, N.; Saito, A.; Kitagawa, O. Enantioselective Synthesis of N−C Axially Chiral Indoles Through Chiral Palladium-Catalyzed 5-Endo-Hydroaminocyclization. *Tetrahedron* **2016**, *72*, 5221−5229. (f) Janke, J.; Ehlers, P.; Villinger, A.; Langer, P. Regioselective Synthesis of Thieno[3,2-b]quinolones by Acylation/Two-Fold Buchwald−Hartwig Reactions. *Eur. J. Org. Chem.* **2019**, *2019*, 7255−7263.

(7) Hagmann, W. K.; Nargund, R. P.; Blizzard, T. A.; Josien, H.; Biju, P.; Plummer, C. W.; Dang, Q.; Li, B.; Lin, L. S.; Cui, M.; Hu, B.; Hao, J.; Chen, Z. *Preparation of Tricyclic Compounds as GPR40 Agonists for Use in Treating Diabetes and Associated Conditions*; Merck Sharp & Dohme Corp., 2014.

(8) (a) Nguyen, B. H.; Perkins, R. J.; Smith, J. A.; Moeller, K. D. Solvolysis, Electrochemistry, and Development of Synthetic Building Blocks from Sawdust. *J. Org. Chem.* **2015**, *80*, 11953−11962. (b) Thalhammer, A.; Mecinović, J.; Loenarz, C.; Tumber, A.; Rose, N. R.; Heightman, T. D.; Schofield, C. J. Inhibition of the Histone Demethylase JMJD2E by 3-Substituted Pyridine 2,4-Dicarboxylates. *Org. Biomol. Chem.* **2011**, *9*, 127−135.

(9) (a) Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. An Inexpensive and Efficient Copper Catalyst for N-Arylation of Amines, Amides and Nitrogen-Containing Heterocycles. *Adv. Synth. Catal.* **2006**, *348*, 2197−2202. (b) Tassone, J. P.; England, E. V.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. PhPAd-DalPhos: Ligand-Enabled, Nickel-Catalyzed Cross-Coupling of (Hetero)aryl Electrophiles with Bulky Primary Alkylamines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2485−2489. (c) Lavoie, C. M.; Stradiotto, M. Bisphosphines: A Prominent Ancillary Ligand Class for Application in Nickel-Catalyzed C−N Cross-Coupling. *ACS Catal.* **2018**, *8*, 7228−7250. (d) Modak, A.; Nett, A. J.; Swift, E. C.; Haibach, M. C.; Chan, V. S.; Franczyk, T. S.; Shekhar, S.; Cook, S. P. Cu-Catalyzed C−N Coupling with Sterically Hindered Partners. *ACS Catal.* **2020**, *10*, 10495−10499.

(10) (a) Laffoon, S. D.; Chan, V. S.; Fickes, M. G.; Kotecki, B. J.; Ickes, A.; Henle, J.; Napolitano, J. G.; Franczyk, T. S.; Dunn, T. B.; Barnes, D. M.; Haight, A. R.; Henry, R. F.; Shekhar, S. Pd-Catalyzed Cross-Coupling Reactions Promoted by Biaryl Phosphorinane Ligands. *ACS Catal.* **2019**, *9*, 11691−11708. (b) Barnes, D. M.; Shekhar, S.; Dunn, T. B.; Barkalow, J. H.; Chan, V. S.; Franczyk, T. S.; Haight, A. R.; Hengeveld, J. E.; Kolaczkowski, L.; Kotecki, B. J.; Liang, G.; Marek, J. C.; McLaughlin, M. A.; Montavon, D. K.; Napier, J. J. Discovery and Development of Metal-Catalyzed Coupling Reactions in the Synthesis of Dasabuvir, an HCV-Polymerase Inhibitor. *J. Org. Chem.* **2019**, *84*, 4873−4892.

(11) (a) Brenstrum, T.; Clattenburg, J.; Britten, J.; Zavorine, S.; Dyck, J.; Robertson, A. J.; McNulty, J.; Capretta, A. Phosphorinanes as Ligands for Palladium-Catalyzed Cross-Coupling Chemistry. *Org. Lett.* **2006**, *8*, 103−105. (b) Ullah, E.; McNulty, J.; Larichev, V.; Robertson, A. J. P-Phenyl-2,2,6,6-tetramethylphosphorinan-4-ol: An Air-Stable P,O-Type Ligand for Palladium-Mediated Cross-Coupling Reactions. *Eur. J. Org. Chem.* **2010**, *2010*, 6824−6830. (c) Ullah, E.; McNulty, J.; Robertson, A. A Novel P,O-type Phosphorinane Ligand for the Suzuki-Miyaura Cross-Coupling of Aryl Chlorides. *Tetrahedron Lett.* **2009**, *50*, 5599−5601.

(12) (a) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. The Phospha-Michael Addition in Organic Synthesis. *Eur. J. Org. Chem.* **2006**, *2006*, 29−49. (b) Rampal, J. B.; Berlin, K. D.; Edasery, J. P.; Satyamurthy, N.; Van der Helm, D. Carbon-Phosphorus Heterocycles. Synthesis and Conformational Analysis of Alkyl-Substituted 1,2,6-Triphenyl-4-Phosphorinanones and Derivatives. *J. Org. Chem.* **1981**, *46*, 1166−1172. (c) Welcher, R. P.; Day, N. E. 4-Phosphorinanones. II. *J. Org. Chem.* **1962**, *27*, 1824−1827. (d) Johnson, G. A.; Wystrach, V. P. 4-PHOSPHORINANONES. *J. Am. Chem. Soc.* **1960**, *82*, 4437−4438. (e) Huang, Y.; Pullarkat, S. A.; Teong, S.; Chew, R. J.; Li, Y.; Leung, P.-H. Palladacycle-Catalyzed Asymmetric Intermolecular Construction of Chiral Tertiary P-Heterocycles by Stepwise Addition of H−P−H Bonds to Bis(enones). *Organometallics* **2012**, *31*, 4871−4875. (f) Doherty, R.; Haddow, M. F.; Harrison, Z. A.; Orpen, A. G.; Pringle, P. G.; Turner, A.; Wingad, R. L. Bulky 4-Phosphacyclohexanones: Diastereoselective Complexations, Orthometallations and Unprecedented [3.1.1]Metallabicycles. *Dalton Trans.* **2006**, 4310−4320.

(13) (a) Wencel-Delord, J.; Colobert, F. A Remarkable Solvent Effect of Fluorinated Alcohols on Transition Metal Catalysed C−H Functionalizations. *Org. Chem. Front.* **2016**, *3*, 394−400. (b) Matsugami, M.; Yamamoto, R.; Kumai, T.; Tanaka, M.; Umecky, T.; Takamuku, T. Hydrogen Bonding in Ethanol−Water and Trifluoroethanol−Water Mixtures Studied by NMR and Molecular Dynamics Simulation. *J. Mol. Liq.* **2016**, *217*, 3−11. (c) Molinaro, A.; De Castro, C.; Lanzetta, R.; Manzo, E.; Parrilli, M. Solvent Effect on the Isomeric Equilibrium of Carbohydrates: The Superior Ability of 2,2,2-Trifluoroethanol for Intramolecular Hydrogen Bond Stabilization. *J. Am. Chem. Soc.* **2001**, *123*, 12605−12610.

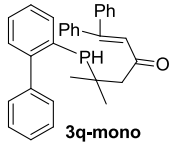
(14) (a) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. *Nat. Rev. Chem.* **2017**, *1*, 0088. (b) Sinha, S. K.; Bhattacharya, T.; Maiti, D. Role of Hexafluoroisopropanol in C−H activation. *React. Chem. Eng.* **2019**, *4*, 244−253.

(15) (a) Fedotova, A.; Crousse, B.; Chataigner, I.; Maddaluno, J.; Rulev, A. Y.; Legros, J. Benefits of a Dual Chemical and Physical Activation: Direct aza-Michael Addition of Anilines Promoted by Solvent Effect under High Pressure. *J. Org. Chem.* **2015**, *80*, 10375−10379. (b) Fedotova, A.; Kondrashov, E.; Legros, J.; Maddaluno, J.; Rulev, A. Y. Solvent Effects in the Aza-Michael Addition of Anilines. *C. R. Chim.* **2018**, *21*, 639−643. (c) Wang, L.; Chen, J.; Huang, Y. Highly Enantioselective Aza-Michael Reaction between Alkyl Amines and *β*-Trifluoromethyl *β*-Aryl Nitroolefins. *Angew. Chem., Int. Ed.* **2015**, *54*, 15414−15418.

(16) See Figure S1 for a discussion.

(17) See Figure S2 for a discussion on the potential role of HFIP in improving the yields of **4a−c**.

(18) Except for **3q**, where 25% of an uncyclized monoaddition intermediate (**3q-mono**) was observed.



3q-mono

(19) The identity of the isolated product as the *meso* isomer for **3n−p** was confirmed by ^{1}H NMR.

(20) 20 mol % TsOH·H_2O, MeCN, 80 °C, 16 h.

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ACS Catal. 2020, 10, 15008−15018

(21) We have observed that ketalization is significantly slower for bulkier phosphacycles. Ketalization was successful for ligands with the same biaryl backbone as **3h** but with less bulky phosphacycle substituents (**3g**,**o**). For **3h**, we suspect that ketalization is very slow and NMe_2 gets protonated instead of the carbonyl group, resulting in poor reactivity. With **3q**, formation of the primary biaryl phosphine **1q** was observed in the presence of acid.
(22) The N-arylated product was found to cyclize under the reaction conditions to the pyrido-quinazolinone product (**10**). For a C−N coupling with 2,3-dichloropyridine followed by cyclization, see: Hostyn, S.; Van Baelen, G.; Lemiere, G. L. F.; Maes, B. U. W. Synthesis of α-Carbolines Starting from 2,3-Dichloropyridines and Substituted Anilines. *Adv. Synth. Catal.* **2008**, *350*, 2653−2660.
(23) No background S_NAr reaction is observed on the basis of control experiments in the absence of Pd.
(24) Beutner, G. L.; Coombs, J. R.; Green, R. A.; Inankur, B.; Lin, D.; Qiu, J.; Roberts, F.; Simmons, E. M.; Wisniewski, S. R. Palladium-Catalyzed Amidation and Amination of (Hetero)aryl Chlorides under Homogeneous Conditions Enabled by a Soluble DBU/NaTFA Dual-Base System. *Org. Process Res. Dev.* **2019**, *23*, 1529−1537.
(25) (a) Satyanarayana, T.; Kagan, H. B. The Multi-Substrate Screening of Asymmetric Catalysts. *Adv. Synth. Catal.* **2005**, *347*, 737−748. (b) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. Investigation of a New Family of Chiral Ligands for Enantioselective Catalysis via Parallel Synthesis and High-Throughput Screening. *J. Org. Chem.* **1998**, *63*, 5312−5313.
(26) (a) Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. Investigations of Pd-Catalyzed ArX Coupling Reactions Informed by Reaction Progress Kinetic Analysis. *J. Org. Chem.* **2006**, *71*, 4711−4722. (b) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C. A General Method for Palladium-Catalyzed Reactions of Primary Sulfonamides with Aryl Nonaflates. *J. Org. Chem.* **2011**, *76*, 4552−4563.
(27) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. Pd-Catalyzed N-Arylation of Secondary Acyclic Amides: Catalyst Development, Scope, and Computational Study. *J. Am. Chem. Soc.* **2009**, *131*, 16720−16734.
(28) The O-bound oxidative addition complexes (**IV-4g-Br** and **IV-4o-Br**, see the Supporting Information) were also considered as potential intermediates in the sequence; these complexes are ∼1 kcal/mol higher in energy than the *ipso* C-bound complexes and thus do not change the overall reaction energy pathway.
(29) (a) Kendall, A. J.; Zakharov, L. N.; Tyler, D. R. Steric and Electronic Influences of Buchwald-Type Alkyl-JohnPhos Ligands. *Inorg. Chem.* **2016**, *55*, 3079−3090. (b) Chen, L.; Ren, P.; Carrow, B. P. Tri(1-adamantyl)phosphine: Expanding the Boundary of Electron-Releasing Character Available to Organophosphorus Compounds. *J. Am. Chem. Soc.* **2016**, *138*, 6392−6395.
(30) Ligands **4a**,**d**,**j**,**n** will be available through Millipore-Sigma in early 2021.

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