Empirical and Computational Insights into N-Arylation Reactions Catalyzed by Palladium meta-Terarylphosphine Catalyst


An in situ generated Pd–Cy*Phine catalyst has been successfully applied to the N-arylation of primary and secondary amines, and it exhibited high performance across multiple substrate classes. The performance induced by the meta-terarylphosphine motif of the Cy*Phine ligand for C–N cross-coupling displayed only subtle differences to that of its biarylphosphine congener XPhos. DFT studies demonstrated comparable reaction energetics in the catalytic cycle steps for both Pd–Cy*-Phine and Pd–XPhos, which was consistent with previous findings. The computational investigation also indicated that a putative rate-determining step occurred after amine binding, which was likely to have annulled the expected benefits of having a meta-terarylphosphine ligand architecture.

Introduction

Palladium-catalyzed C–N cross-coupling (also referred to as Buchwald–Hartwig amination)[1,2] has revolutionized the synthesis of N-arylated alkyl and aryl amines industrially[3–5] and academically.[6] There exists a plethora of literature that describes palladium-catalyzed N-arylation by using a variety of ligand designs.[6–11] Among the different ligand architectures, phosphine-based ligands are the most commonly employed.[7–10] The structure of these phosphine ligands range from simple motifs, such as trialkylphosphines (e.g., tBu3P),[7] to more sophisticated designs, such as triaminophosphines (i.e., P(Ni(Bu)CH2CH2)2N)[10ab] ferrocenyl monophosphines (e.g., Q-Phos),[10c,16] and ferrocenyl diphosphines (e.g., DIBP[16e] and Josiphos[16b]). Nonetheless, bulky, multiringed phosphines featuring N-substituted heterocycles (e.g., cataCIXium PlentB[16d] or biaryl-based backbones, pioneered by the groups of Beller[13] and Buchwald[13], respectively, have proven to be among the most versatile and popular ligand types.

Despite considerable advancements, the eclectic collection of N-arylation catalysts often operate under different reaction conditions for different substrate classes, or their performance may be limited to specific substrate classes or types. Palladium catalysts that utilize ligands such as tBu3P, Q-Phos, and N-heterocyclic carbenes[11] have the propensity to be excellent for the N-arylation of secondary amines, but less reactive towards the coupling of primary amines.[2b] Similarly, RuPhos is touted as the recommended option for the palladium-catalyzed N-arylation of secondary amines,[2b,8] whereas ligands such as Josiphos and BrettPhos are very effective for the N-arylation of primary amines, demonstrating outstanding activity and selectivity.[2a,8,9] The relationship between these ligand designs and their reactivity profile is often unclear. Further complications arise with numerous other factors that play influential roles (e.g., choice of bases, amines, palladium sources, solvent, and temperature), which could significantly affect the reactivity outcome and the mechanism of palladium-catalyzed N-arylation reactions.[14]

Recent studies by Fey et al.[15] and Norrby et al.[16] provided valuable insight into the mechanism of the coupling of phenylbromide and morpholine. Key findings by Fey et al. included evidence from DFT studies of a β-hydride elimination pathway that competed with reductive elimination (RE).[15] However, in this instance, the use of bulky phosphine ligands disfavored the former pathway. Norrby et al. investigated the effects of different bases in various solvents for palladium-catalyzed N-arylation by employing either mono- (tBu3P) or bidentate (2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP)) ligands.[16] Computationally, the effectiveness of the use of a tert-butoxide base in both polar and nonpolar solvents was rationalized.
To date, the palladium catalyst system that provides the widest substrate scope (accessing both primary and secondary amines), with high selectivity and reactivity, is the concurrent use of RuPhos and BrettPhos ligands. This combination approach effectively manifests complementary catalysis of different active species during the reaction. [17, 18]

Recently, the monodentate meta-terarylphosphine architecture has proven to be an excellent promoter of palladium-catalyzed C-C, C-B, and C-F cross-coupling reactions, exhibiting a significant advantage over their respective biarylphosphine analogues. [19]

Reactions such as copper-free Sonogashira coupling, [20] the Mizoroki–Heck reaction, [21] decarboxylative coupling, [22] and borylation/Suzuki–Miyaura sequences [23] have recently been reported with the Cy*Phine ligand (Figure 1). Advancements in nucleophilic aryl fluorination have been demonstrated by using the HGPhos and AlPhos ligands. [24] Encouraged by the excellent performance and broad applicability of Pd–Cy*Phine in various C-C bond-forming reactions (Scheme 1), [20–23] we envisaged that this system might also achieve enhanced performance for N-arylation.

Results and Discussion

A survey of literature conditions for palladium-catalyzed N-arylation reactions revealed several notable trends, such as the use of [Pd(dba)3] (dba = dibenzylideneacetone) and Pd(OAc)2, with tBuONa or lithium bis(trimethylsilyl)amide (LiHMDS) as the base. Also, these combinations were proven effective in dioxane, toluene, or THF solvents. In our studies, we focus on aryl chlorides because they are more cost-effective and readily available than other aryl halides and pseudo-halides. Therefore, for our initial comparative studies of the use of Pd–Cy*Phine in N-arylation, we chose to investigate the coupling of aniline (S2) with 3-chloropyridine (Table 1). N-Arylation with chloroaniline proved to be very successful, providing 3c in 99% yield with [Pd2(dba)3], tBuONa in THF; toluene was also evaluated, but was less proficient for benzyl and secondary alkyl amines (Table 1, 3a–3d; yields shown in parentheses). [25] Encouraged by the success of our initial results, we proceeded to investigate the scope and applicability of these general conditions to a more diverse set of substrates. Selected results are given in Table 1 and an extended range of substrates is provided in the Supporting Information (Table S1 A–ok).

An evaluation of the substrate diversity revealed good to excellent catalyst performance across all four classes of amine.

**Table 1.** The representative scope of the Pd-Cy*Phine catalyzed N-arylation of aryl chlorides or heteroaryl chlorides using the general protocol. [a]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>3a</td>
<td>90% (24%)</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
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<tr>
<td>3b</td>
<td>99% (25%)</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3c</td>
<td>99% (92%)</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3d</td>
<td>99% (94%)</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3e</td>
<td>81%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3f</td>
<td>88%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3g</td>
<td>84%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3h</td>
<td>99%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3i</td>
<td>86%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3j</td>
<td>65% [25]</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3k</td>
<td>89%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
</tr>
<tr>
<td>3l</td>
<td>93%</td>
<td>tBuONa (1.4 equiv) in THF, 100 °C, 15 h</td>
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</table>

[a] Unless otherwise stated, the reactions were carried out with alkyl or aryl amines (0.6 mmol), aryl chlorides or heteroaryl chlorides (0.5 mmol), Pd2(dba)3 (1 mol%), Cy*Phine (4 mol%), tBuONa (1.4 equiv) in THF (0.75 mL) at 100 °C for 15 h. Isolated yield (average of two runs). [b] Toluene was used instead of THF; yields were obtained by 1H NMR using hexamethylbenzene as an internal standard. [c] 2 mol% of [Pd2(dba)3] and 8 mol% Cy*Phine were used instead.
substrates under the same reaction conditions. However, the results also indicated that Pd–Cy*Phine was comparatively less effective when the amines were at the extremes of being electron rich (3e, 3i), conjugated (3g), or electron poor (3k). Challenges also arose with increasing complexity of the chloro-hetero-coupling partner increased (3b > 3f > 3j). Because these trends are commonly exhibited by other state-of-the-art palladium catalysts, our results indicate that Pd–Cy*Phine is competitive in C–N cross-coupling reactions.

The performance similarity between Pd–Cy*Phine and Pd–XPhos in N-arylation reactions became evident after an evaluation under identical conditions (Table 2). From the comparison,

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Pd-Cy*Phine [b]</th>
<th>Pd-XPhos [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3e</td>
<td>&gt; 99 (83:0:17)</td>
<td>&gt; 99 (89:0:11)</td>
</tr>
<tr>
<td>2</td>
<td>3m</td>
<td>76 (64:4:8)</td>
<td>79 (47:29:3)</td>
</tr>
<tr>
<td>3</td>
<td>3n</td>
<td>&gt; 99 (99)</td>
<td>&gt; 99 (99)</td>
</tr>
</tbody>
</table>

[a] Each reaction was carried out with amine (1.2 mmol), aryl chloride or heteroaryl chloride (1.0 mmol), Pd2(dba)3 (1 mol%), Cy*Phine or XPhos (4 mol%), tBuONa (1.4 equiv) in THF (1.5 mL) at 100 °C for 1 hour. [b] Values referred to substrate conversion and product(s) distribution in parentheses. [c] Product ratio represents the ratio of mono-N-arylation vs. di-N-arylation vs. proto-dehalogenation observed for both Pd-Cy*Phine and Pd-XPhos catalyst systems.

The study was initiated with the investigation of four key reaction steps in the generally accepted catalytic cycle for N-arylation by using S1 and S2 as model substrates (Figure 2). Consideration of both the cis and trans arrangements of complexes LM2, LM3, and LM4 and their respective spatial arrangements are detailed in Figure S1 in the Supporting Information. For clarity, the discussion herein is based on the more likely cis conformers.

The Gibbs free energies of activation (ΔG*) and reaction (ΔG) at 298 K of the steps in the catalytic cycle for both Pd–Cy*Phine and Pd–XPhos are provided in Table S1 in the Supporting Information. For clarity, only the Gibbs free energy reaction profile for the N-arylation mediated by the cis conformer of Pd–Cy*Phine is shown in Figure 3. A cursory inspection revealed that the AB step had the highest barriers (ΔG* = 123.3 and 84.6 kJ mol−1 for Pd–Cy*Phine and Pd–XPhos, respectively) and appeared to be rate determining. However, an alternative fate is plausible for LM2 with a potentially lower barrier for both Pd–XPhos and Pd–Cy*Phine. Drawing on our insights from the previous study on the mechanism of copper-free Sonogashira cross-coupling reactions, a likely possibility is a BAB pathway for LM2 to LM3A (Figure 3, blue). In this case, BAB for Cy*Phine has a much lower barrier of 25.7 kJ mol−1, corresponding to the coordination of tBuO− to S2, which provides a viable off-cycle route of LM2 towards the end products. The BAB barriers for Pd–XPhos are expected to be same to those of Pd–Cy*Phine because the reactants in the pathway are common and do not include the catalyst. The existence of the off-cycle BAB pathway is consistent with the results reported by Shekhar and Hartwig,[28] who show that reaction rates are independent of the concentration of base.

Other unlikely but possible fates of LM2 considered include 1) direct binding of the tBuO− base, 2) C–P bond rotation, and 3) deamorphen rearrangement (DR) of the ligand.

The direct binding of the tBuO− base is likely to progress through low barrier and highly exergonic steps (Table S2 in the Supporting Information); this was attributed by Norbby et al.[16] and McMullin et al.[29] to be a diffusion-controlled process. Although this is energetically favorable, a mechanism that describes the removal of coordinated Cl− from the Pd center has yet to be elucidated. Second, the rotation of the C–P bond in LM2 can facilitate subsequent amine binding, as proposed by Buchwald et al.[14,30] It is noteworthy that this torsional rotation
was shown to have a barrier of approximately 77 kJ mol\(^{-1}\), as calculated by Barder et al.,\(^{[30]}\) which was higher than the barrier calculated for BAB. This process was also calculated to be endergonic for Pd–XPhos and Pd–Cy*Phine, by 39.8 and 47.7 kJ mol\(^{-1}\), respectively (Table S2 in the Supporting Information).

Intermediate LM2 may also undergo off-cycle DR pathways, in which the ligand L may be modified. In our previous study on copper-free Sonogashira cross-coupling, the influence of the \(\text{meta}\)-terarylphosphine architecture was shown to hinder the deleterious off-cycle DR of the catalyst.\(^{[27]}\) Herein, the barriers for DR were calculated to be notably higher than that for the AB step, at 102.1 and 164.7 kJ mol\(^{-1}\) for Pd–XPhos and Pd–Cy*Phine, respectively. The availability of the low-barrier BAB off-cycle pathway facilitates rapid conversion of LM2 into LM3A and other post-amine-added intermediates, minimizing the buildup of LM2 to undergo inefficient DR processes and catalyst modification. A summary of the Gibbs free energies of the possible reactions of LM2 along with the barriers (where available) is provided in Table S2 in the Supporting Information for reference and comparison.

In comparison to the DFT studies by Fey et al.\(^{[15]}\) and Norrby et al.\(^{[16]}\) our investigation is differentiated primarily by the use of a different catalyst architecture, as well as a different amine; both of which are expected to impact on the outcome significantly. For example, morpholine (p\(K_a\) = 8.49), the system studied by Norrby et al.,\(^{[16]}\) is more Lewis basic than \(\text{S}_2\) (p\(K_a\) = 4.6),\(^{[31]}\) which is used in our models. As a result, the former was computationally assessed to only deprotonate after coordination to palladium, but such a determination with \(\text{S}_2\) was less clear. Norrby et al. addressed the possible sequence of events as follows: 1) a base coordinates to palladium and the halide is eliminated sequentially; or 2) an external base deprotonates the amine, which stays coordinated to palladium. The binding of the weaker proton donor, morpholine, to palladium is necessary for subsequent deprotonation by \(t\text{BuOH}\), but this may not be the case for \(\text{S}_2\), for which our proposed off-cycle BAB route is independent of the catalyst. A common consideration in the mechanistic proposal of Norrby et al.\(^{[16]}\) is the dissociation of the coordinated halide from the palladium center before the coordination to palladium. In our mechanistic proposal, we considered an alternative scenario, in which a five-coordinate palladium complex is formed, and the halide, Cl\(^{-}\), is removed along with the protonated base, \(t\text{BuOH}\), as a hydrogen-bonded complex, \(t\text{BuOH}−\text{Cl}\). Pd–Cl dissociation in the style of Norrby et al.\(^{[16]}\) is not considered because the Pd–Cl bond is much stronger than the Pd–Br bond; the bond dissociation energy of Pd\(^{II}\)–Cl was calculated...
by Houk et al.\textsuperscript{[22]} to be 384.5 kJ mol\(^{-1}\); this value is too high for this process to be feasible given the mild experimental conditions.

The varying benefits of different ligand architectures can be drawn when our investigation is compared with that by Fey et al.\textsuperscript{[15]} The steric bulk of the \(\text{Bu}_3\text{P}\) ligand was proposed to prevent unwanted side reactions, such as dimerization and \(\beta\)-hydride elimination. In the case of Pd–Cy*Phine, the Cy*Phine ligand may prevent the deleterious off-cycle DR of the catalyst, which is not a factor for \(\text{Bu}_3\text{P}\) systems.

The barriers for the post-amine binding steps (amine deprotonation (AD) and RE, 69.2 and 73.9 kJ mol\(^{-1}\), respectively) are calculated to be significantly higher than that of the BAB barrier of 25.7 kJ mol\(^{-1}\) (Figure 3). Despite the differences, the assignment of the rate-determining step and identification of the resting state of the catalyst are difficult owing to similar activation barriers for AD and RE. Furthermore, assignment of the resting state will also depend on the nature of the amine. Nonetheless, with the putative rate-determining step for N-arylation is likely to occur post-amine addition; this suggests that biarylphosphine ligands (i.e., XPhos) are not likely to be susceptible to unproductive off-cycle events and their LM2 state.\textsuperscript{[23]}

The increased distance between the palladium center and ring B for LM3, LM3A, LM3B, and LM4 (Table S3 in the Supporting Information) further supports the rationale. This evidence, together with similar reaction barriers between Pd–Cy*Phine and Pd–XPhos, corroborate the similar performance observed for Pd–Cy*Phine and Pd–XPhos in N-arylation catalysis.

As multiringed phosphine ligands are being used more widely, gaining access to a relevant mechanistic understanding of the 3\(^{rd}\) substitution becomes more critical to facilitate catalyst selection and development. As such, efforts in our group to apply this knowledge for the benefit of other cross-coupling applications are underway.

### Conclusion

We have demonstrated that the meta-terarylphosphine-based catalyst, Pd–Cy*Phine, is broadly efficient for N-arylation reactions. Generic reaction conditions were developed to couple four classes of amines with heteroaryl chlorides. However, the performance exhibited was comparable to that of its biarylphosphine-based analogue, Pd–XPhos, for which DFT studies were employed to rationalize the results. Computational data indicated that the rate-determining step of the Pd–Cy*Phine catalytic cycle, occurring after the amine-binding step, negated the benefits of having the meta-terarylphosphine ligand architecture. This information provides a greater understanding of how the mechanistic component of various cross-coupling reactions correlates with the catalyst architecture. Despite the many complexities involved in cross-coupling reactions, the evidence presented herein can serve as a general guideline to facilitate catalyst selection and development for N-arylation and other cross-coupling applications.

### Experimental Section

#### General procedure for the N-arylation of alkyld and aryl amines

A sealable reaction tube was charged with [Pd(dba)\(_2\)] (0.001 equiv), Cy*Phine (0.004 equiv), \(\text{Bu}_2\text{ONa}\) (1.4 equiv), and THF (0.666 ml). Next, the aryl halide (0.5 mmol) and amine (1.2 equiv) were added to this reaction vial, which was sealed with a Teflon-lined septum and stirred at 100 °C for 15 h. The reaction mixture was then cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of Celite. The solvent of the combined organic extracts was removed under reduced pressure. The crude product was purified by column chromatography on silica gel to afford the N-arylated product. The identity and purity of known products were confirmed by \(^1\)H and \(^{13}\)C NMR spectroscopic analysis.

#### N-Benzyl-(3-pyridyl)amine (3a)\textsuperscript{[33,34]}

The general procedure with benzylamine (0.0655 mL, 0.6 mmol) and 3-chloropyridine (0.0476 mL, 0.5 mmol) gave a crude product that was purified by flash chromatography with 60:40 petroleum ether/ethyl acetate to afford 3a as a yellow solid (83 mg, 90%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.08\) (d, \(J = 3.0\) Hz, 1H), 7.96 (dd, \(J = 4.7, 1.4\) Hz, 1H), 7.39–7.32 (m, 4H), 7.32–7.26 (m, 1H), 7.10–7.03 (m, 1H), 6.88 (ddd, \(J = 8.3, 2.9, 1.4\) Hz, 1H), 4.34 ppm (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 144.3, 138.8, 138.6, 136.1, 128.9, 127.6, 127.5, 123.9, 118.8, 48.0\) ppm.

#### N-(3-Pyridyl) morpholine (3b)\textsuperscript{[35,36]}

The general procedure with morpholine (0.0525 mL, 0.6 mmol) and 3-chloropyridine (0.0476 mL, 0.5 mmol) gave a crude product that was purified by flash chromatography with 60:40 petroleum ether/ethyl acetate to afford 3b as yellow oil (82 mg, 99%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.16\) (t, \(J = 1.9\) Hz, 1H), 7.98 (t, \(J = 3.0\) Hz, 1H), 7.05 (dd, \(J = 3.2, 1.7\) Hz, 2H), 3.79–3.67 (m, 4H), 3.10–2.98 ppm (m, 4H), 3.0 Hz, 1H), 2.8 ppm (m, 4H), 1.4 Hz, 1H), 1.2 ppm (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 146.9, 140.8, 138.0, 123.5, 122.1, 66.5, 48.5\) ppm.

#### N-Phenyldipyridin-3-amine (3c)\textsuperscript{[34,37]}

The general procedure with \(\text{Ph}_2\text{S}\) (0.0547 mL, 0.6 mmol) and 3-chloropyridine (0.0476 mL, 0.5 mmol) gave a crude product that was purified by flash chromatography with 60:40 petroleum ether/ethyl acetate to afford 3c as yellow solid (84 mg, 99%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.40\) (d, \(J = 2.8\) Hz, 1H), 8.15 (dd, \(J = 4.8, 1.4\) Hz, 1H), 7.43 (ddd, \(J = 8.3, 2.8, 1.4\) Hz, 1H), 7.38–7.24 (m, 2H), 7.18 (ddd, \(J = 8.3, 4.7\) Hz, 1H), 7.12–7.06 (m, 2H), 7.00 (tt, \(J = 7.4, 1.2\) Hz, 1H), 5.96 ppm (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 142.0, 141.5, 140.3, 139.9, 129.7, 123.9, 122.3, 118.7\) ppm.

#### N-Methyl-N-phenylpyridin-3-amine (3d)\textsuperscript{[38]}

The general procedure with N-methylniline (0.0649 mL, 0.6 mmol) and 3-chloropyridine (0.0476 mL, 0.5 mmol) gave a crude product that was purified by flash chromatography with 68:32 petroleum ether/ethyl acetate to afford 3d as a yellow oil (92 mg, 99%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.30\) (d, \(J = 2.8\) Hz, 1H), 8.12 (dd, \(J = 4.7, 1.4\) Hz, 1H), 7.36–7.27 (m, 2H), 7.21 (ddd, \(J = 8.4, 2.9, 1.5\) Hz, 1H), 7.16–7.02 (m, 4H), 3.31 ppm (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 146.9, 140.8, 138.0, 123.5, 122.1, 66.5, 48.5\) ppm.
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N-Hexyl-2-methoxyaniline (3e)\textsuperscript{19}

The general procedure with hexylamine (0.0785 mL, 0.6 mmol) and 2-chloroanisol (0.0635 mL, 0.5 mmol) gave a crude product that was purified by flash chromatography with 96:4 petroleum ether/ethyl acetate to afford 3e as a yellow solid (84 mg, 81%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textit{\delta} = 6.91 (tdd, J = 7.6, 1.4 Hz, 1H), 6.80 (dd, J = 7.9, 1.4 Hz, 1H), 6.73–6.61 (m, 2H), 3.88 (s, 3H), 3.16 (t, J = 7.2 Hz, 2H), 1.78–1.62 (m, 2H), 1.52–1.29 (m, 6H), 1.06–0.86 ppm (m, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \textit{\delta} = 159.2, 141.9, 133.5, 130.9, 66.6, 44.9 ppm.

4-(Pyrazin-2-yl)morpholine (3f)\textsuperscript{33}

The general procedure with morpholine (0.0525 mL, 0.6 mmol) and 2-chloropyrazine (0.0703 mL, 0.6 mmol) gave a crude product that was purified by flash chromatography with 50:10 petroleum ether/ethyl acetate to afford 3f as a yellow oil (73 mg, 99%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textit{\delta} = 7.51 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.26 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.12–7.03 (m, 2H), 6.71 (dd, J = 17.6, 10.9 Hz, 1H), 5.71 (dd, J = 17.6, 1.0 Hz, 1H), 5.17 ppm (d, J = 10.9 Hz, 1H). \textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}CN): \textit{\delta} = 149.1, 141.3, 137.2, 134.7, 133.4, 128.3, 121.0, 120.7, 118.3, 116.1, 113.0, 101.9 ppm; HRMS (ESI): m/z calcd for C\textsubscript{22}H\textsubscript{16}N\textsubscript{2}O, [M+H]\textsuperscript{+}: 221.1073; found: 221.1067.

6-Methoxy-N-methyl-N-phenylpyrazidin-3-amine (3h)\textsuperscript{40}

The general procedure with N-methylaniline (0.130 mL, 1.2 mmol) and 3-chloro-6-methoxypyridazine (0.145 g, 1.0 mmol) gave a crude product that was purified by flash chromatography with 85:15 petroleum ether/ethyl acetate to afford 3h as a yellow solid (213 mg, 99%). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): \textit{\delta} = 7.38 as a yellow solid (161.0, 156.9, 146.7, 130.0, 126.0, 125.8, 120.4, 118.8, 54.4, 39.3 ppm.

4-(tert-Butyl)-N-cyclohexylaniline (3i)\textsuperscript{40}

The general procedure with cyclohexylamine (0.0686 mL, 0.6 mmol) and 1-tert-butyl-4-chlorobenzene (0.0835 mL, 0.5 mmol) gave a crude product that was purified by flash chromatography with 10:1 petroleum ether/ethyl acetate to afford 3i as a yellow liquid (100 mg, 86%). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): \textit{\delta} = 7.32–7.26 (m, 2H), 6.68–6.62 (m, 2H), 5.49 (s, 1H), 3.37–3.28 (m, 1H), 2.37–2.33 (m, 1H), 2.19–2.11 (m, 2H), 1.86 (dt, J = 13.6, 4.1 Hz, 2H), 1.75 (dt, J = 13.1, 4.2 Hz, 1H). 13C NMR (151 MHz, CDCl\textsubscript{3}): \textit{\delta} = 150.8, 148.4, 143.6, 138.4, 137.0, 127.3, 127.1, 124.9, 123.5, 122.7, 117.5 ppm; HRMS (ESI): m/z calcd for C\textsubscript{20}H\textsubscript{13}N\textsubscript{2}S, [M+H]\textsuperscript{+}: 277.0721; found: 277.0795.

Computational methods

Local minima and transition states were first optimized for geometries by using the PBE density functional\textsuperscript{40} with the LanLDZ basis set and associated effective core potentials (ECPs).\textsuperscript{34, 46} Analysis of harmonic vibrational frequencies were performed to determine the nature of these stationary points; all local minima were real and transition states had only one imaginary frequency. Single-point energy corrections were then performed on these reference geometries by using the hybrid PBE0 functional,\textsuperscript{45, 46} with the empirical dispersion correction of Chai and Head-Gordon.\textsuperscript{47} The def2-TZVP basis set and associated ECP\textsuperscript{40} was used for palladium and the cc-pVTZ basis set was used for all other atoms. The effect of a solvent with a dielectric constant of 7.52, corresponding to THF, was implicitly included in this single-point energy correction by using the switching Gaussian implementation of the solvation model of integral equation formalism combined with the polarizable continuum model (IEF-PCM)\textsuperscript{48, 50} and Bondi atomic radii.\textsuperscript{51, 52} The calculations were performed by using the Q-Chem program suite.\textsuperscript{53} Intrinsic reaction coordinate (IRC) calculations were performed...
formed, and the forward and backward reaction paths were fol-
lowed to verify that each computed transition state truly corre-
sponded to the process described. Single-point calculations were
repeated for the key stationary points depicted in Figure 3, with
PB0 and the long-range dispersion correction of Chai and Head-
Gordon, as described above.[41] The larger def2-TZVP basis set
and associated pseudopotential for palladium and the maycc-
pvTZ basis set of Truhlar et al.[33] which added s and p diffuse
functions for all heavy atoms, were used. Calculated $\Delta G_{298}$ and
$\Delta G_{298} \nu$ values differed by a maximum of 5.7 and 3.5 kJ mol$^{-1}$,
respectively, and did not substantially alter the conclusions drawn.

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Conflict of interest

The authors declare no conflict of interest.

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Although the selectivity improvement is a welcomed result, it is not fully understood at this time.
Empirical and Computational Insights into N-Arylation Reactions Catalyzed by Palladium \textit{meta}-Terarylphosphine Catalyst

Get cross! The Pd–Cy*Phine catalyst generated in situ was successfully applied to the N-arylation cross-coupling of primary and secondary amines (see figure), and it exhibits high performance across multiple substrate classes. Computational investigations also indicate that a putative rate-determining step occurs after amine binding, which is likely to annul the expected benefits of the \textit{meta}-terarylphosphine ligand architecture. 

New \#ligands for general \#Pd N-arylation catalysis expand scope of the reaction \#crosscoupling \@astar research

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