Room Temperature Cu-Catalyzed Amination of Aryl Bromides Enabled by DFT-Guided Ligand Design

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ABSTRACT: Ullman-type C–N coupling reactions represent an important alternative to well-established Pd-catalyzed approaches due to the differing reactivity and the lower cost of Cu. While the design of anionic Cu ligands, particularly those by Ma, has enabled the coupling of various classes of aryl halides and alkyl amines, most methods require conditions that can limit their utility on complex substrates. Herein, we disclose the development of anionic N^1,N^2-diarylbenzene-1,2-diamine ligands that promote the Cu-catalyzed amination of aryl bromides under mild conditions. Guided by DFT-calculations, these ligands were designed to (1) increase the electron density on Cu, thereby facilitating the rate of oxidative addition of aryl bromides, and (2) stabilize the active anionic Cu^I complex *via* a π-interaction. Under optimized conditions, structurally diverse aryl and heteroaryl bromides and a broad range of alkyl amine nucleophiles, including pharmaceuticals bearing multiple functional groups, were efficiently coupled at room temperature. Combined computational and experimental studies support a mechanism of C–N bond formation that follows a catalytic cycle akin to the well-explored Pd-catalyzed variants. Modification of the ligand structure to include a naphthyl residue resulted in a lower energy barrier to oxidative addition, providing a 30-fold rate increase relative to what is seen with other ligands. Collectively, these results establish a new class of anionic ligands for Cu-catalyzed C–N couplings which we anticipate may be extended to other Cu-catalyzed C–heteroatom and C–C bond-forming reactions.

N-aryl amines are among the most prevalent structural features found in natural products,[1-4] pharmaceuticals,[1, 5-7] agrochemicals,[8-9] and organic materials.[10-12] While a number of approaches to form C–N bonds have been developed, transition-metal-catalyzed aryl amination reactions have emerged as some of the most widely utilized methods due to their versatility and functional group tolerance.[13-15] In particular, our group has developed an array of dialkylbiaryl monophosphine ligands[16-17] to support Pd catalysts that have enabled the coupling of many classes of aryl (pseudo)halide electrophiles with a broad range of amine nucleophiles.[18-20] Despite these advances, the cost, and issues of removal[21-22] of Pd have motivated the development of alternative metal catalysts. Metal-catalyzed coupling reactions are notably prevalent in the active pharmaceutical ingredient (API) forming step of many pharmaceuticals where residual metal toxicity matters immensely,[22-24] rendering innocuous metal catalysts particularly advantageous. Accordingly, Ullman-type couplings have been reexamined as viable methods to form structurally diverse C–N bonds due to the diminished cost and immunotoxicity of Cu,[8, 25-26] as well as the orthogonal reactivity to Pd.[27-28]

Since the initial report of Cu-catalyzed C–N coupling by Ullmann,[29-30] the development of several ligand scaffolds has enabled these aminations to proceed under increasingly milder conditions with broader reaction scopes.[8, 25, 31] Early variations involved the use of neutral ligands, such as trans-*N*,*N*′-dimethylaminocyclohexane-1,2-diamine, to facilitate amidation[32-38] or *N*-heterocycle arylation (**Figure 1A**).[35, 39] However, many of these systems were not readily adopted to the coupling of alkyl amines and aryl halides, likely due to the energetically unfavorable oxidative addition of aryl

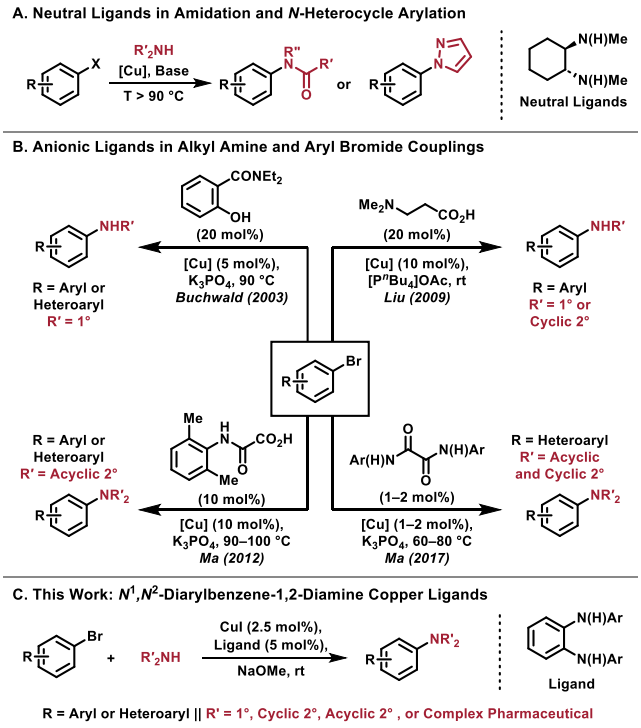


Figure 1. Cu-catalyzed C–N bond formation. (A) Amidation and *N*-arylation of heterocycles enabled by neutral ligands. (B) Coupling of aryl bromides and alkyl amines employing anionic ligands. (C) This work in which N^1,N^2-diarylbenzene-1,2-diamine ligands enable a general Cu-catalyzed amination of aryl bromides under mild conditions.

halides to the corresponding ligated Cu-species. Anionic ligands readily accessed through deprotonation under the

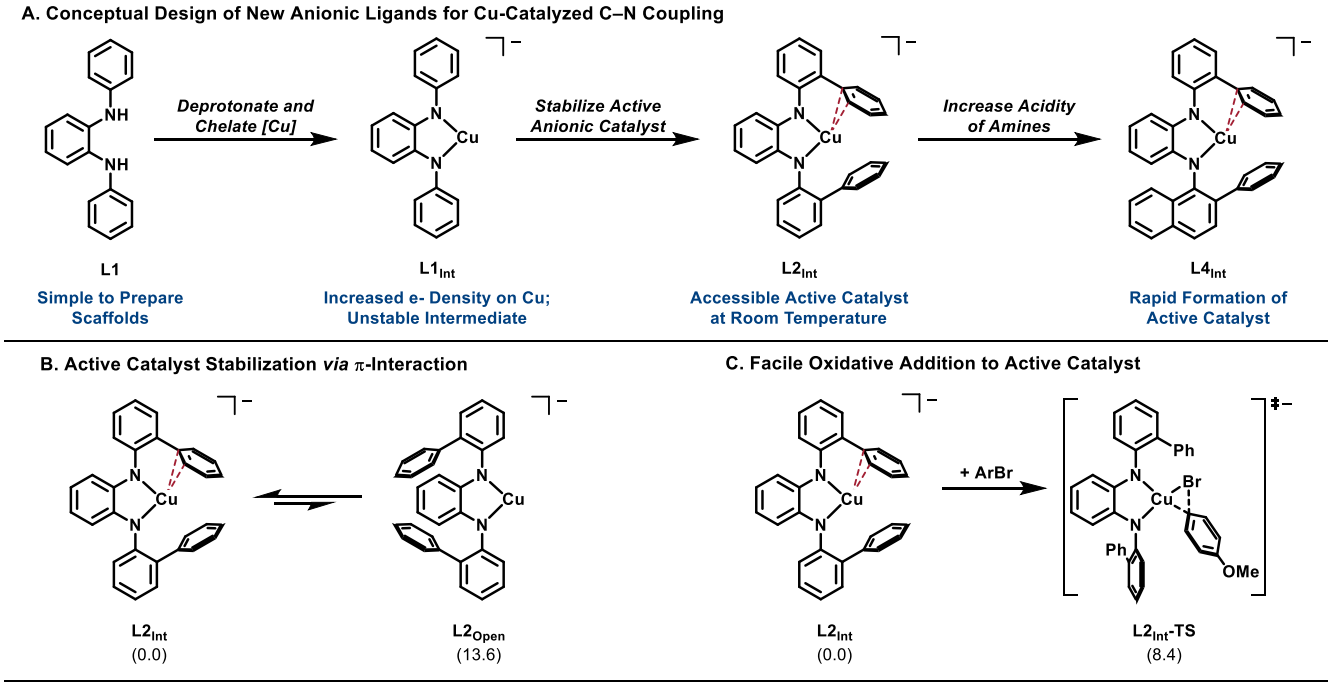


Figure 2. Ligand design through computational and experimental optimization. (A) Conceptual design of the N^1,N^2-diarylbenzene-1,2-diamine scaffold. (B) Stabilization of active catalyst *via* π-interaction. (C) Oxidative addition barrier of 4-bromoanisole to **L2** ligated Cu.

basic reaction conditions have been demonstrated to lower the energetic barrier to oxidative addition, thereby enabling the coupling of alkyl amines and various aryl halides (**Figure 1B**).[40-43] For instance, our group has employed anionic phenol-based ligands to facilitate the couplings of primary alkyl amines and aryl bromides.[44] Similarly, Liu disclosed a system relying on *N*,*N*-dimethylglycine and an ionic organic base which allowed the coupling to proceed at room temperature.[45] In an effort to build on their original methods utilizing proline and *N*-methylglycine ligands[42] and to expand the generality of this approach, Ma has pioneered the use of oxoacetic acid and oxalamide ligands for the coupling of various aryl halides with a variety of alkyl amines,[46-48] aniline derivatives,[49-50] and ammonia surrogates.[8, 48, 51] With optimized ligand systems, the Ma group has achieved efficient catalysis with low loadings of Cu that rival those in comparable Pd-catalyzed reactions.[48-49, 51] Despite this noteworthy progress, a majority of these methods are unable to effect the efficient coupling of acyclic secondary amines and rely on somewhat forcing conditions that, in some instances, hamper their applicability to increasingly complex substrates, including pharmaceuticals bearing multiple functional groups. With these considerations in mind, we aimed to develop a new class of anionic Cu ligands that would enable the general coupling of structurally diverse aryl halides and alkyl amines under mild conditions.

Here, we report the development of a new class of anionic ligands based on an N^1,N^2-diarylbenzene-1,2-diamine scaffold that enable Cu-catalyzed C–N bond formation at room temperature and is widely tolerant of many functional groups. Several iterations of ligand design afforded a catalyst system that enables the efficient coupling of structurally diverse aryl and heteroaryl bromides with a range of alkyl amine nucleophiles, including pharmaceuticals bearing multiple functional groups. A combination of computational and experimental studies demonstrated that the mechanism of C–N bond formation follows a catalytic cycle akin to related Pd-mediated transformations, where initial oxidative addition of the aryl bromide is followed by coordination and deprotonation of the amine, and a final reductive elimination to form the desired product. The optimized ligand yielded a 30-fold increase in the rate of C–N bond formation by facilitating rate-determining oxidative addition.

We commenced our investigations by targeting ligands based on N^1,N^2-diarylbenzene-1,2-diamine scaffolds, which upon deprotonation would form the corresponding doubly anionic bidentate ligands (**Figure 2A**). In addition to strongly coordinating Cu, these ligands are expected to increase the electron density of Cu in the active catalyst resulting in facile oxidative addition. However, in the absence of additional stabilizing interactions, the active catalyst supported by the simplest ligand in this class (**L1**) was predicted to be unstable at room temperature. Consistent with this, **L1**-ligated Cu was unable to affect the coupling of 4-bromoanisole (**1a**) and morpholine (**2a**) to form *N*-arylamine **3a** (**Table 1, Entry 1**).

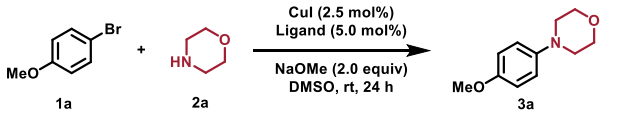
Given many examples of non-covalent interactions shown to have positive effects on transition metal catalysts,[16-18] we set out to design ligands capable of stabilizing the catalytically active Cu intermediate. Accordingly, pendant phenyl groups were installed onto the ligand scaffold to stabilize the corresponding Cu(I) complex *via* a π-interaction with the metal center (**L2, Figure 2A**). According to our calculations, upon establishing a π-interaction with the biphenyl arm of **L2** (**$L2_{Int}$, Figure 2B**), the active Cu catalyst was stabilized by 13.6 kcal/mol relative to its open form (**$L2_{Open}$**).[52] In addition, these calculations revealed that the energy barrier to oxidatively add 4-bromoanisole to **$L2_{Int}$** could be traversed at room temperature (**Figure 2C**) and that deactivation of the catalyst *via* reductive elimination of the aryl

halide with the ligand would be impeded by the pendant phenyl groups. When **L2** was employed in the coupling of **1a** and **2a**, *N*-arylamine **3a** was formed in quantitative yield utilizing NaOMe as the base and DMSO as the solvent ([**1a**] = 1M, **Table 1, Entry 2**). The use of alternative alkoxide bases such as NaO*i*Pr (**Table 1, Entry 3**) or NaO*t*Bu (**Table 1, Entry 4**) resulted in a significant decrease in the observed yield. Consistent with the required deprotonation of the N–H bonds of these ligands to form the active catalyst, weaker inorganic bases, such as K_2CO_3, resulted in 0% conversion (**Table 1, Entry 5**). Other polar aprotic solvents, such as MeCN, DMF, and NMP, resulted in poor conversion (See Supporting Information). Notably, when the aryl halide was changed from **1a** to a coordinating *N*-heterocycle, 3-bromopyridine, a significant decrease in yield was observed (**Table 1, Entry 6**).

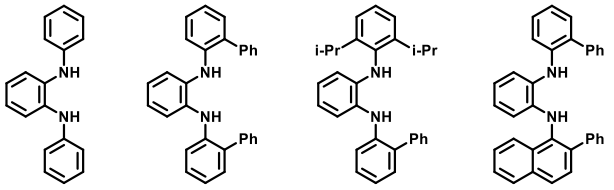
The installation of larger substituents onto the ligand (**L2**) was hypothesized to increase the yield by preventing coordination of the pyridine to Cu. However, changing the ligand structure from **L2** to **L3** did not affect the observed yield (**Table 1, Entry 7**), suggesting alternative designs would be needed to allow the efficient amination of heteroaryl bromides. The ligand structure was accordingly modified to increase the acidity of one of the amines, thereby facilitating the rapid formation of the active catalyst (**Figure 2A**). Upon installation of a naphthyl group (**L4**), 3-bromopyridine was coupled with morpholine in excellent yield (90%, **Table 1, Entry 8**).[53] The ability of the complex resulting from **L4**-ligated Cu to functionalize challenging substrates was also demonstrated in the coupling of morpholine with *N*-methyl-4-bromopyrazole (80% yield). In addition to allowing the transformation *N*-heterocycles, **L4** was found to offer an advantage in that larger alkoxide bases, such as NaO*i*Pr (**Table 1, Entry 10**) or NaO*t*Bu (**Table 1, Entry 11**), could be utilized without significant loss in yield (92% and 81%, respectively). This is important for the coupling of substrates that are sensitive to nucleophilic attack by methoxide. Importantly, the coupling reaction of **1a** and **2a** exhibited a significant rate increase when **L4** was utilized in place of **L1** (**Table 1, Entry 12**), with the reaction reaching completion in only one hour.

We first set out to determine the substrate scope using the catalyst derived from **L4**. The process was found to proceed at room temperature for a range aryl bromides (**Scheme 2**). Both electron-rich and electron-poor arenes were readily combined with primary (**1b, 1e, 1f, 1g, 1h, 1k, 1l,** and **1o**), acyclic secondary (**1n**), or cyclic secondary (**1a, 1c, 1d, 1i, 1j, 1m, 1p, and 1q**) amines in good-to-excellent yields. The reaction was found to be tolerant of a number of common functional groups as shown in Scheme 1, most notably a sulfone (**1b**), aryl chloride (**1e**), pendant heterocycles (**1f** and **1q**), acetal (**1h**), ketone (**1i**), nitrile (**1j**), alcohol (**1n**), tetrahydropyran (**1o**), and amide (**1p**). The room temperature conditions of this method allowed for the coupling of base sensitive 2,2,2-trifluoroethylamine in moderate yield (**1g**). Notably, the presence of relatively small groups at the ortho position on the aryl halide, such as methoxy (**1e** and **1l**) or thiomethyl (**1k**) groups were well tolerated. Additionally, an *ortho*-fluoride containing aryl bromide (**1h**) was coupled in good yield. With respect to limitations, the reactions of morpholine with arenes

Table 1. Substrate Scope of the Copper-Catalyzed Amination of Aryl Bromides[a]



Entry	Ligand	Deviation From Standard	Yield (%)
1	L1	None	0%
2	L2	None	99%
3	L2	Base = NaO*i*Pr	73%
4	L2	Base = NaO*t*Bu	21%
5	L2	Base = K_2CO_3	0%
6	L2	1a = 3-Bromopyridine	45%
7	L3	1a = 3-Bromopyridine	46%
8	L4	1a = 3-Bromopyridine	90%
9	L4	None	99%
10	L4	Base = NaO*i*Pr	92%
11	L4	Base = NaO*t*Bu	81%
12	L4	Time = 1 h	99%
13	None	None	0%
14	L4	No CuI	0%

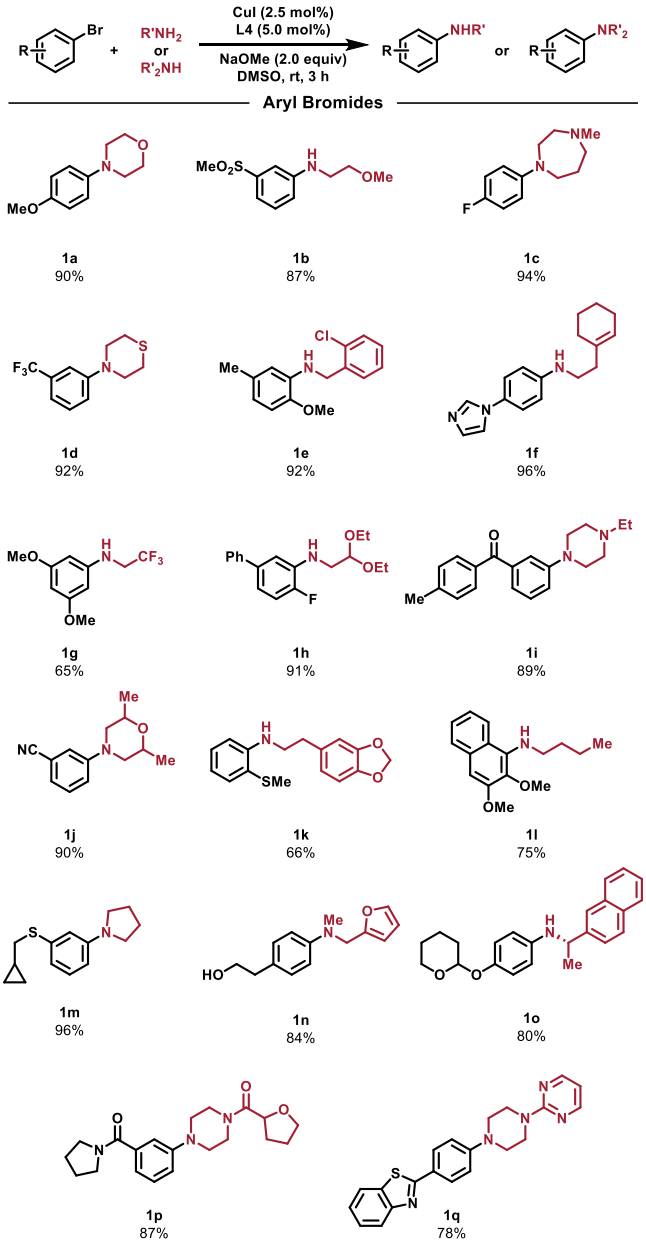


[a]Standard reaction conditions: aryl halide (**1a**, 0.20 mmol, 1.0 equiv), morpholine (**2a**, 0.24 mmol, 1.2 equiv), NaOMe (0.40 mmol, 2.0 equiv), CuI (2.5 mol%), Ligand (5.0 mol%), DMSO (0.20 mL), rt, 24 h. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.

containing primary or secondary amides, aniline motifs with acidic protons, unprotected phenols, esters, or enolizable ketones led to little or no formation of the desired product (See Supporting Information).

A variety of heteroaryl bromides were combined with an array of amines to provide the desired aryl amine products (**Scheme 2**). Heterocycles which often present difficulties in metal-catalyzed coupling reactions, due to their propensity to coordinate with the catalyst,[54] were good substrates in reactions with primary and cyclic secondary amines. *N*-heterocyclic aryl bromides including pyridine (**2a**), *N*-methylindazoles (**2b** and **2h**), *N*-methlyindole (**2d**), *N*-methypyrazole (**2e**), pyrimidine (**2f**), pyrazine (**2g**), and carbazole (**2i**) were all aminated in good-to-excellent yield. However, when 5-bromodindole featuring a free N-H heterocycle was utilized, 0% conversion was observed, presumably as a result of catalyst inhibition by the deprotonated heterocycle (for further details see Supporting Information). Additionally, attempting to couple aryl bromides derived from 1,3-azoles resulted in substrate decomposition (See Supporting Information), as is typically observed in the presence of strong alkoxide bases.[55-56] In the case of coupling a pyrazine derivative with 2-piperazinylpyridine, the standard

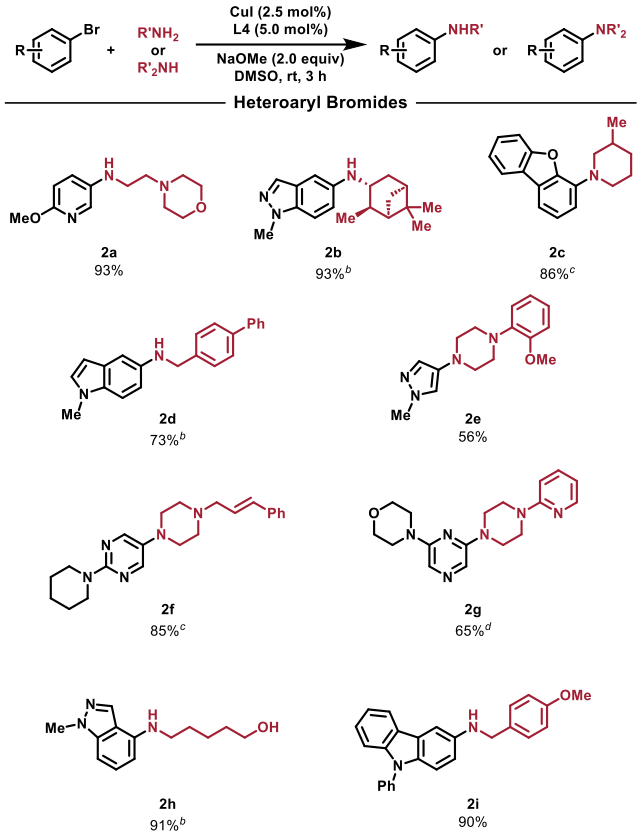
Scheme 1. Substrate Scope of the Copper-Catalyzed Amination of Aryl Bromides[a]



[a]All yields represent the average of two isolated yields. Standard reaction conditions: aryl halide (0.5 mmol), amine (0.6 mmol), NaOMe (1.0 mmol), CuI (2.5 mol%), **L4** (5.0 mol%), DMSO (0.5 mL), rt, 3 h.

reaction conditions yielded minimal amounts of the desired product (**2g**, 13% ^{1}H NMR yield). Instead, the product arising from a competitive S_NAr by methoxide ion was observed. To circumvent this problem, substitution of the less nucleophilic NaO*t*Bu resulted in a good yield of the desired coupling product (**2g**). In addition to *N*-containing heterocycles, the reaction proceeded efficiently in the presence of other heteroatom containing heterocycles, such as dibenzofuran (**2c**). The reaction tolerated various functional groups on both the heteroaryl halide and amine, including an aliphatic alcohol (**2h**), olefin (**2f**), and pendant heterocycle (**2a** and **2g**).

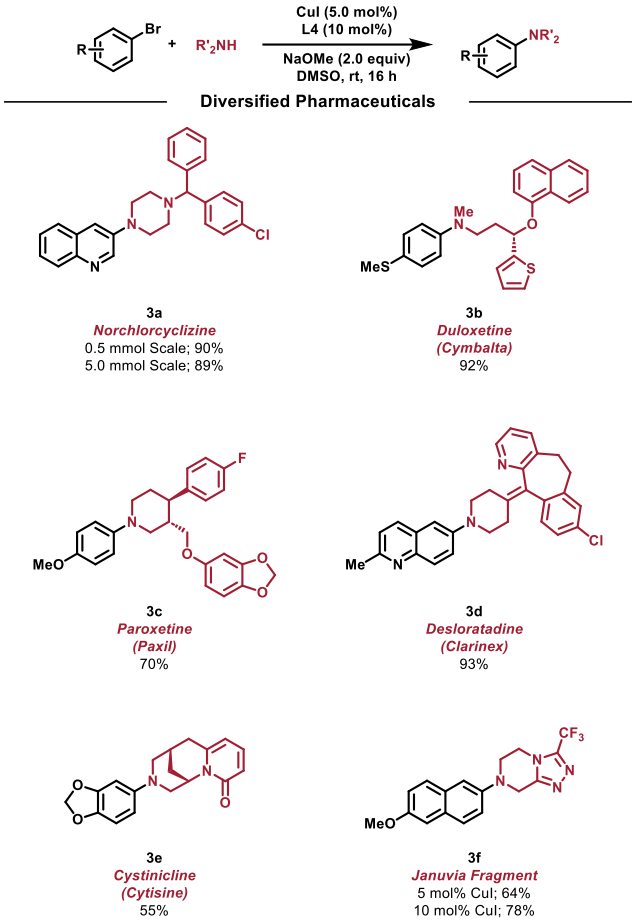
Scheme 2. Substrate Scope of the Copper-Catalyzed Amination of Heteroaryl Bromides[a]



[a]All yields represent the average of two isolated yields. Standard reaction conditions: aryl halide (0.5 mmol), amine (0.6 mmol), NaOMe (1.0 mmol), CuI (2.5 mol%), **L4** (5.0 mol%), DMSO (0.5 mL), rt, 3 h. [b]Reactions employed 5 mol% CuI and 10 mol% **L4** while keeping all other conditions the same as the standard reaction conditions. [c]Reactions were run for 16 h while keeping all other conditions the same as the standard reaction conditions. [d]NaO*t*Bu replaced NaOMe as the base for the coupling reaction to mitigate undesired S_NAr reactivity. Reactions also employed 5 mol% CuI, and 10 mol% **L4**.

To further highlight the synthetic utility and generality of this method, severally structurally complex pharmaceuticals bearing secondary amines were coupled with aryl (**3b**, **3c**, **3e**, and **3f**) or heteroaryl (**3a** and **3d**) bromides (**Scheme 3**). C–N cross-coupling reactions involving pharmaceutical derivatives bearing multiple functional groups have been shown to exhibit a high failure rate, even under Pd-catalysis.[57-59] Utilizing a **L4**-ligated Cu catalyst, various pharmaceuticals including Norchlorcyclizine (**3a**), Desloratadine (**3d**), and Duloxetine (**3b**) were all diversified to form the corresponding aminated products in excellent yields at room temperature. The newly developed catalyst system was found to be amenable to preparative scale synthesis. Using standard Schlenk techniques, the coupling of Norchlorcyclizine and 3-bromoquinoline was scaled up by a factor of 10 (5.0 mmol) to provide **3a** in excellent yield (89%, 1.85 g). Paroxetine was also coupled with 4-bromoanisole to provide **3c** in good yield. Additional pharmaceuticals bearing coordinating substituents were also

Scheme 3. Diversification of Pharmaceuticals Using this Copper-Catalyzed Aryl Halide Amination Protocol[a]



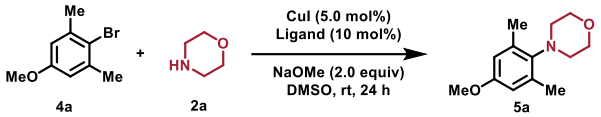
[a]All yields represent the average of two isolated yields. Standard reaction conditions: aryl bromide (0.5 mmol), amine (0.6 mmol), NaOMe (1.0 mmol), CuI (5.0 mol%), **L4** (10 mol%), DMSO (0.5 mL), rt, 16 h.

coupled with aryl bromides in moderate-to-good yields. Cystinicline, a smoking cessation aid bearing a 2-pyridone substructure, was coupled with 3,4-(methylenedioxy)bromobenzene (**3e**). Additionally, a fragment of the antidiabetic Januvia bearing a functionalized triazole was coupled with 2-bromo-6-methoxynaphtalene in 64% yield (**3f**). Increasing the catalyst loading to 10 mol% and diluting the reaction mixture to 0.5 M with respect to the aryl halide resulted in an increase in **3f** yield to 78%. Collectively, the ability of this method to perform efficient C–N couplings on complex pharmaceuticals is particularly noteworthy and further establishes its generality.

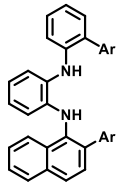
Despite the ability of the **L4**-based Cu catalyst to efficiently aminate a wide variety of aryl and heteroaryl bromides, the installation of *ortho*-alkyl groups on the aryl bromide resulted in a severely diminished yield. For instance, attempting to couple morpholine with a model hindered aryl bromide, 3,5-dimethyl-4-bromoanisole (**4a**), resulted in poor yield and conversion (**Scheme 4A, Entry 1**). Additional substrates were evaluated to further probe this observation. As an example, while **4b** was isolated in good yield, the introduction of a single *ortho*-methyl group resulted in a significant decrease in the isolated yield (**4c**). The introduction of

Scheme 4. Optimization of Ligand Structure to Enable the Coupling of Hindered Aryl Bromides and α-Tertiary Amines

A. Model Reaction Utilizing Hindered Aryl Bromide[a]

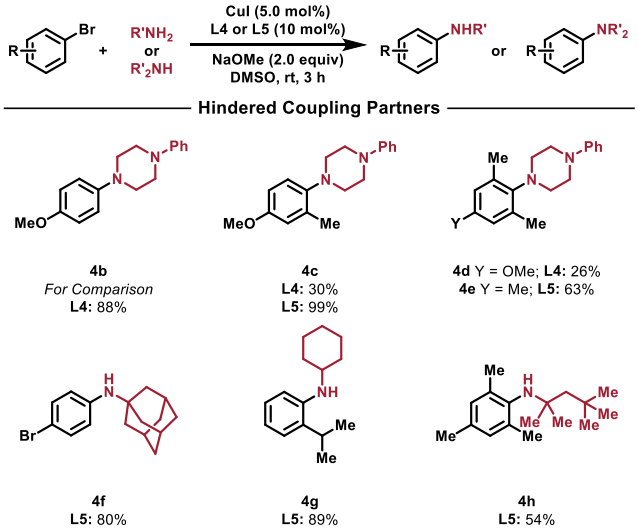


Entry	Ligand	Deviation From Standard	Yield (%)
1	L4	None	35%
2	L5	None	74%
3	None	None	0%
4	L5	No CuI	0%



L4: Ar = Ph
L5: Ar = 3,5-(*t*-Bu)$_2$C$_6$H$_3$

B. Substrate Scope of Hindered Coupling Partners[b]



[a]Standard reaction conditions: aryl halide (**1a**, 0.20 mmol, 1.0 equiv), morpholine (**2a**, 0.24 mmol, 1.2 equiv), NaOMe (0.40 mmol, 2.0 equiv), CuI (5.0 mol%), Ligand (10 mol%), DMSO (0.20 mL), rt, 24 h. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [b]All yields represent the average of two isolated yields. Standard reaction conditions: aryl bromide (0.5 mmol), amine (0.6 mmol when utilizing **L4**, 0.7 mmol when utilizing **L5**), NaOMe (1.0 mmol), CuI (5.0 mol%), **L4** or **L5** (10 mol%), DMSO (0.5 mL), rt, 3 h.

a second *ortho*-methyl group had negligible additional impact on the yield (**4d**). In both cases, the remaining mass balance was made up by unreacted starting material. We hypothesized that the poor conversion of the hindered bromides was a result of catalyst deactivation, presumably *via* an intramolecular C–H amination of **L4**. In order to retard this undesired process, while retaining the crucial design elements of **L4**, we installed *tert*-butyl groups on the pendant phenyl arms of **L4** to afford **L5**. Utilizing **L5** in the coupling of **4a** resulted in a significant yield increase (**Scheme 4A, Entry 2**), enabling a ligand that can be utilized the coupling of hindered coupling partners such as *ortho*-substituted aryl bromides or α-tertiary amines. Consistent with the model reaction, **L5** ligated Cu efficiently aminated 2-bromocumene (**4g**). **L5** also enabled the efficient coupling of α-tertiary amines, such as adamantylamine to yield the

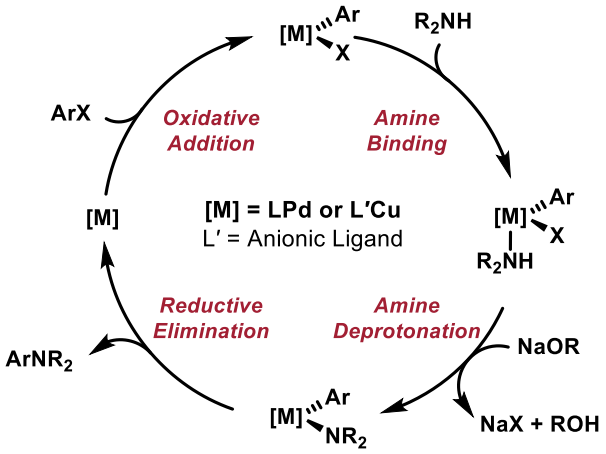


Figure 3. Commonly accepted mechanism of C–N cross-couplings catalyzed by phosphine ligated Pd or Cu species ligated with anionic ligands.

psychostimulant Bromantane (**4f**), and 1,1,3,3-tetramethylbutylamine (**4h**) which was coupled with an aryl bromide bearing two *ortho*-methyl groups. Additionally, **4c** and a structurally similar molecule to **4d** (**4e**) were reevaluated with **L5**, and significant increases in yields were observed. Taken together **L5** overcomes limitations in the coupling of hindered aryl bromides and amines, further establishing the generality of this method.

The mechanism of the Cu-catalyzed aryl halide amination was explored using a combined experimental and computational approach. The commonly accepted mechanism for reactions catalyzed by Cu ligated with anionic ligands is similar to Pd-catalyzed C-N couplings.[25, 60] In these systems, oxidative addition is followed by sequential amine binding and deprotonation, and reductive elimination to provide the aminated product (**Figure 3**). Conversely, Cu-based systems employing charge-neutral ligands typically engage in amine binding/deprotonation prior to oxidative addition which may account for why these systems are generally inefficient in the coupling of alkyl amines and aryl halides.[25, 60-61]

To elucidate the mechanism of the described catalytic system we first turned to DFT-calculations.[50] The energy profile of the most probable mechanism is illustrated in **Figure 4**. The catalytic cycle begins with the formation of the active catalyst. *In situ* generated $[Cu(OMe)_2]^-$ (**1**) deprotonates **L4** to yield the **L4** ligated complex **2** at –3.6 kcal/mol, which represents the resting state in the proposed mechanism. Subsequent deprotonation of **L4** *via* **2-TS** with an overall barrier of 15.3 kcal/mol followed by dissociation of a methoxide ion forms the catalytically active complex (**4**), which features a stabilizing π-interaction between the metal center and the biphenyl arm of **L4**. Oxidative addition of 4-bromoanisole to the active Cu catalyst proceeds with an overall barrier of 17.5 kcal/mol (*via* **4-TS**) with respect to the resting state. Dissociation of the bromide ion from oxidative addition complex **5** followed by binding (**7**) and deprotonation of morpholine yields **8**, which produces the desired *N*-aryl amine *via* an energetically facile, post-rate limiting reductive elimination. Overall, the results of these calculations predict oxidative addition to be rate-limiting and are consistent with the observation that the entire reaction sequence can take place at room temperature.[62]

To experimentally probe the mechanism proposed by DFT calculations, we determined the experimental rate law for the coupling of 4-bromoanisole and morpholine catalyzed by **L4** ligated Cu using initial rate measurements.[63]

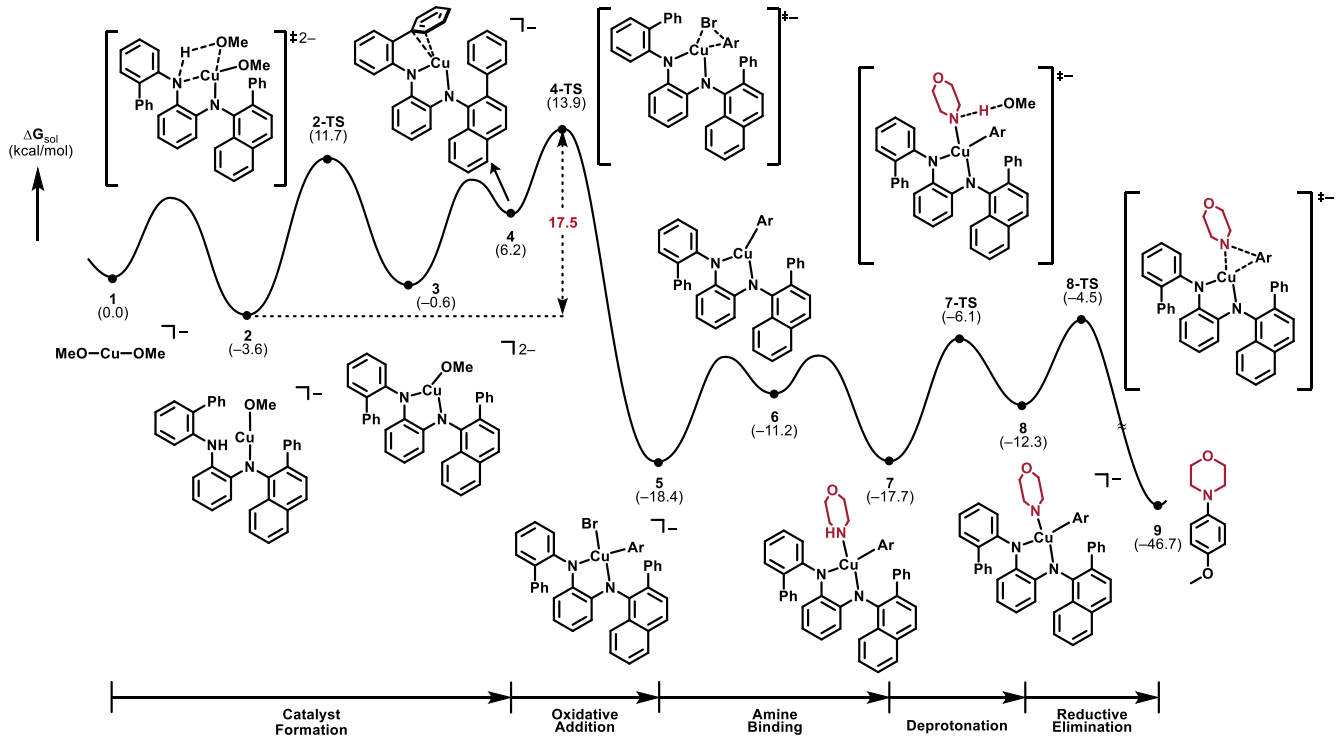


Figure 4. Energy profile of the proposed mechanism for the coupling of 4-bromoanisole and morpholine by copper species supported by **L4**.

Independently varying the concentrations of morpholine or NaOMe did not impact initial rate of the transformation, discounting the possibility that amine binding and deprotonation or catalyst formation were rate-limiting. The reaction exhibited a positive first order dependence on both the concentration of 4-bromoanisole and Cu/**L4**, consistent with a rate-limiting oxidative addition event. In addition to probing the reaction kinetics by initial rates, a Hammett analysis (see Supporting Information for details) of the reaction rates of various 4-substituted bromobenzene derivatives revealed a positive ρ value (+0.27), in-line with observations made in the study of related Cu-catalyzed transformations featuring rate-limiting oxidative addition.[60] Taken together, the results of the kinetic experiments support the results of the DFT-calculations, and are consistent with the mechanism commonly proposed for Cu-catalyzed C–N couplings employing anionic ligands.

We next set out to determine the origin of the rate enhancement displayed by reactions utilizing **L4** relative to those using **L2**. Initial rate experiments in the presence of varying numbers of equivalents of 4-bromoanisole demonstrated that reactions catalyzed by **L2** ligated Cu exhibited a first order rate dependence, suggesting that ligand identity does not alter the operative mechanism. Comparison of the initial rates of reactions employing **L2** and **L4** revealed a 30-fold rate enhancement in the case of the latter, suggesting that **L4** plays a significant role in lowering the energy barrier to the rate-determining oxidative addition (**Figure 5A**). DFT calculations were utilized to probe the impacts of the naphthyl group on the apparent lowering of the barrier to oxidative addition (**Figure 5B**). Within the oxidative addition transition state (**4-TS**), the incoming aryl halide can approach in one of two orientations: the aryl ring can position itself either parallel to the naphthyl group (**4-TS**) or the biphenyl arm of **L4** (**4-TS′**). Calculations revealed that positioning the incoming aryl halide over the naphthyl ring leads to a significant lowering of the energetic barrier (4.6 kcal/mol). To clarify the factors responsible for this energy difference, **4-TS** and **4-TS′** were studied using a distortion-interaction analysis by partitioning the transition state structures into substrate and ligated metal fragments (**Figure 5C**).[64-65] As shown in **Figure 5C**, the analysis revealed that the energy difference between **4-TS** and **4-TS′** originates primarily from the differences in interaction energies (6.6 kcal/mol). Furthermore, this analysis implies that **L4** enables facile oxidative addition by leveraging the stabilizing π-π interaction between the incoming aryl halide and naphthyl residue, thereby leading to the observed rate increase. Collectively, the results of the DFT calculations and kinetic experiments highlight the importance of non-covalent interactions in this catalyst design to (1) stabilize the active catalyst and (2) accelerate oxidative addition.

In summary, we have developed a general method for Cu-catalyzed amination of aryl bromides at room temperature. Central to this advance was the design of new anionic ligands that substantially lower the energy barrier to oxidative addition and stabilize the active catalyst through non-covalent interactions. This method was successfully applied to the amination of structurally diverse aryl and heteroaryl halides using a variety of amine nucleophiles, including pharmaceuticals bearing multiple functional groups.

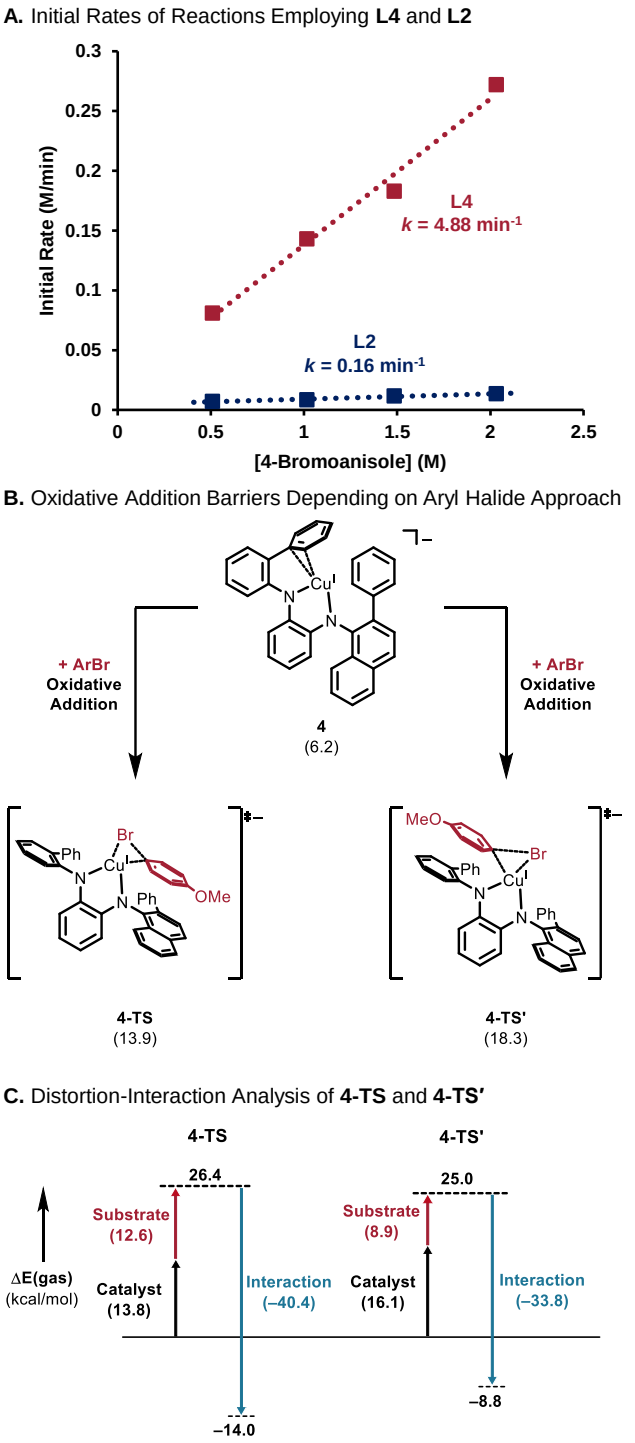


Figure 5. Interactions underlying rate enhancements of reactions employing **L4** vs **L2**. (A) Comparison of initial rates of reactions employing **L4** (red) and **L2** (blue) to couple 4-bromoanisole and morpholine. (B) Energy barriers to oxidative addition when the aryl bromide approaches parallel to the naphthyl group of **L4** (**4-TS**) vs parallel to the biphenyl group of **L4** (**4-TS′**). (C) Distortion-interaction analysis of **4-TS** and **4-TS′**. Energies in (B) and (C) are referenced to $[Cu(OMe)_2]^-$ and are expressed in kcal/mol.

Combined experimental and computational experiments demonstrate that amination takes place by a mechanism akin to the well-explored Pd-analogues, and that the naphthyl group of **L4** plays a crucial role in accelerating the

transformation by stabilizing the rate-limiting oxidative addition transition state through π-stacking aromatic interactions. We anticipate that the results of this study will motivate further explorations into Cu-catalyzed C–heteroatom bond-forming reactions.

ASSOCIATED CONTENT

The Supporting Information is available free of charge at https://pubs.acs.org.

Experimental procedures, spectral data, additional kinetic data, and information regarding the DFT calculations (PDF)

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REFERENCES

1. Vitaku, E.; Smith, D. T.; Njardarson, J. T., Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014,** *57*, 10257-10274.
2. Mari, M.; Bartoccini, F.; Piersanti, G., Synthesis of (−)-Epi-Indolactam V by an Intramolecular Buchwald–Hartwig C–N Coupling Cyclization Reaction. *J. Org. Chem.* **2013,** *78*, 7727-7734.
3. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S., Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine. *Angew. Chem. Int. Ed.* **2011,** *50*, 2716-2719.
4. Konkol, L. C.; Guo, F.; Sarjeant, A. A.; Thomson, R. J., Enantioselective Total Synthesis and Studies into the Configurational Stability of Bismurrayaquinone A. *Angew. Chem. Int. Ed.* **2011,** *50*, 9931-9934.
5. Sperry, J. B.; Price Wiglesworth, K. E.; Edmonds, I.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Piatnitski Chekler, E. L.; Langille, J.; Coe, J. W., Kiloscale Buchwald–Hartwig Amination: Optimized Coupling of Base-Sensitive 6-Bromoisoquinoline-1-carbonitrile with (S)-3-Amino-2-methylpropan-1-ol. *Org. Proc. Res. Dev.* **2014,** *18*, 1752-1758.
6. Affouard, C.; Crockett, R. D.; Diker, K.; Farrell, R. P.; Gorins, G.; Huckins, J. R.; Caille, S., Multi-Kilo Delivery of AMG 925 Featuring a Buchwald–Hartwig Amination and Processing with Insoluble Synthetic Intermediates. *Org. Proc. Res. Dev.* **2015,** *19*, 476-485.
7. Ku, Y.-Y.; Chan, V. S.; Christesen, A.; Grieme, T.; Mulhern, M.; Pu, Y.-M.; Wendt, M. D., Development of a Convergent Large-Scale Synthesis for Venetoclax, a First-in-Class BCL-2 Selective Inhibitor. *J. Org. Chem.* **2019,** *84*, 4814-4829.
8. Yang, Q.; Zhao, Y.; Ma, D., Cu-Mediated Ullmann-Type Cross-Coupling and Industrial Applications in Route Design, Process Development, and Scale-up of Pharmaceutical and Agrochemical Processes. *Org. Proc. Res. Dev.* **2022,** *26*, 1690-1750.
9. 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.
10. Shukla, J.; Ajayakumar, M. R.; Mukhopadhyay, P., Buchwald-Hartwig Coupling at the Naphthalenediimide Core: Access to Dendritic, Panchromatic NIR Absorbers with Exceptionally Low Band Gap. *Org. Lett.* **2018,** *20*, 7864-7868.
11. Astridge, D. D.; Hoffman, J. B.; Zhang, F.; Park, S. Y.; Zhu, K.; Sellinger, A., Polymer Hole Transport Materials for Perovskite Solar Cells via Buchwald–Hartwig Amination. *ACS Appl. Polym. Mater.* **2021,** *3*, 5578-5587.
12. Chen, J.; Yan, W.; Townsend, E. J.; Feng, J.; Pan, L.; Del Angel Hernandez, V.; Faul, C. F. J., Tunable Surface Area, Porosity, and Function in Conjugated Microporous Polymers. *Angew. Chem. Int. Ed.* **2019,** *58*, 11715-11719.
13. Ruiz-Castillo, P.; Buchwald, S. L., Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016,** *116*, 12564-12649.
14. Brown, D. G.; Boström, J., Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016,** *59*, 4443-4458.
15. Wang, Q.; Su, Y.; Li, L.; Huang, H., Transition-metal catalysed C–N bond activation. *Chem. Soc. Rev.* **2016,** *45*, 1257-1272.
16. Surry, D. S.; Buchwald, S. L., Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. *Chem. Sci.* **2011,** *2*, 27-50.
17. Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L., Biaryl monophosphine ligands in palladium-catalyzed C–N coupling: An updated User's guide. *Tetrahedron* **2019,** *75*, 4199-4211.
18. Surry, D. S.; Buchwald, S. L., Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2008,** *47*, 6338-6361.
19. Martin, R.; Buchwald, S. L., Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008,** *41*, 1461-1473.
20. McCann, S. D.; Reichert, E. C.; Arrechea, P. L.; Buchwald, S. L., Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability. *J. Am. Chem. Soc.* **2020,** *142*, 15027-15037.
21. Chatzopoulou, M.; Madden, K. S.; Bromhead, L. J.; Greaves, C.; Cogswell, T. J.; Da Silva Pinto, S.; Galan, S. R. G.;

Georgiou, I.; Kennedy, M. S.; Kennett, A.; Apps, G.; Russell, A. J.; Wynne, G. M., Pilot Study to Quantify Palladium Impurities in Lead-like Compounds Following Commonly Used Purification Techniques. *ACS Med. Chem. Lett.* **2022,** *13*, 262-270.

22. Garrett, C. E.; Prasad, K., The Art of Meeting Palladium Specifications in Active Pharmaceutical Ingredients Produced by Pd-Catalyzed Reactions. *Adv. Syn. Catal.* **2004,** *346*, 889-900.

23. Magano, J., Large-Scale Applications of Transition Metal Removal Techniques in the Manufacture of Pharmaceuticals. In *Transition Metal-Catalyzed Couplings in Process Chemistry*, 2003; pp 313-355.

24. Roughley, S. D.; Jordan, A. M., The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011,** *54*, 3451-3479.

25. Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D., Selected Copper-Based Reactions for C–N, C–O, C–S, and C–C Bond Formation. *Angew. Chem. Int. Ed.* **2017,** *56*, 16136-16179.

26. Elemental Impurities - Limits. United States Phamocopedia (USP) Website https://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/key-issues/c232-usp-39.pdf (accessed Oct 17, 2022).

27. Ueda, S.; Buchwald, S. L., Catalyst-Controlled Chemoselective Arylation of 2-Aminobenzimidazoles. *Angew. Chem. Int. Ed.* **2012,** *51*, 10364-10367.

28. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L., Expanding Pd-Catalyzed C–N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions. *J. Am. Chem. Soc.* **2003,** *125*, 6653-6655.

29. Ullmann, F.; Bielecki, J., Ueber Synthesen in der Biphenylreihe. *Berichte der deutschen chemischen Gesellschaft* **1901,** *34*, 2174-2185.

30. Ullmann, F., Ueber eine neue Bildungsweise von Diphenylaminderivaten. *Berichte der deutschen chemischen Gesellschaft* **1903,** *36*, 2382-2384.

31. Surry, D. S.; Buchwald, S. L., Diamine ligands in copper-catalyzed reactions. *Chem. Sci.* **2010,** *1*, 13-31.

32. Altman, R. A.; Buchwald, S. L., Cu-catalyzed Goldberg and Ullmann reactions of aryl halides using chelating N- and O-based ligands. *Nat. Protocols* **2007,** *2*, 2474-2479.

33. Cicco, L.; Hernández-Fernández, J. A.; Salomone, A.; Vitale, P.; Ramos-Martín, M.; González-Sabín, J.; Presa Soto, A.; Perna, F. M.; Capriati, V.; García-Álvarez, J., Copper-catalyzed Goldberg-type C–N coupling in deep eutectic solvents (DESs) and water under aerobic conditions. *Org. Biomol. Chem.* **2021,** *19*, 1773-1779.

34. Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L., The Role of Chelating Diamine Ligands in the Goldberg Reaction: A Kinetic Study on the Copper-Catalyzed Amidation of Aryl Iodides. *J. Am. Chem. Soc.* **2005,** *127* (12), 4120-4121.

35. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L., A General and Efficient Copper Catalyst for the Amidation of Aryl Halides and the N-Arylation of Nitrogen Heterocycles. *J. Am. Chem. Soc.* **2001,** *123*, 7727-7729.

36. Klapars, A.; Huang, X.; Buchwald, S. L., A General and Efficient Copper Catalyst for the Amidation of Aryl Halides. *J. Am. Chem. Soc.* **2002,** *124*, 7421-7428.

37. Crawford, K. R.; Padwa, A., Copper-catalyzed amidations of bromo substituted furans and thiophenes. *Tet. Lett.* **2002,** *43*, 7365-7368.

38. Goldberg, I., Ueber Phenylirungen bei Gegenwart von Kupfer als Katalysator. *Berichte der deutschen chemischen Gesellschaft* **1906,** *39*, 1691-1692.

39. Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L., Copper–Diamine-Catalyzed N-Arylation of Pyrroles, Pyrazoles, Indazoles, Imidazoles, and Triazoles. *J. Org. Chem.* **2004,** *69*, 5578-5587.

40. Bernhardson, D. J.; Widlicka, D. W.; Singer, R. A., Cu-Catalyzed Couplings of Heteroaryl Primary Amines and (Hetero)aryl Bromides with 6-Hydroxypicolinamide Ligands. *Org. Proc. Res. Dev.* **2019,** *23*, 1538-1551.

41. 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.

42. Ma, D.; Cai, Q.; Zhang, H., Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides. *Org. Lett.* **2003,** *5*, 2453-2455.

43. Zhang, H.; Cai, Q.; Ma, D., Amino Acid Promoted CuI-Catalyzed C–N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles. *J. Org. Chem.* **2005,** *70*, 5164-5173.

44. Kwong, F. Y.; Buchwald, S. L., Mild and Efficient Copper-Catalyzed Amination of Aryl Bromides with Primary Alkylamines. *Org. Lett.* **2003,** *5*, 793-796.

45. Yang, C.-T.; Fu, Y.; Huang, Y.-B.; Yi, J.; Guo, Q.-X.; Liu, L., Room-Temperature Copper-Catalyzed Carbon–Nitrogen Coupling of Aryl Iodides and Bromides Promoted by Organic Ionic Bases. *Angew. Chem. Int. Ed.* **2009,** *48* (40), 7398-7401.

46. Zhang, Y.; Yang, X.; Yao, Q.; Ma, D., CuI/DMPAO-Catalyzed N-Arylation of Acyclic Secondary Amines. *Org. Lett.* **2012,** *14* (12), 3056-3059.

47. Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D., CuI/Oxalic Diamide Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amines. *J. Am. Chem. Soc.* **2015,** *137*, 11942-11945.

48. Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D., Discovery of N-(Naphthalen-1-yl)-N′-alkyl Oxalamide Ligands Enables Cu-Catalyzed Aryl Amination with High Turnovers. *Org. Lett.* **2017,** *19*, 2809-2812.

49. Chen, Z.; Ma, D., Cu/N,N′-Dibenzyloxalamide-Catalyzed N-Arylation of Heteroanilines. *Org. Lett.* **2019,** *21*, 6874-6878.

50. Li, S.; Huang, X.; Gao, Y.; Jin, J., Oxalamide/Amide Ligands: Enhanced and Copper-Catalyzed C–N Cross-Coupling for Triarylamine Synthesis. *Org. Lett.* **2022,** *24*, 5817-5824.

51. Fan, M.; Zhou, W.; Jiang, Y.; Ma, D., Assembly of Primary (Hetero)Arylamines via CuI/Oxalic Diamide-Catalyzed Coupling of Aryl Chlorides and Ammonia. *Org. Lett.* **2015,** *17*, 5934-5937.

52. The calculations are carried out employing B3LYP-D3/LACVP/6-31G** level of theory for the geometry optimization, vibration, and solvation energy calculations. The electronic energies of all optimized structures were reevaluated with B3LYP-D3/LACV3P/cc-pVTZ(-f). Greater details pertaining to the computation methods are given in the supporting information.

53. For a full account of all ligands screened, see Supporting Information.

54. Sather, A. C.; Martinot, T. A., Data-Rich Experimentation Enables Palladium-Catalyzed Couplings of Piperidines and Five-Membered (Hetero)aromatic Electrophiles. *Org. Proc. Res. Dev.* **2019,** *23*, 1725-1739.

55. Casey, M. L.; Kemp, D. S.; Paul, K. G.; Cox, D. D., Physical organic chemistry of benzisoxazoles. I. Mechanism of the base-catalyzed decomposition of benzisoxazoles. *J. Org. Chem.* **1973,** *38*, 2294-2301.

56. Kemp, D. S.; Casey, M. L., Physical organic chemistry of benzisoxazoles. II. Linearity of the Broensted free energy relation for the base-catalyzed decomposition of benzisoxazoles. *J. Am. Chem. Soc.* **1973,** *95*, 6670-6680.

57. Kutchukian, P. S.; Dropinski, J. F.; Dykstra, K. D.; Li, B.; DiRocco, D. A.; Streckfuss, E. C.; Campeau, L.-C.; Cernak, T.; Vachal, P.; Davies, I. W.; Krska, S. W.; Dreher, S. D., Chemistry informer libraries: a chemoinformatics enabled approach to evaluate and advance synthetic methods. *Chem. Sci.* **2016,** *7*, 2604-2613.

58. Lin, S.; Dikler, S.; Blincoe, W. D.; Ferguson, R. D.; Sheridan, R. P.; Peng, Z.; Conway, D. V.; Zawatzky, K.; Wang, H.; Cernak, T.; Davies, I. W.; DiRocco, D. A.; Sheng, H.; Welch, C. J.; Dreher, S. D., Mapping the dark space of chemical reactions with extended

nanomole synthesis and MALDI-TOF MS. *Science* **2018,** *361* (6402), eaar6236.

59. Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L., Pharmaceutical diversification via palladium oxidative addition complexes. *Science* **2019,** *363*, 405-408.

60. Ribas, X.; Güell, I., Cu(I)/Cu(III) catalytic cycle involved in Ullmann-type cross-coupling reactions. *Pure Appl. Chem.* **2014,** *86*, 345-360.

61. Casitas, A.; Ribas, X., The role of organometallic copper(iii) complexes in homogeneous catalysis. *Chem. Sci.* **2013,** *4*, 2301-2318.

62. Additional details and a more in-depth discussion of the possible mechanisms can be found in the supporting information.

63. Initial rates were conducted for operational simplicity and conversions were kept under 50% to insure linearity. In all cases, reactions were found to be well-behaved and had perfect mass balances.

64. Bickelhaupt, F. M.; Houk, K. N., Analyzing Reaction Rates with the Distortion/Interaction-Activation Strain Model. *Angew. Chem. Int. Ed.* **2017,** *56*, 10070-10086.

65. Green, A. G.; Liu, P.; Merlic, C. A.; Houk, K. N., Distortion/Interaction Analysis Reveals the Origins of Selectivities in Iridium-Catalyzed C–H Borylation of Substituted Arenes and 5-Membered Heterocycles. *J. Am. Chem. Soc.* **2014,** *136*, 4575-4583.