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Article

AshPhos Ligand: Facilitating Challenging Aminations in Five- and Six-Membered Heteroaryl Halides Using Cyclic Secondary and Bulky Amines

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Cite This: JACS Au 2025, 5, 91−98
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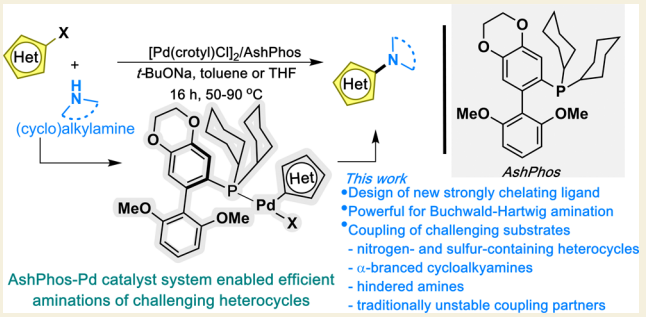
ABSTRACT: Our newly developed AshPhos ligand represents a significant advancement in Buchwald−Hartwig aminations, overcoming many limitations of existing ligands. Created from affordable and accessible materials, AshPhos enhances catalytic performance, especially for extremely difficult substrates, by emphasizing the principles of ligand chelation and cooperativity. Its successful synthesis and application in catalytic aminations underscore its potential for use in the sustainable synthesis of compounds important to medicinal chemistry, materials, and energy. Further studies validated AshPhos's effectiveness in coupling challenging heteroaryl bromides and chlorides with various amines, including hindered amines and those with multiple heteroatoms. Slightly elevated temperatures were essential to avoid forming inactive species, ensuring consistent catalytic turnover. A control nuclear magnetic resonance spectroscopy study suggests the formation of catalytically dormant species or deligation of AshPhos from palladium at room temperature due to the coordination of multiple substrate molecules with the palladium species. Analyses showed cost-effectiveness of AshPhos, making it a significant advancement in catalytic amination for more efficient and sustainable chemical processes. The diverse substrate scope, covering challenging coupling partners and forming over 55 substrates in good-to-excellent yields, further demonstrated the efficiency of AshPhos.



KEYWORDS: *ligand design, cross-couplings, aminations, heteroaryl halides, palladium catalysis*

INTRODUCTION

The significance of C−N bond formation in medicinal chemistry is underscored by the fact that over 62% of bioactive molecules discussed in the literature feature C−N bonds;[1,2] a few representative examples are highlighted in Scheme 1A. While nucleophilic aromatic substitution (S_NAr) reactions can form C−N bonds when aryl halides are activated,[3,4] the Buchwald−Hartwig amination stands out as the preferred method for constructing such bonds in unactivated substrates.[5,6] Its prominence is evident by being one of the top 20 most utilized reactions in the field.[7,8] Despite its broad applicability, the Buchwald−Hartwig amination is often challenging for certain substrates.[9−11] Hindered or sterically demanding amines, as well as five- and six-membered heteroaryl halides, often show reduced or no reactivity.[12,13] This is typically due to the decomposition of ligated palladium species or the active catalyst or substrate, necessitating the use of specialized ligands.[14] For example, a moderate base can prevent the base-mediated decomposition of sensitive five-membered heteroarenes, which can otherwise lead to no catalysis. Additionally, a Pd catalyst supported by optimal donicity and steric could effectively resist heteroarene-induced catalyst deactivation while promoting efficient coupling.

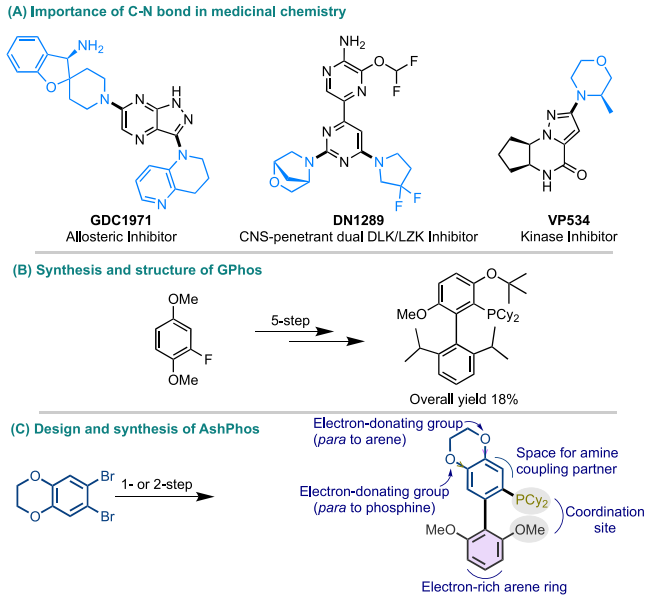
To overcome these challenges, a remarkable ligand GPhos is known for its exceptional reactivity.[14,15] However, its cost and tedious synthesis can be prohibitive, especially when required in large volumes (Scheme 1B).[16] While GPhos presents considerable benefits in Buchwald−Hartwig amination reactions, developing sustainable alternative ligands is imperative. These alternatives should mitigate the limitations of GPhos and expand the efficiency and scope of this crucial synthetic transformation.

To achieve efficient and scalable Buchwald−Hartwig aminations of challenging substrates, we designed a new phosphine ligand that promotes chelation, comes from a cheaper starting material, and involves fewer synthetic steps, i.e., one to two steps. Its design is rooted in the concepts of chelation and cooperativity, with the aim of facilitating

Received: August 22, 2024
Revised: December 3, 2024
Accepted: December 5, 2024
Published: December 19, 2024

https://doi.org/10.1021/jacsau.4c00772
JACS Au 2025, 5, 91−98

Scheme 1. Overview of Buchwald–Hartwig Amination[a]



[a](A) Importance in medicinal chemistry. (B) Synthesis and structure of GPhos. (C) Scalable and resource-efficient design of AshPhos ligand.

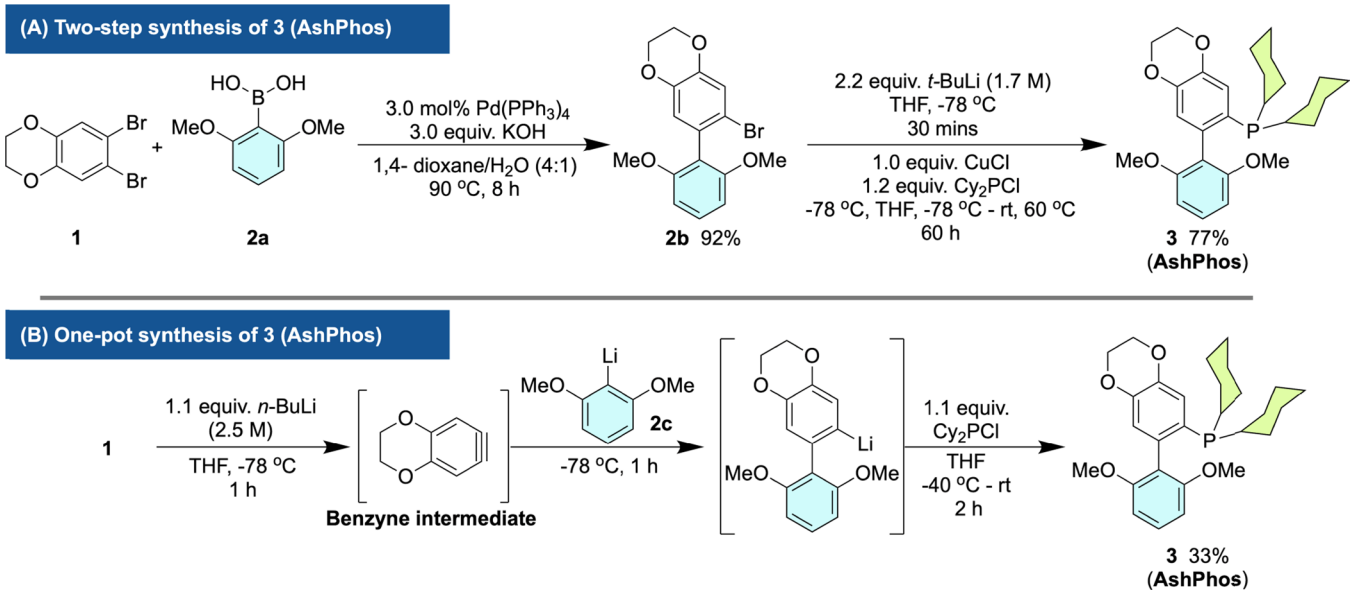
chelation without synthetic complications.[17−19] The design process also prioritized using inexpensive materials, cost-effectiveness, and synthesis that conserves resources, thereby promoting advancements in sustainable catalysis. Thus, to enhance the efficiency and scalability of Buchwald–Hartwig aminations for difficult coupling partners, we have developed a new phosphine ligand, AshPhos (Scheme 1C).

RESULTS AND DISCUSSION

Our design hypothesis for the new ligand, called AshPhos, posits that 6,7-dibromo-2,3-dihydrobenzo[*b*][1,4]dioxine **1**, an affordable starting material featuring two ether units, is ideal for the installation of phosphine at the para position relative to one ether. At the same time, an electron-rich aryl ring can be introduced para to the second ether unit and ortho to the electron-rich phosphine. This configuration is anticipated to yield a highly electron-rich and stable phosphine, conducive to facile oxidative addition and effective chelation to palladium. The choice of the 2,6-dimethoxyphenyl ring as the secondary aryl ring is judicious due to its cost-effectiveness, natural derivation from resorcinol, electron-rich nature, and chelating properties. The preference for a dioxane ring over a dimethoxy substituent stems from its conformational rigidity and stability.[19] The absence of substituents at sp^2 carbon atoms of the benzodioxane ring ensures sufficient space for the amine coupling partner to interact with palladium. Additionally, the absence of a substituent at the 4-position of the lower aryl ring is expected to create a more open environment in the catalyst, allowing bulky nucleophiles to bind effectively for trans-metalation. Consequently, the bespoke ligand is designed to enhance chelation, facilitate oxidative addition, and promote efficient transmetalation, thereby enabling effective amination of challenging substrates.

Guided by our design hypothesis, we successfully synthesized the ligand AshPhos utilizing two distinct synthetic pathways (for details, see the Supporting Information, pages S2–S6). The first approach, a high-yielding two-step synthesis, commenced with the installation of the aryl ring using arylboronic acid **2a** to 6,7-dibromo-2,3-dihydrobenzo[*b*][1,4]-dioxine **2b** through Suzuki–Miyaura cross-coupling, followed by the introduction of the phosphine moiety, leading to the formation of **3** (Scheme 2A). Alternatively, we explored a moderately yielding one-pot synthesis that entailed a benzyne formation, followed by the subsequent entrapment of the benzyne intermediate with 2,6-dimethoxyphenyllithium **2c**. In the same pot, the resulting intermediate was further reacted with dicyclohexylphosphine chloride to yield the desired AshPhos ligand **3** (Scheme 2B).

Scheme 2. Synthesis of AshPhos Ligand[a]



[a](A) Two-step route involving cross-coupling and lithiation chemistry. (B) One-pot synthesis involving benzyne intermediate.

https://doi.org/10.1021/jacsau.4c00772
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After obtaining the AshPhos ligand, we investigated its binding affinity with $[Pd(crotyl)Cl]_2$. The resulting complex of AshPhos exhibited a propensity for oxidative addition of (hetero)aryl bromides, followed by transmetalation using *t*-$BuNH_2$ and reductive elimination. We chose $[Pd(crotyl)Cl]_2$ over $Pd(OAc)_2$, $Pd(dppb)_2$, and $PdCl_2$ due to its ease of characterization and the facile generation of Pd(0) species for oxidative addition, as demonstrated in Colacot and co-workers' precatalyst development study.[20,21] The ^{31}P NMR signal of AshPhos appeared at −10.2 ppm, while the signal for [Pd(crotyl)(AshPhos)Cl] was observed at 31.8 ppm, confirming the chelation of AshPhos with palladium (Figure 1). This

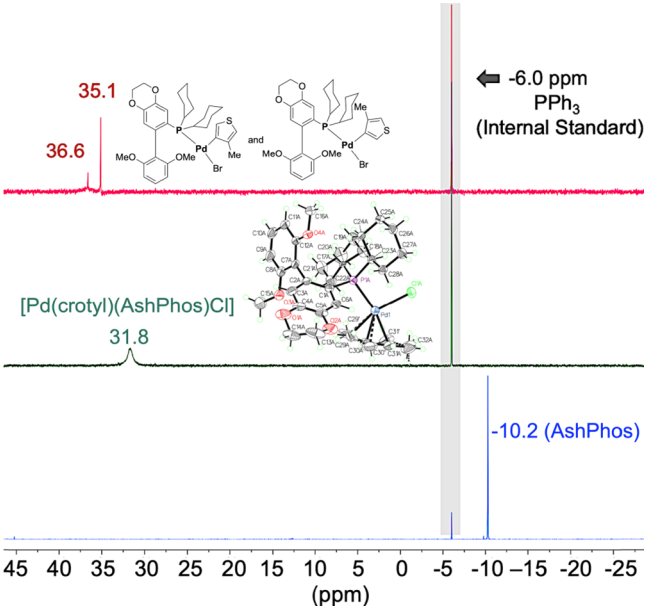
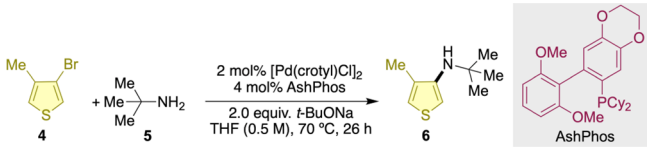


Figure 1. ^{31}P NMR study of AshPhos, [Pd(crotyl)(AshPhos)Cl], and oxidative addition complex.

chelation was further verified through X-ray single-crystal analysis (for details, see the Supporting Information, page S7). Upon treatment with 3-bromo-4-methylthiophene, the resulting complex rapidly formed an oxidative addition complex, which remained stable even after passing through silica gel during column chromatography. The oxidative addition complex existed in two rotamers: a major rotamer with a chemical shift of 35.1 ppm and a minor rotamer observed at 36.6 ppm. Thus, this study indicated that the palladium complex of AshPhos can be a suitable candidate for catalysis due to ease of handling and facile oxidative addition, as observed in the initial study.

In the optimization of reaction conditions for catalytic amination, thiophenyl bromide **4** and *tert*-butylamine **5** were used as coupling partners (for details, see the Supporting Information, pages S10−S12). As anticipated, $[Pd(crotyl)Cl]_2$ proved to be the optimal palladium source, while sodium *tert*-butoxide served as the preferred base, and THF (tetrahydrofuran) was the optimal solvent. Under these optimized conditions, the coupling product **6** was obtained with a 90% yield (Table 1, entry 1). However, substituting $[Pd(crotyl)Cl]_2$ with $Pd(OAc)_2$ resulted in a lower yield of **6** (38%, entry 2). Similarly, Pd_2dba_3 provided only 70% yield (entry 3), likely due to competition between dba (dibenzylideneacetone) and ligand. Other palladium sources, such as $[Pd(allyl)Cl]_2$ and

Table 1. Optimization Study[a]



entry	conditions	5 (%)[b]
1	**no deviation**	**90**[c]
2	2 mol % $Pd(OAc)_2$ instead of $[Pd(crotyl)Cl]_2$	38
3	2 mol % Pd_2dba_3 instead of $[Pd(crotyl)Cl]_2$	70
4	*t*-BuOK instead of *t*-BuONa	35
5	KOH or Cs_2CO_3 or Et_3N or *i*-$PrNEt_2$ instead of *t*-BuONa	0
6	1 mol % $[Pd(crotyl)Cl]_2$, instead of 2 mol %	25
7	toluene instead of THF	81
8	*t*-BuOH or EtOH instead of THF	0
9	MTBE instead of THF	56
10	reaction temperature RT, instead of 70 °C	8
11	reaction time 2 h, instead of 26 h	77
12	reaction time 16 h, instead of 26 h	87[c]
13	1.0 equiv. NaBr as an additive	50

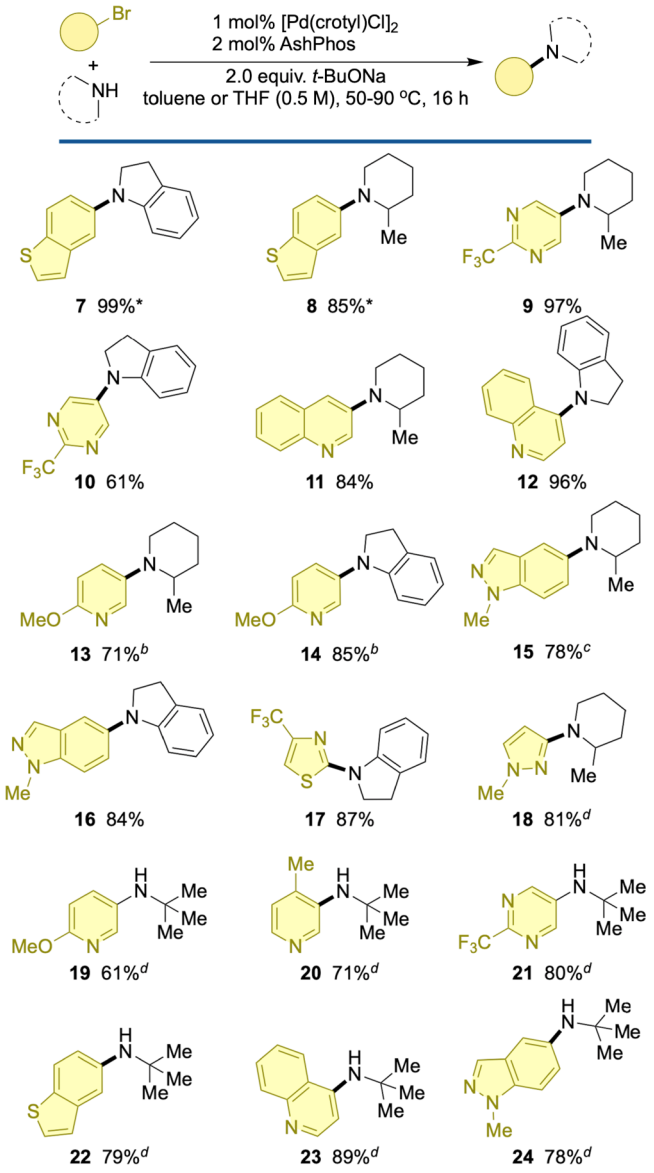
[a]Conditions. **4** (0.5 mmol), **5** (0.6 mmol), 2 mol % $[Pd(crotyl)Cl]_2$, 4 mol % AshPhos, *t*-BuONa (2.0 equiv), 1 mL THF, 70 °C, 26 h. [b]Conversion to **6** based on GC-MS using mesitylene (0.5 mmol) as an internal standard. [c]Isolated yield.

$Pd(cod)Cl_2$, yielded inferior results for this transformation (see the Supporting Information, pages S10). The choice of cation in the base significantly impacted catalytic efficiency. Using potassium *tert*-butoxide as the base led to a yield of only 35% for **6** (entry 4), likely due to its lower solubility than sodium *tert*-butoxide (25 g/100 g THF vs 32 g/100 g THF)[22,23] or the counterion effect. Comparatively weak bases like cesium carbonate, potassium hydroxide, triethylamine, and diisopropylethylamine were ineffective (entry 5). Maintaining a 1:1 ratio of palladium to ligand was optimal; reducing the palladium loading to 1 mol % resulted in only a 25% yield of **6** (entry 6). The catalytic reaction also demonstrated effectiveness in toluene, yielding 81% product, although it was less effective than in THF (entry 7). *tert*-Butanol and ethanol proved to be ineffective solvents, with no product formation detected in these cases (entry 8). Only 56% of the product was obtained in methyl-*tert*-butyl ether (MTBE) (entry 9). A reaction temperature of 70 °C was optimal; at room temperature (rt), only an 8% yield of **6** was obtained (entry 10). Interestingly, the reactions were almost completed within 2 h, yielding 77% of **6** (entry 11), while extending the reaction time to 16 h resulted in 87% yield (entry 12). This suggests either catalyst decomposition during the reaction or the formation of less active ligated palladium aggregates. The addition of sodium bromide as an additive decreased the yield due to interference with the base's optimal solubility (entry 13).

Following the optimized conditions, we expanded the substrate scope to include the coupling of heteroaryl bromides with α-branched secondary amines, such as indoline and 2-methylpiperidine (Table 2, **7**−**18**). Notably, only 1 mol % $[Pd(crotyl)Cl]_2$ and 2 mol % AshPhos were needed for preparing most of these compounds. Bromobenzothiophene was effectively coupled with both indoline and 2-methylpiperidine, affording excellent yields (**7** and **8**). Interestingly, despite the strong binding affinity of 2-methylpiperidine to palladium, it did not adversely affect catalytic activity. In all cases where 2-

https://doi.org/10.1021/jacsau.4c00772
JACS Au 2025, 5, 91−98

Table 2. Substrate Scope: Couplings of (Hetero)aryl Bromides with α-Branched and Hindered Amines[a]



[a]Conditions. Unless noted, (hetero)aryl bromide (0.25 mmol, 1.0 equiv), α-branched amine (0.3 mmol, 1.2 equiv) *t*-BuONa (0.5 mmol, 2.0 equiv), $[Pd(crotyl)Cl]_2$ (1 mol %), AshPhos (2 mol %), toluene or THF (0.5 M), 70 °C, 16 h. THF was a reaction solvent for **11**, **12**, **15**, **16**, and **18**–**24**. Toluene was a reaction solvent for **7**–**10**, **13**, **14**, and **17**. Reaction temperature: 60 °C for **7**–**15**; 90 °C for **15**, **16**, and **18**–**24**. *Reaction time 12 h. [b]2 mol % $[Pd(crotyl)Cl]_2$ and 4 mol % AshPhos. [c]2.5 mol % $[Pd(crotyl)Cl]_2$ and 5 mol % AshPhos. [d]3 mol % $[Pd(crotyl)Cl]_2$ and 6 mol % AshPhos.

methylpiperidine was used as a nucleophile, the desired coupling products were obtained in good-to-excellent yields (**8**, **9**, **11**, **13**, **15**, and **18**). Electrophiles containing pyrimidine (**9** and **10**) and benzopyrazole (**15** and **16**) were also successfully coupled with both indoline and 2-methylpiperidine. Notably, the more challenging thiazole and pyrazole bromides reacted favorably with the amines, resulting in product yields of 93 and 84%, respectively (**17** and **18**).

Various heteroaryl bromides were also coupled with *tert*-butylamine (Table 2, entries **19**–**24**). In these examples, 3 mol % of $[Pd(crotyl)Cl]_2$ and 6 mol % of AshPhos loading was necessary, as lower loadings resulted in low conversions in some cases. Nitrogen-containing heterocycles demonstrated good-to-excellent yields (examples **19**–**21**, **23**, and **24**). Pyridines with electron-donating or -releasing substituents at the 2- or 4-position effectively coupled with *tert*-butylamine, providing good yields (**19** and **20**). Electrophiles containing pyrimidine (**21**), benzothiophene (**22**), and quinoline (**23**) provided excellent yields. Similarly, electrophiles featuring benzopyrazole rings also coupled well with *tert*-butylamine (**24**).

After confirming the generality observed in Tables 2, it became evident that the newly designed ligand is highly effective for coupling challenging heteroaryl bromides with amines. We subsequently expanded our investigation to include more functionally diverse coupling partners, with a focus on chelating secondary cycloalkyl amines containing multiple heteroatoms (Table 3, **25**–**53**). Substituted pyridines successfully coupled with various amines, such as difluorinated azetidine (**25**), morpholine (**26**), difluorinated pyrrolidine (**27**), tetrahydroisoquinoline (**28** and **30**), and 4-methoxypiperidine (**29** and **34**), achieving good-to-excellent yields. Notably, secondary amines with multiple nitrogen atoms, such as 1-(pyridine-2-yl)piperazine (**31** and **32**) and 2-(piperazine-1-yl)pyrimidine (**33** and **44**), participated effectively in the catalytic reactions, highlighting the strong binding of AshPhos with palladium. Without this robust interaction, these highly chelating amines could have adversely affected catalytic activity. The reactivity trend for coupling pyrimidine bromides was excellent, as demonstrated in examples **35**–**38**. Additionally, more chelating heterocycles, such as pyrrolopyridine, were well-tolerated as electrophiles, resulting in excellent yields (**39**–**42**). Remarkably, even in example **41**, where both coupling partners exhibited high binding affinity with palladium, excellent reactivity was observed. Benzothiophene heterocycles, serving as electrophiles, were also effectively coupled with various nitrogen-enriched secondary cycloalkylamines (**43**–**46**). Notably, excellent yields were achieved even when the nucleophile contained four nitrogen atoms, as seen in example **44**. However, the reaction yield was moderate when bromobenzothiophene was coupled with morpholine (**45**). Electrophiles containing benzopyrazole (**47**), pyrazole (**48**, **49**), and thiazole (**50**) were also well-tolerated across a variety of amines, yielding good-to-excellent products. The thiazole electrophile, where the more acidic proton (located on the carbon between the sulfur and nitrogen atoms) is available for side reactions, reacted exclusively in the desired cross-coupling reaction in examples **51** and **52.** Notably, the most acidic methynic proton in example **52** remained intact and did not interfere with the desired reactivity. Interestingly, an electrophile from Merck's Informer Library successfully coupled with amines possessing four nitrogen atoms (**53**). The moderate yield in this case was attributed to product loss during purification. Finally, examples involving strained cyclic amines (**25**, **42**), such as azetidine, coupled smoothly without decomposition of the strained ring. In all examples except **47**–**49**, and **53**, 1 mol % [Pd] and 2 mol % AshPhos were required, which may be considered reasonable given the complexity of the substrates.

We further tested the efficiency of our catalytic approach on heteroaryl chlorides, as the oxidative addition of these substrates is more challenging than that of the corresponding heteroaryl bromides. As demonstrated in Table 4, heteroaryl chlorides of thiophene, pyridine, and pyrazine (**54**–**61**)

https://doi.org/10.1021/jacsau.4c00772
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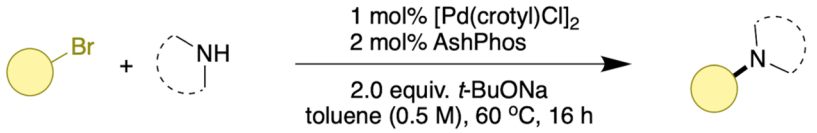
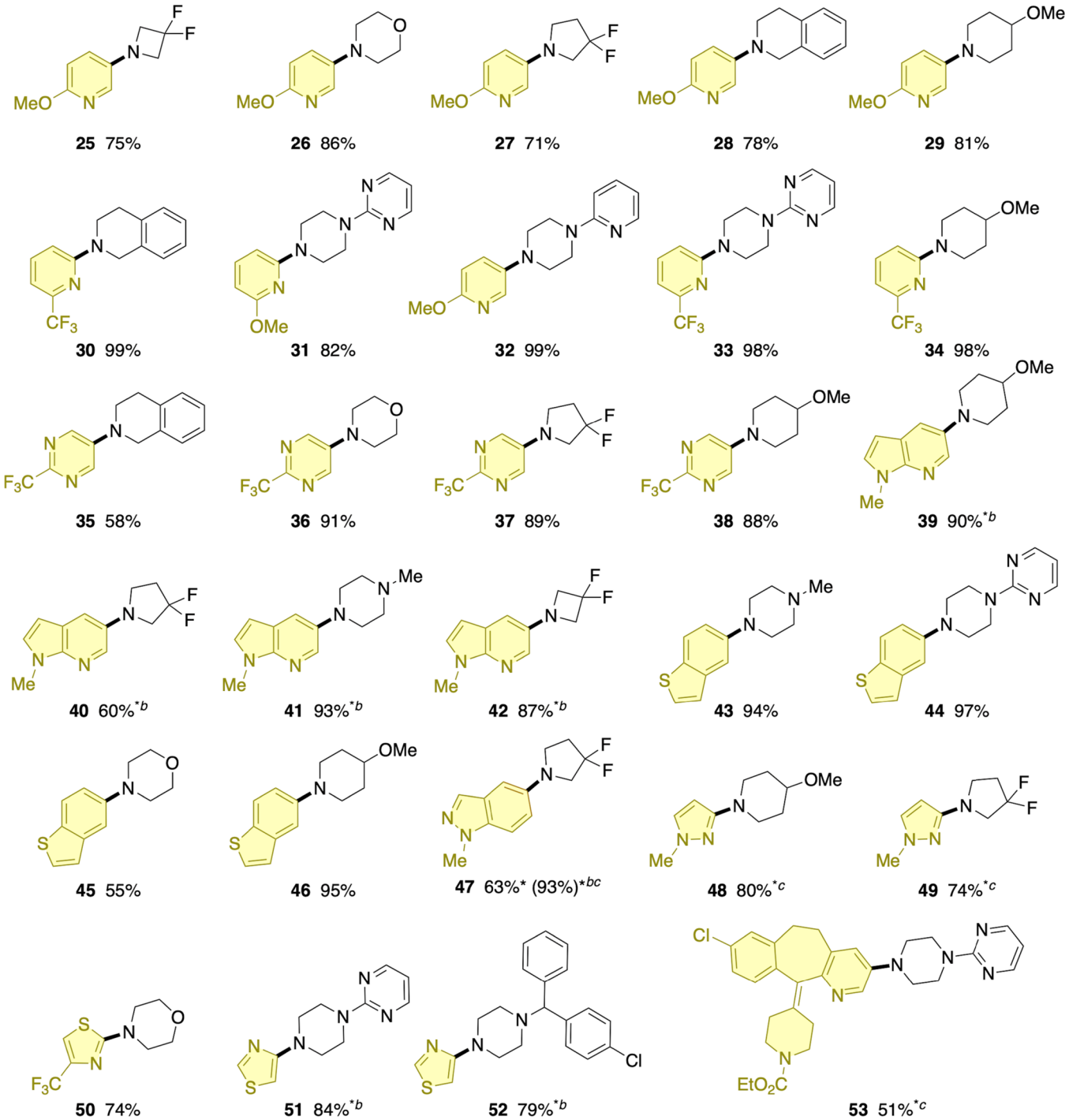
Table 3. Substrate Scope: Couplings of (Hetero)aryl Bromides with Unbranched Cyclic Secondary Amines[a]



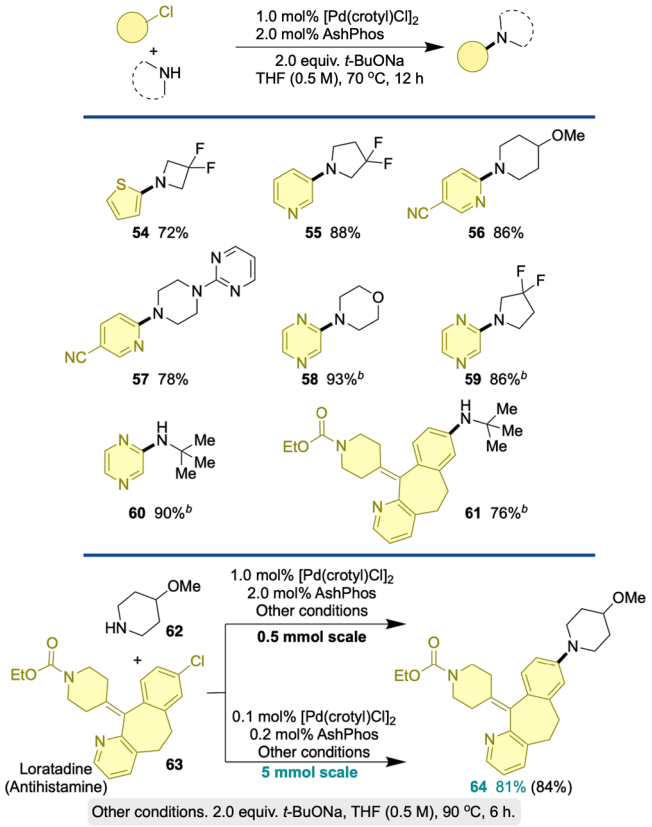


[a]Conditions. Unless noted, (hetero)aryl bromide (0.25 mmol, 1.0 equiv), α-unbranched 2° amine (0.3 mmol, 1.2 equiv), *t*-BuONa (0.5 mmol, 2.0 equiv), $[Pd(crotyl)Cl]_2$ (1 mol %), AshPhos (2 mol %), toluene (0.5 M), 60 °C, 16 h. *THF was a reaction solvent instead of toluene. [b]Reaction temperature 90 °C instead of 60 °C. [c]3 mol % $[Pd(crotyl)Cl]_2$ and 6 mol % AshPhos. *t*-BuONa 1.0 equiv. instead of 2.0.

participated well in the desired reaction pathway, yielding good-to-excellent products. In all these cases, 1 mol % $[Pd(crotyl)Cl]_2$ and 2 mol % AshPhos were required. The pyridyl-containing nitrile functional group demonstrated favorable reactivity, yielding 86% of **56** and 78% of **57**, the latter of which contains six nitrogen atoms. Both secondary

https://doi.org/10.1021/jacsau.4c00772
JACS Au 2025, 5, 91−98

Table 4. Substrate Scope: Couplings of (Hetero)aryl Chlorides with Cyclic Secondary and Hindered Amines[a]



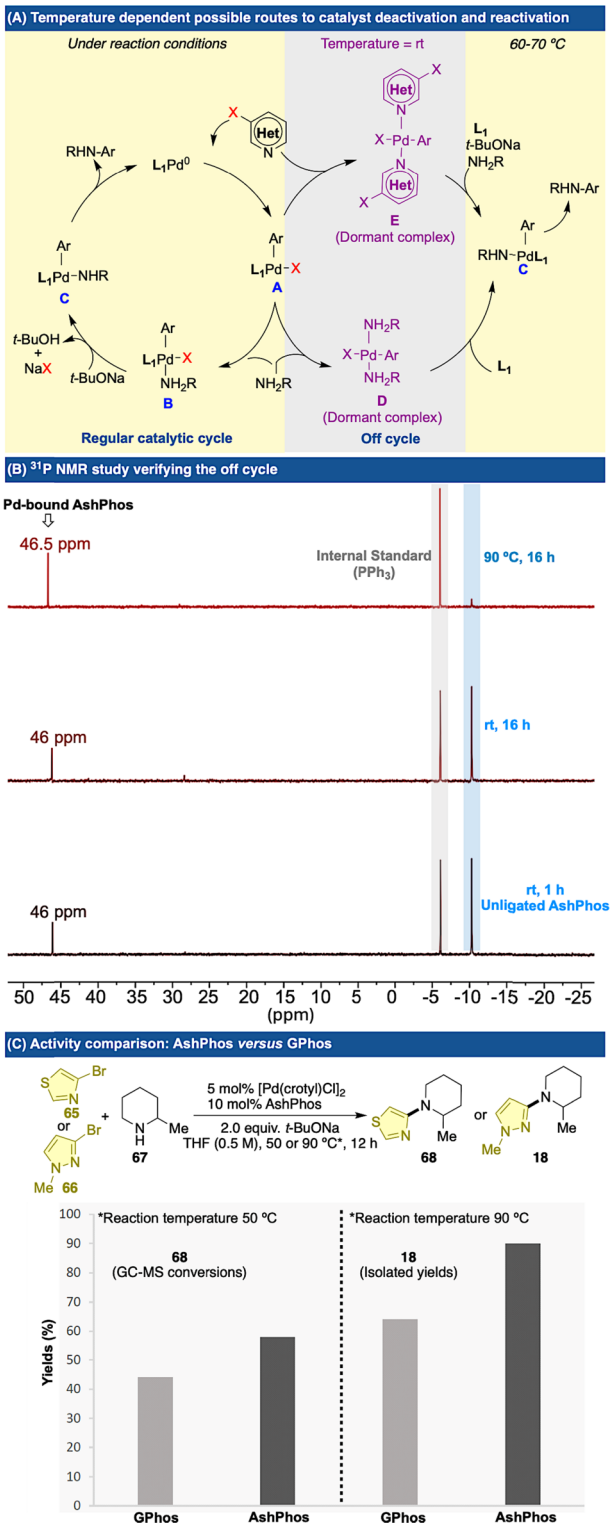
[a]Conditions. Unless noted, (hetero)aryl chloride (0.5 mmol, 1.0 equiv), amine (0.6 mmol, 1.2 equiv), *t*-BuONa (1.0 mmol, 2.0 equiv), $[Pd(crotyl)Cl]_2$ (1 mol %), AshPhos (2 mol %), THF (0.5 M), 70 °C, 12 h. [b]Reaction temperature 90 °C instead of 60 °C and reaction time 6 h instead of 12 h.

alkyl amines (**54**−**59**) and hindered *tert*-butyl amines (**60** and **61**) proved effective in the catalytic process. In example **61**, transesterification was not observed when the reactions were performed using *t*-BuONa. It is noteworthy that this example involved an electrophile sourced from Merck's Informer Library.

Furthermore, the scalability of our catalytic approach was tested using an electrophile from the Merck Informer Library. Initially, the reaction was tested on a 0.5 mmol scale under standard conditions, where heteroaryl chloride **63** and amine **62** were subjected to the reaction conditions, yielding 84% of product **64**. To our delight, when the reaction was scaled up to 5 mmol using the same coupling partners but with lower catalyst loading (0.1 mol % $[Pd(crotyl)Cl]_2$ and 0.2 mol % AshPhos), 81% of product **64** was obtained. This yield was comparable to that of the small-scale reaction, despite the catalyst loading being 10 times lower.

The need for elevated reaction temperature was further justified by studying the formation of off-cycle palladium species that release the AshPhos ligand, rendering the palladium species catalytically dormant. In Scheme 3A, after the oxidative addition of heteroaryl bromide, an intermediate **A** can proceed to the desired catalytic cycle through amine binding, deprotonation, and reductive elimination, forming intermediates **B** and **C**, respectively. Simultaneously, we propose that an excess of heteroaryl bromide and nucleophilic

Scheme 3. Role of Ligand in Catalysis[a]



[a](A) A plausible explanation of the need for elevated temperature. (B) Detection of free ligand at RT or in off-cycle by ^{31}P NMR spectroscopy. (C) Activity comparisons between AshPhos and GPhos.

amine compared to the catalytic palladium species can lead to the binding of amine nucleophile and heteroaryl bromide via nitrogen atoms, resulting in the catalytically dormant species **D** and **E**. However, this binding is less favorable at elevated

https://doi.org/10.1021/jacsau.4c00772
JACS Au 2025, 5, 91−98

temperatures that facilitate a normal catalytic cycle. At RT, the formation of **D** and **E** is anticipated.

To verify this hypothesis, we conducted a control study using ^{31}P NMR (Scheme 3B). Initially, when the reaction between heteroaryl bromide **66** and amine **67** was performed at RT under the conditions described in Scheme 3C, slight formation of the oxidative addition complex was observed at 46 ppm, while the majority of free AshPhos ligand was detected as indicated by the ^{31}P signal at −10.2 ppm. After running the same reaction at RT for 16 h, no significant changes in the ^{31}P NMR were observed, supporting the idea that off-cycle species readily form at RT; even though oxidative addition is also possible, no transmetalation was observed in the analysis. The formation of catalytically dormant species hinders productive transmetalation and reductive elimination. However, when the reaction mixture was heated to 90 °C for 16 h, predominantly the oxidative addition-transmetalated complex was observed, as revealed by the appearance of ^{31}P signal at 46.5 ppm. *Ca.* 90% product formation was also observed in the same reaction mixture. Notably, when the reaction mixture was initially stirred at RT for 1 h and then stirred at 90 °C for the next 15 h, the dormant species were converted to catalytically active species, as evidenced by a significant ^{31}P signal at 46.5 ppm (for details, see the Supporting Information, pages S20−S21). These control experiments justify the need for elevated reaction temperature that prevents the formation of catalytically dormant palladium species.

Next, the activity of AshPhos and the state-of-the-art GPhos in two different reactions was compared (Scheme 3C). AshPhos outperformed in these examples, and it only required inexpensive sodium *tert*-butoxide base and THF solvent. For instance, in a reaction between heteroaryl bromide **65** and amine **67**, GPhos yielded 45% of product **68**, while AshPhos achieved a 60% yield of the same product. Similarly, coupling between **66** and **67** resulted in a 65% yield of product **18** with GPhos, whereas AshPhos provided an impressive 90% isolated yield of product **18**.

CONCLUSIONS

In conclusion, the development of the AshPhos ligand represents a significant advancement in the field of Buchwald−Hartwig amination. Derived from cost-effective and readily available starting materials, AshPhos addresses the limitations of existing ligands by offering enhanced catalytic performance, particularly for challenging substrates. Its design emphasizes chelation and cooperativity, leading to improved turnover rates and selectivity. The successful synthesis and characterization of AshPhos, along with its demonstrated efficacy in catalytic amination reactions, highlight its potential for scalable and sustainable applications in synthetic chemistry. AshPhos has proven highly effective for coupling challenging heteroaryl bromides and chlorides with various amines, including those containing multiple heteroatoms. The ligand's strong binding with palladium facilitates excellent yields across a diverse range of substrates. Slightly elevated reaction temperatures are crucial to preventing the formation of catalytically dormant species, ensuring efficient catalytic cycles. Overall, AshPhos represents a valuable advancement in the field of catalytic amination, promoting more efficient and sustainable chemical processes.

METHODS

General Procedure for Catalytic Couplings

AshPhos-Pd(crotyl)Cl Stock Solution Preparation. In the preferred solvents, THF or toluene, 0.05 M stock solution of AshPhos-Pd(crotyl)Cl was prepared using $[Pd(crotyl)Cl]_2$ (19.7 mg, 0.05 mmol) and AshPhos (46.9 mg, 0.10 mmol) in 2 mL of solvent and stored under a nitrogen atmosphere. Freshly prepared stock solutions were used for subsequent reactions.

General Procedure for Buchwald−Hartwig Amination. In an 8 mL reaction vial equipped with a magnetic stir bar, sodium *tert*-butoxide base (96.5 mg, 1.0 mmol, 2.0 equiv) was added under a nitrogen atmosphere. Subsequently, a heteroaryl halide (0.5 mmol, 1.0 equiv), an aliphatic primary or secondary amine (0.6 mmol, 1.2 equiv), and anhydrous THF (0.8 mL per reaction) were introduced into the vial. From the prepared stock catalyst solution, 200 μL of the solution (corresponding to 2 mol % of AshPhos-Pd(crotyl)Cl, with the amount adjusted as described in the substrate scope) was added to the reaction mixture using a microliter syringe. The vial was then capped and placed on a preheated oil bath for stirring at 70 °C for 16 h under a nitrogen atmosphere. Upon complete consumption of the starting materials, as monitored by TLC and GC-MS, the vial was removed from the oil bath and allowed to cool to room temperature. The vial was opened, and the contents were filtered through a Celite plug, which was subsequently rinsed with EtOAc (3 × 5 mL). The volatiles were then evaporated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using EtOAc/hexanes as the eluent.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00772.

Optimization study, detailed procedures, synthetic protocols, X-ray analysis of precatalyst, and all analytical data (PDF)

X-ray analysis (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Ashish Dusunge** conceptualization, data curation, formal analysis, investigation, methodology, writing - original draft; **David K. Leahy** funding acquisition, methodology, project administration, resources, supervision, validation, writing - original draft, writing - review & editing; **Sachin Handa** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology,

https://doi.org/10.1021/jacsau.4c00772
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project administration, resources, software, supervision, validation, visualization, writing - original draft, writing - review & editing.

Funding

S.H. acknowledges the US National Science Foundation (NSF) for providing partial support to fulfill broader impacts (CHE 2044778 and 2345856).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge Steven Kelley for assistance in the single-crystal analysis of the precatalyst.

■ ABBREVIATIONS

COD:1,5-cyclooctadiene; Dba:dibenzylideneacetone; GC-MS:gas chromatography−mass spectrometry; MTBE:methyl *tert*-butyl ether; NMR:nuclear magnetic resonance; THF:tetrahydrofuran.

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