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Cu-Catalyzed Amination of Base-Sensitive Aryl Bromides and the Chemoselective N- and O-Arylation of Amino Alcohols

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c05246.

Experimental procedures, spectral data, additional calorimetry data, additional substrates not featured in the manuscript, and details of DFT calculations (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c05246

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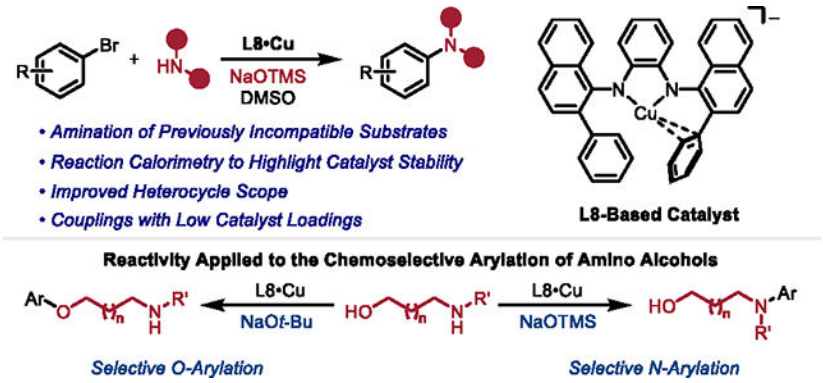
Abstract

We report a general and functional-group-tolerant method for the Cu-catalyzed amination of base-sensitive aryl bromides including substrates possessing acidic functional groups and small five-membered heteroarenes. The results presented herein substantially expand the scope of Cu-catalyzed C–N coupling reactions. The combination of **L8**, an anionic N^1,N^2-diarylbenzene-1,2-diamine ligand, along with the mild base NaOTMS leads to the formation of a stable yet reactive catalyst that resists deactivation from coordination to heterocycles or charged intermediates. This system enables the use of low catalyst and ligand loadings. Exploiting the differences in nucleophile deprotonation in C–O and C–N coupling reactions catalyzed by Cu·**L8** we developed a method to chemoselectively *N*- and *O*-arylate a variety of amino alcohol substrates. Employing NaO*t*-Bu as the base resulted exclusively in C–O coupling when the amino alcohols featured primary alcohols and more hindered amines or aniline groups. Utilizing NaOTMS enabled the ability to override the steric-based selectivity of these reactions completely and exclusively promoted C–N coupling regardless of the structure of the amino alcohol. The ability to invert the observed chemoselectivity is distinct from previously described methods that require protecting group manipulations or rely entirely on steric effects to control reactivity. These results substantially improve the scope of Cu-catalyzed C–N coupling reactions using N^1,N^2-diarylbenzene-1,2-diamine ligands and introduce a new chemoselective method to arylate amino alcohols.

Graphical Abstract



INTRODUCTION

N-aryl amines are among the most important structural features found in pharmaceuticals,[1–6] natural products,[7–9] agrochemicals,[10–13] and organic materials.[14–16] In recent years, Cu-catalyzed approaches to C–N bond formation have emerged as promising alternatives

to well-established Pd-catalyzed methods by offering the use of a metal catalyst with diminished cost and toxicity,[17–20] along with, in some cases, orthogonal reactivity.[21,22] Central to these advances has been the development of new ligands to support the Cu-centered catalyst. Early ligand designs involved charge-neutral molecules, such as *trans*-cyclohexane-1,2-diamine[23,24] and phenanthroline derivatives,[25] to facilitate amidation or *N*-heterocycle arylation. Despite the efficacy of these catalysts, even on process scale,[26,27] the coupling of alkyl amines and aryl halides has remained challenging. One strategy to overcome this limitation is to generate electron-rich Cu intermediates through the use of anionic ligands.[19,28–31] Such ligands accelerate challenging oxidative addition of aryl halides, thereby overcoming the limitations of systems relying on charge-neutral ligands.[32,33] This strategy has resulted in the development of several families of anionic ligands, beginning with amino acids, with the most notable being the oxalic acid- and oxalamide-based ligands pioneered by Ma.[34–38]

Recently, we reported a new class of anionic Cu ligands based on the N^1,N^2-diarylbenzene-1,2-diamine scaffold.[32] Guided by density functional theory (DFT) calculations, these ligands were designed to substantially increase the electron density on Cu while stabilizing the active anionic catalyst through a Cu–π interaction (Figure 1A). Including a naphthyl residue in the backbone of the optimal ligand, **L4**, played a critical role in lowering the barrier to arene oxidative addition, enabling rapid C–N bond formation at room temperature. While the catalyst derived from **L4** promoted the coupling of many aryl bromides with aliphatic amines, it required the use of strong alkoxide bases (NaOMe or NaO*t*-Bu). These compromised functional group compatibilities, especially with base-sensitive groups such as enolizable ketones, secondary amides, and carboxylic acids. Furthermore, the previously described method was unable to affect the coupling of small five-membered heteroaryl halides (i.e., thiazole, pyrazole, triazole, etc.) due to their propensity to decompose in the presence of a strong base.[39–41] Given that these are ubiquitous structural components in pharmaceuticals,[42] we set out to improve upon our previous report by designing a catalyst system that can form C–N bonds using a weaker base.

One challenge we identified was that the activation of the N^1,N^2-diarylbenzene-1,2-diamine ligand family is reliant on ligand deprotonation. We hypothesized that the use of a ligand featuring more acidic N–H bonds would be crucial. In addition to the need to efficiently deprotonate the ligand to form the active catalyst, deprotonation of many base-sensitive substrates yields charged small molecules with a propensity to coordinate to, and subsequently deactivate, many metal catalysts.[41,43,44] For instance, it was not until recently that we reported a general Pd-catalyzed method to efficiently aminate base-sensitive heteroarenes using the mild base NaOTMS (Figure 1B).[45] These challenges are magnified when analyzing many Cu-catalyzed methods in which couplings involving arenes bearing base-sensitive functional groups or halogenated heteroarenes are often limited in scope. To overcome these challenges, we surmised that a successful catalyst would likely need to be resistant to coordination-induced catalyst deactivation pathways. We thus set out to explore the use of NaOTMS in our Cu-catalyzed C–N coupling chemistry to expand the scope and potential usefulness of this emerging ligand class (Figure 1C).

RESULTS AND DISCUSSION

We began by examining the coupling of 4-bromoanisole (**1a**) with morpholine (**2a**) to yield *N*-aryl amine **3a** (Figure 2A). Our recent finding that the mild base NaOTMS was useful in the Pd-catalyzed amination of aryl halides,[45] induced us to examine its utility with the catalyst derived from **L8**.[46] We reasoned that the presence of naphthyl groups on both of the amine residues would enhance the acidity of the N–H bonds of **L8** relative to those in the ligands previously described (**L4** and **L5**) that were not able to efficiently form **3a** using NaOTMS as the base.[32,47] DFT calculations demonstrated lower energy barriers to access the oxidative addition transition state when **L8** was utilized with NaOTMS, relative to **L4** under analogous conditions.[47] DFT calculations also demonstrated a higher energy barrier to destructive ligand arylation in the catalyst derived from **L8**, relative to the catalyst derived from **L4**. Similar observations were also made in a recent report on C–O coupling reactions.[46] In practice, the use of NaOTMS as the base in the coupling reaction enabled quantitative formation of **3a** at room temperature (Figure 2A, entry 1). Alternative bases such as K_2CO_3, Et_3N, and DBU resulted in 0% conversion of **1a**, presumably due to their inability to activate **L8** (Figure 2A, entries 2–4). Phosphazene bases[48] resulted in poor to moderate yields of **3a** (Figure 2A, entries 5–7) even employing elevated reaction temperatures or concentrations.

Recently, Hartwig reported on the Cu-catalyzed coupling of phenols and aryl halides that proceeded through oxidative addition to a Cu(II) complex, aided by electron delocalization onto the anionic oxalamide-based ligand.[49] While we found the use of $CuBr_2$ as the Cu-source led to good yields of **3a** (Figure 2A, entry 9), C–N coupling with our catalyst system did not proceed when conducted open to the air. This finding is inconsistent with an active Cu(II) catalyst. Additionally, the use of a Cu(II) precursor in the reaction was accompanied by a 15 min induction period that was noticeably absent when a Cu(I) source was used.[47] We attribute this induction period to the reduction of Cu(II) to Cu(I) by excess amine or base in the reaction before productive catalysis can occur. This points to the mechanistic differences between our catalyst and Hartwig's.

To improve the versatility of this C–N coupling method, alternative polar aprotic solvents were screened as potential DMSO replacements.[50,51] The use of DMAc and 1,3-dimethyl-2-imidazolidinone (DMI) led to the quantitative formation of **3a**, while *N*,*N*′-dimethylpropyleneurea (DMPU) resulted in a moderate yield (Figure 2A, entries 10–12). The use of less polar solvents, such as THF, resulted in 0% conversion of **1a** (Figure 2A, entry 13). We hypothesize that the requisite use of polar aprotic solvents involves their role in stabilizing the active anionic catalyst. Finally, omitting either CuI or **L8** from the reaction mixture resulted in 0% conversion (Figure 2A, entries 14 and 15), an observation that is consistent with potential trace Pd from the preparation of **L8** not solely being responsible for the observed catalysis.

One limitation of our previously described Cu-catalyzed C–N coupling catalyst system was that reactions involving many base-sensitive and/or coordinating heterocycles led to little or no yield of the desired product.[32] To assess the stability of the catalyst derived from **L8** toward deactivation by small heteroarenes, and the stability of the arenes themselves

under the reaction conditions, the coupling of **1a** and **2a** was run in the presence of various heteroarene additives (Figure 2B).[52] Notably, while many heteroarenes exhibit an inhibitory effect at room temperature, likely by coordination with the metal center, increasing the reaction temperature to 50 °C resulted in excellent yields of **3a** for all heterocycles examined besides *N*-methylimidazole, which also required elevated CuI/**L8** loadings to obtain good yields of **3a**. Importantly, no decomposition of the heteroarenes was observed (^{1}H NMR) under these conditions. These results demonstrate that the catalyst derived from **L8** is resistant to deactivation by coordination-induced ligand displacement and that a reaction temperature of 50 °C may be viable for reactions involving five-membered heteroaryl bromides.

Upon optimizing the reaction conditions, we set out to assess the scope of compatible aryl bromides and amines. We first targeted arenes containing functional groups incompatible with our previously described method (Scheme 1).[32] Specifically, arenes containing an amide (**1a** and **1e**), enolizable ketone (**1b** and **1d**), *tert*-butyl ester (**1g**), and a carboxylic acid (**1h**) were all coupled with primary or secondary amines in good to excellent yields. Additionally, base-sensitive amines (**1c** and **1f**) were transformed into the corresponding *N*-aryl amines in good to excellent yield. Lastly, three α-tertiary amines, including adamantylamine, were arylated in moderate to good yield (**1i**, **1j**, and **1t**).

Nitrogen-containing heterocycles often present difficulties in metal-catalyzed coupling reactions due to their propensity to coordinate to and deactivate the catalyst.[41] In addition to heterocycle coordination, many small 1,2- and 1,3-azoles are susceptible to base-mediated decomposition pathways involving sequential C–H deprotonation and ring-opening.[39–41] Designing reaction conditions to enable the functionalization of these substrates is of particular interest as they are common substructures in pharmaceuticals.[42] Notably, very few Cu-catalyzed methods exist that reliably aminate five-membered heteroaryl halides. Using the combination of **L8**·Cu and NaOTMS, several five-membered heteroaryl bromides were aminated in good to excellent yields including a thiazole (**1k**), triazole (**1l**), pyrazole (**1m** and **1n**), and pyrrole (**1o**). We observed that 1,3-azoles lacking substitution at the 2-position, such as 4-bromothiazole, yield a minimal amount (<10%) of C–N-coupled product along with small degrees of decomposition. We speculate that these decomposition products are responsible for the observed catalyst inhibition and efforts are underway in our laboratory to develop new ligands to promote these challenging coupling reactions. Several benzene-fused heteroarenes were also converted to products including an indazole (**1p**), benzotriazole (**1s**), and benzoxazole (**1r**). Notably, many of these substrates exhibited poor yields when the **L4**/NaOMe conditions were used in our previous report.[32] Finally, several pharmaceuticals and natural products including Desloratadine (**1u**), Norchlorcyclizine (**1v**), Abietylamine (**1w**), and a fragment of the antidiabetes medication Januvia (**1x**) were coupled to heteroarene-containing aryl bromides in good to excellent yields. The efficient arylation of the Januvia fragment is particularly apt as the base sensitivity of the electron-deficient triazole previously required elevated catalyst loadings (10 mol % CuI, 20 mol % **L4**) to obtain a modest yield of the desired product.[32] In contrast, the method described herein led to an excellent yield of **1x** without the need for excess catalyst or other forcing reaction conditions. We observed that the coupling of alkyl amines with aryl bromides containing

phenols or unprotected *N*-heterocycles resulted in no conversion of the aryl halide. This inhibition of productive catalysis by these substrates is likely due to the coordination of the phenolate and deprotonated *N*-heterocycle to Cu, respectively. To successfully carry out reactions involving substrates possessing these functional groups, various protecting groups were surveyed. While R_3Si-based phenol-protecting groups were unstable under the reaction conditions, a THP-protected phenol was aminated in good yield (**1y**). In addition to *N*-heterocycle alkylation (**1z**), *N*-protection by a SEM group enabled productive catalysis (**1aa**). *N*-Boc and *N*-tosyl groups were found to be unstable under the reaction conditions, leading to deprotection and catalyst inhibition. Due to decomposition, aldehyde-containing aryl bromides were incompatible with the amination protocol. However, performing the C–N coupling using the brominated diethylacetal followed by an *in situ* deprotection with 2 M HCl afforded the aldehyde-containing *N*-aryl amine in excellent yield over two steps (**1ab**).

We sought to expand the scope of nucleophiles to include aniline derivatives and ammonia equivalents (Scheme 2). In our previous report, substrates with aniline groups possessing acidic protons resulted in complete catalyst inhibition.[32] We speculated that rapid deprotonation of the aniline by NaOMe and coordination with Cu prevented the desired reactivity. The use of NaOTMS prevented this process from occurring. Using the conditions previously optimized for the coupling of alkyl amines and aryl bromides, aniline derivatives, including those with ortho substituents, were coupled to aryl (**2b, 2c, 2d**) and heteroaryl bromides (**2a**). The same conditions also enabled C–N coupling of benzophenone imine (**2e** and **2f**), an ammonia equivalent. To the best of our knowledge, this represents the first Cu-catalyzed coupling of aryl halides with benzophenone imine.[11]

In addition to improving the scope of the reaction, we set out to investigate the robustness of the catalyst derived from **L8** by conducting the reaction to form *N*-aryl amines with substantially reduced catalyst loadings. To begin, we carried out Blackmond same-excess experiments measured by reaction calorimetry.[53] In these experiments, two reactions are monitored where the excess of morpholine is equal, but the initial concentration of 4-bromoanisole is different. As demonstrated by the overlay of the reaction rate vs [4-bromoanisole] plots, requiring the catalyst to undergo more turnovers does not have an impact on the observed rate (Figure 3A). This is consistent with the Cu catalyst derived from **L8** being stable throughout the reaction and that lower catalyst loadings might be employed. With this in mind, the coupling of 4-bromo-1-methylindazole and morpholine utilizing 0.8 mol % CuI was executed with a good yield (937 mg, 87% Yield, Figure 3B) using standard Schlenk techniques.

To further assess the catalyst system's stability, same-excess experiments were also carried out with a diminished L/Cu ratio to determine the minimal amount of excess ligand that is necessary to promote the desired reactivity. This is important as the benefits of using a cheaper metal catalyst (i.e., Cu vs Pd) are mitigated if the reaction requires large amounts of a relatively expensive ligand. Unlike in the same-excess experiments that featured a 1:2 ratio of CuI/**L8**, reactions utilizing equimolar amounts of CuI and **L8** (3 mol %) demonstrated substantial catalyst deactivation, with the reaction requiring more catalyst turnovers only reaching 77% yield.[47] We hypothesized that a minimal excess of **L8** or use of slightly increased reaction temperatures could be used to mitigate the deactivation

pathways preventing the reaction from reaching completion. Indeed, the use of either (1) 20% molar excess of **L8** relative to CuI (Figure 3C), (2) a reaction temperature of 50 °C, or (3) increased catalyst and ligand loadings (5 mol % CuI, 5 mol % **L8**) were sufficient to promote excellent yields in the coupling of morpholine with either 4-bromoanisole or 3-bromopyridine.[47] The utility of the protocol with minimal excess ligand and reduced CuI loadings was demonstrated in the gram-scale coupling of 3-bromopyridine and 4-methoxybenzyl amine (1.01 g, 94% Yield, Figure 3D). This coupling was performed using standard Schlenk techniques without the use of a N_2-filled glovebox. These results highlight that the catalyst derived from **L8** is remarkably stable and can be used on preparative scales with minimal amounts of both CuI and **L8**.

We next investigated the coupling of amino alcohol substrates. The transition-metal-catalyzed arylation of amino alcohols is challenged by chemoselectivity issues, with most catalytic methods leading to *N*-arylation, and/or ligand displacement upon both *N*- and *O*-coordination.[54,55] Despite this, several small-molecule pharmaceuticals rely on the chemoselective incorporation of groups containing contending alcohol and amine nucleophiles.[42,56–60] The most common strategy employed to obtain the *O*-arylated derivative of amino alcohols is using *N*-protecting groups. As an example, a discovery chemistry group at Novartis reported on the Pd-catalyzed C–O coupling of amino alcohols in which the amine component was protected with a Boc group.[55] While this approach is quite general, the need for a protection-deprotection sequence diminishes its efficiency. In addition to the use of protecting groups, selectivity can be achieved by controlling the steric environment surrounding both the alcohol and amine nucleophiles. Recently, Stradiotto disclosed that a CyPAd-DalPhos-based Ni catalyst was capable of affecting *O*-arylation in amino alcohols featuring branched primary or secondary amine residues, or *N*-arylation in amino alcohols featuring less sterically hindered amines.[54] To enable the chemoselective arylation of amino alcohols without a steric bias, our group has previously reported on the Cu-catalyzed arylation of amino alcohols using a diketone-based ligand to favor *N*-arylation and a (tetramethyl)phenanthroline-based ligand to favor *O*-arylation.[61]

Throughout our investigations into the chemistry enabled by the catalyst derived from **L8**, we noted a mechanistic dichotomy between C–N and C–O coupling pathways which we thought could be used advantageously to provide selectivity in the coupling of amino alcohols. Specifically, the mechanism of C–N coupling involves complexation of the amine and Cu catalyst which leads to acidification of the N–H bond, thereby allowing the use of a mild base to facilitate C–N coupling (Figure 4A). However, the analogous C–O coupling protocol required the use of a strong base, NaO*t*-Bu, even given the enhanced acidity of the alcohol relative to the amine (Figure 4B). This observation is consistent with the deprotonation of the alcohol not being aided by coordination to Cu.[46] With this in mind, we hypothesized that the use of NaOTMS could enable the selective *N*-arylation of amino alcohols regardless of structure.

We began our investigations into the arylation of amino alcohols by understanding the inherent selectivity in the competitive coupling of alcohol and amine nucleophiles. To this end, we performed a competition-style experiment in which 4-bromoanisole was subjected to the reaction conditions in the presence of both *n*-butanol and various alkyl amines

(Figure 4C). Using NaO*t*-Bu as the base, the *O*- vs *N*-selectivity of the reaction was found to be governed by the steric environment of the nucleophiles, with the reaction favoring C–N coupling of unhindered amines. Notably, C–O coupling of primary alcohols was favored over the C–N coupling of cyclic secondary amines, α tertiary amines, and anilines. Consistent with our initial hypothesis, the use of NaOTMS as the base enabled the ability to override the inherent selectivity of the reactions and exclusively favored the formation of the C–N-coupled product, regardless of the structure of the amine (Figure 4C).

To highlight the utility of this observation, several amino alcohols were selectively *N*- and *O*-arylated in good to excellent yields. Using NaO*t*-Bu as the base, amino alcohols containing a primary alcohol and a secondary amine were selectively *O*-arylated (**4a** and **4c**). An amino alcohol with a primary alcohol and an aniline residue exclusively underwent C–O coupling when NaO*t*-Bu was used as the base (**4e**), the opposite of what was observed in the previously described Ni-catalyzed reaction.[54] Showcasing the utility of our base-controlled reaction selectivity strategy, the same amino alcohols were exclusively *N*-arylated when NaOTMS was used (**4b**, **4d**, and **4f**). In addition to inverting the observed reactivity, the use of NaOTMS can provide selectivity in reactions that exhibit poor selectivity with NaO*t*-Bu. Arylating 4-hydroxypiperidine or 4-amino-4-methylpentan-1-ol utilizing NaO*t*-Bu as the base resulted in an ~3:2 ratio of products favoring *N*-arylation.[47] Employing NaOTMS as the base provides complete selectivity for the *N*-arylated products (**4i** and **4j**). Despite presenting challenges in many transition-metal-catalyzed coupling reactions due to chelation to the metal catalyst, 1,2-amino alcohols are historically useful substructures in pharmaceutical development. For example, nearly the entire class of β-blockers contain a 1-aminopropan-2,3-diol substructure with variable substitution patterns.[55] In the functionalization of these nucleophiles using NaO*t*-Bu as the base, the C–N-coupled product, along with the doubly arylated product (i.e., C–N and C–O coupling) was observed.[47] Using the catalyst derived from **L8** and NaOTMS, excellent yields of the *N*-arylated product were obtained using acyclic (**4k**) and cyclic (**4l**) 1,2-amino alcohols. Importantly, the use of NaOTMS as the base prevents overreaction to yield products featuring both *N*- and *O*-arylation.[47] One limitation of this method is highlighted in the coupling of 6-aminohexan-1-ol, in which *N*-arylation is exclusively favored regardless of the base used in the reaction (**4h**). To form the desired aryl–alkyl ether in the presence of a primary amine, several *N*-protecting groups were surveyed; ultimately, we identified that protecting the amine as the 2,5-dimethylpyrrole allowed for C–O coupling to take place in good yield (**4g**). Lastly, while many amino alcohols containing a secondary amine and a primary alcohol were amenable to this synthetic strategy, we noticed that C–O selectivity could only be observed if the amine and alcohol were separated by more than three carbon atoms. In the case of amino alcohols where the reactive handles were separated by three carbons, the reactions favored C–N coupling regardless of the base, as is the case in the preparation of **4m**. Highlighting this anomalous reactivity, utilizing the same amino alcohol that had been homologated by a single carbon enabled exclusive formation of either the *O*- or *N*-arylated products when NaO*t*-Bu (**4n**) and NaOTMS (**4o**) were used, respectively. A dependence of selectivity on the distance between nucleophiles has also been observed by our group[61] and Stradiotto in his recent Ni-catalyzed report.[54] One hypothesis for this phenomenon is that the initially formed alkoxide deprotonates

the amine residue via a six-membered transition state involving the coordination of both nucleophiles to Cu. Collectively, these results introduce a new chemoselective method in the functionalization of amino alcohols that is distinct from prior methods that rely on protecting group manipulations or outcomes that are solely determined by a steric bias.

CONCLUSIONS

In summary, we have developed a general method for the C–N coupling of base-sensitive aryl bromides using the catalyst derived from **L8** and the mild base NaOTMS. This catalyst system was found to enable the coupling of substrates that yielded little to no C–N-coupled products using the previously reported **L4**/NaOMe system. The optimized reaction was found to operate efficiently on many base-sensitive substrates, including arenes bearing enolizable ketones, carboxylic acids, and secondary amides. Importantly, this method also enabled the amination of many base-sensitive and coordinating heterocycles, which are prevalent substructures in many functional molecules. Kinetic experiments support the stability of the catalyst derived from **L8** and that coupling reactions could be performed with minimal catalyst and ligand loadings. Finally, mechanistic differences in the behavior of Cu-catalyzed C–O and C–N coupling reactions catalyzed by **L8**·Cu were leveraged to develop a chemoselective arylation of amino alcohols reliant on the identity of the base. We anticipate that the results of this study will motivate further improvements to Cu-catalyzed C–heteroatom bond-forming reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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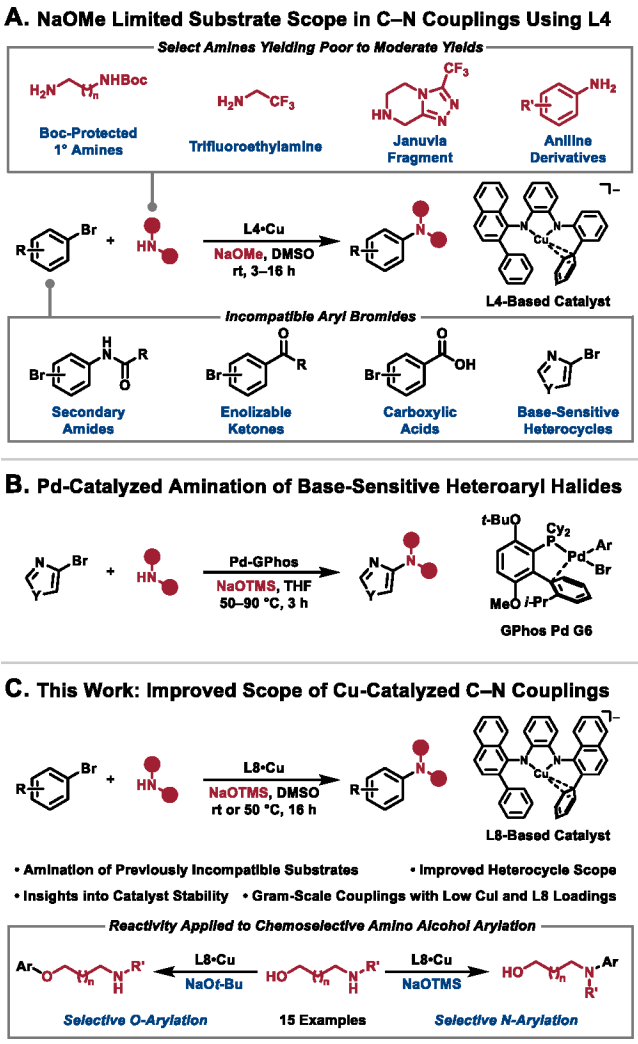
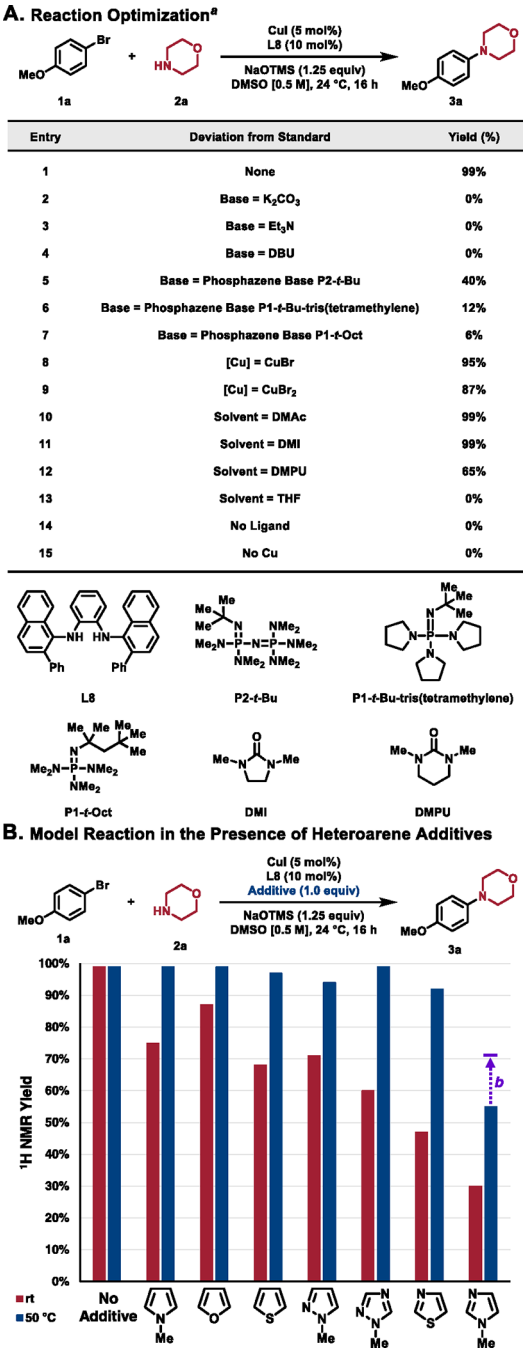


Figure 1.

Effects of base identity on substrate scope in transition-metal-catalyzed C–N coupling reactions. (A) Previously reported C–N coupling using the catalyst derived from **L4** and NaOMe. (B) Pd-catalyzed amination of base-sensitive heteroaryl halides using a GPhos-derived catalyst and NaOTMS. (C) This work in which the catalyst derived from **L8** and NaOTMS greatly expands the scope and applicability of C–N coupling reactions using N^1,N^2-diarylbenzene-1,2-diamine ligands.



Entry	Deviation from Standard	Yield (%)
1	None	99%
2	Base = K_2CO_3	0%
3	Base = Et_3N	0%
4	Base = DBU	0%
5	Base = Phosphazene Base P2-*t*-Bu	40%
6	Base = Phosphazene Base P1-*t*-Bu-tris(tetramethylene)	12%
7	Base = Phosphazene Base P1-*t*-Oct	6%
8	[Cu] = CuBr	95%
9	[Cu] = $CuBr_2$	87%
10	Solvent = DMAc	99%
11	Solvent = DMI	99%
12	Solvent = DMPU	65%
13	Solvent = THF	0%
14	No Ligand	0%
15	No Cu	0%

Figure 2.

(A) Optimization of the coupling of 4-bromoanisole and morpholine and (B) the impacts of base-sensitive and coordinating heteroarene additives. [a]Standard reaction conditions: 4-bromoanisole (**1a**, 0.10 mmol, 1.0 equiv), morpholine (**2a**, 0.12 mmol, 1.2 equiv), NaOTMS (0.125 mmol, 1.25 equiv), CuI (5 mol %), **L8** (10 mol %), dimethyl sulfoxide (DMSO, 0.2 mL), 24 °C, 16 h. Yields determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using 1,1,2,2-tetrachloroethane as an internal standard. [b]Reactions utilized 10 mol % CuI and 20 mol % **L8**.

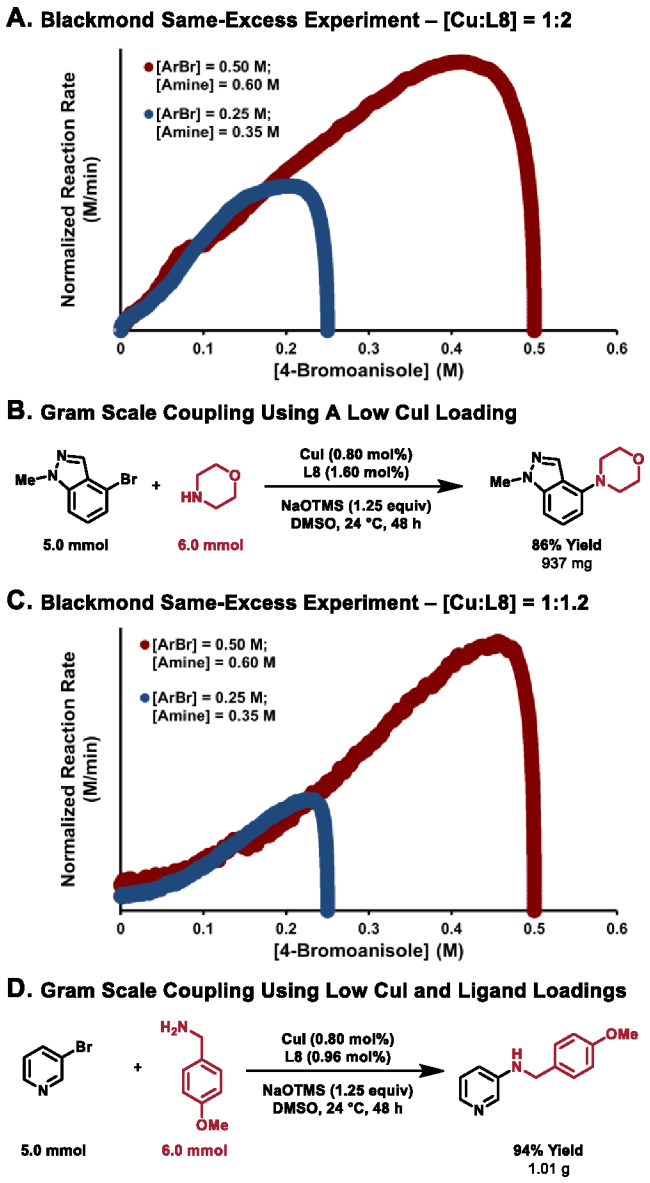
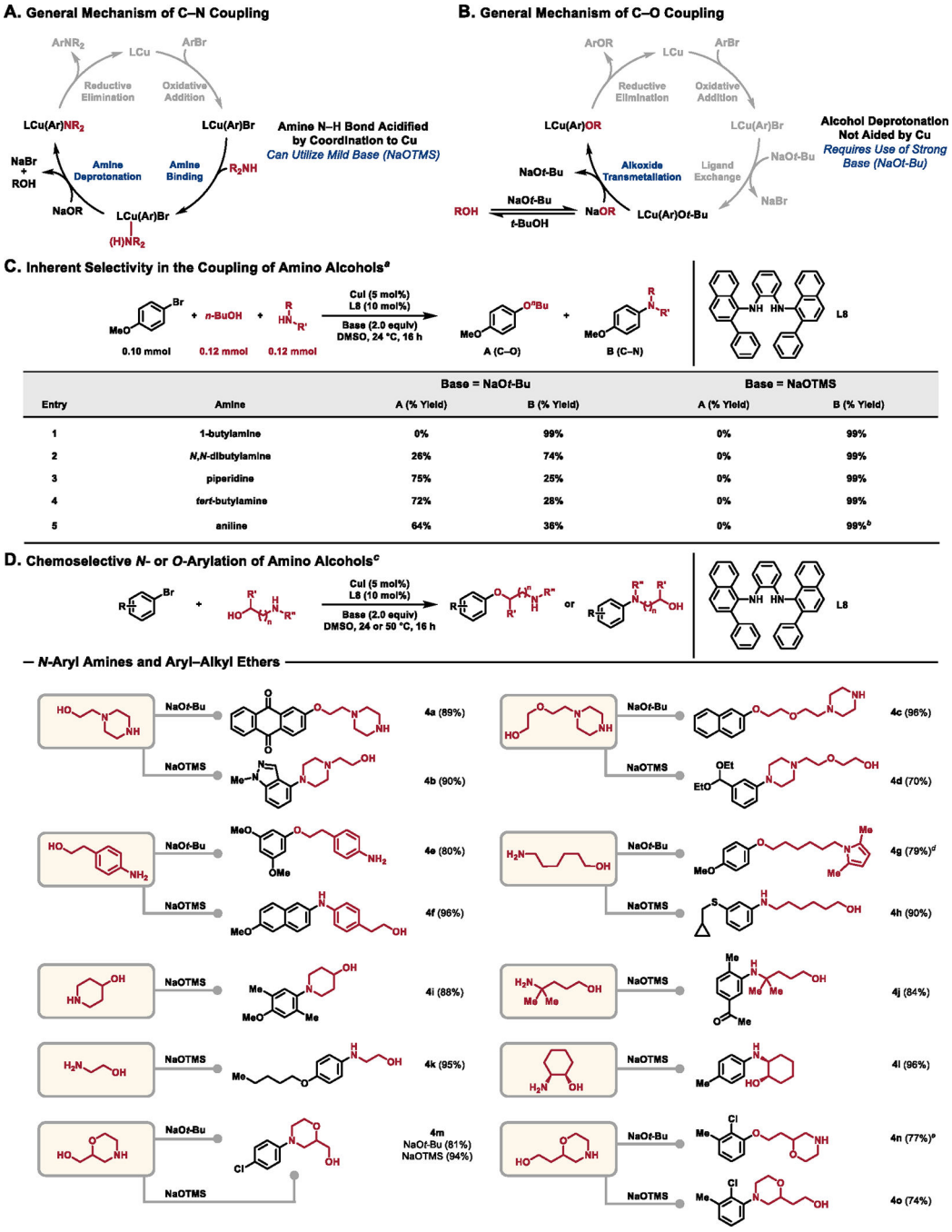


Figure 3.

(A) Blackmond same-excess experiment used to probe the stability of the catalyst derived from **L8** using a 1:2 ratio of CuI/**L8**. (B) Coupling of 4-bromo-1-methylindazole and morpholine using a low CuI loading. (C) Blackmond same-excess experiment used to probe the stability of the catalyst derived from **L8** using a 1:1.2 ratio of CuI/**L8**. (D) Coupling of 3-bromopyridine and 4-methoxybenzyl amine using low CuI and **L8** loadings.

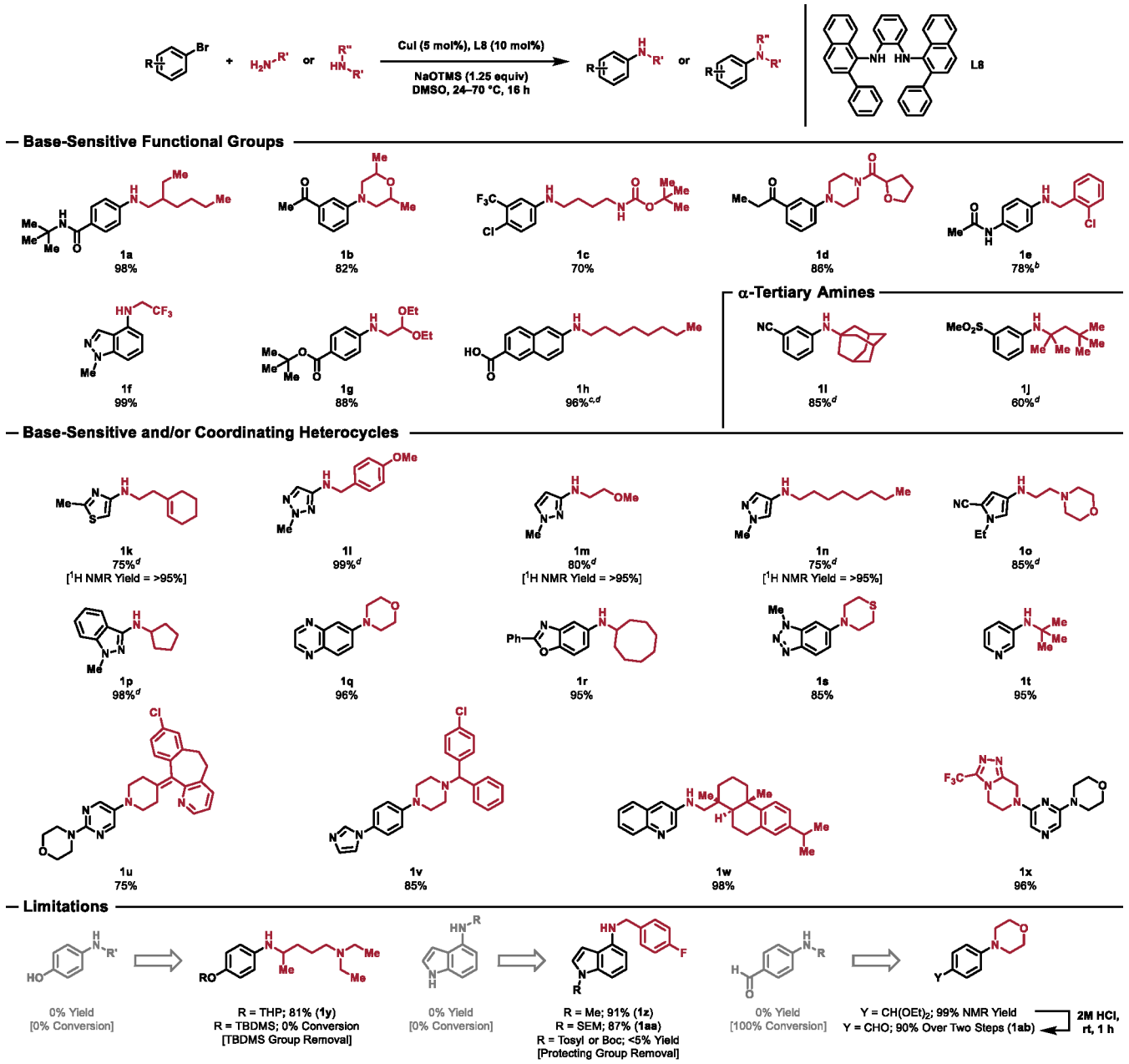


Entry	Amine	Base = NaOt-Bu A (% Yield)	Base = NaOt-Bu B (% Yield)	Base = NaOTMS A (% Yield)	Base = NaOTMS B (% Yield)
1	1-butylamine	0%	99%	0%	99%
2	*N,N*-dibutylamine	26%	74%	0%	99%
3	piperidine	75%	25%	0%	99%
4	*tert*-butylamine	72%	28%	0%	99%
5	aniline	64%	36%	0%	99%[b]

Figure 4.

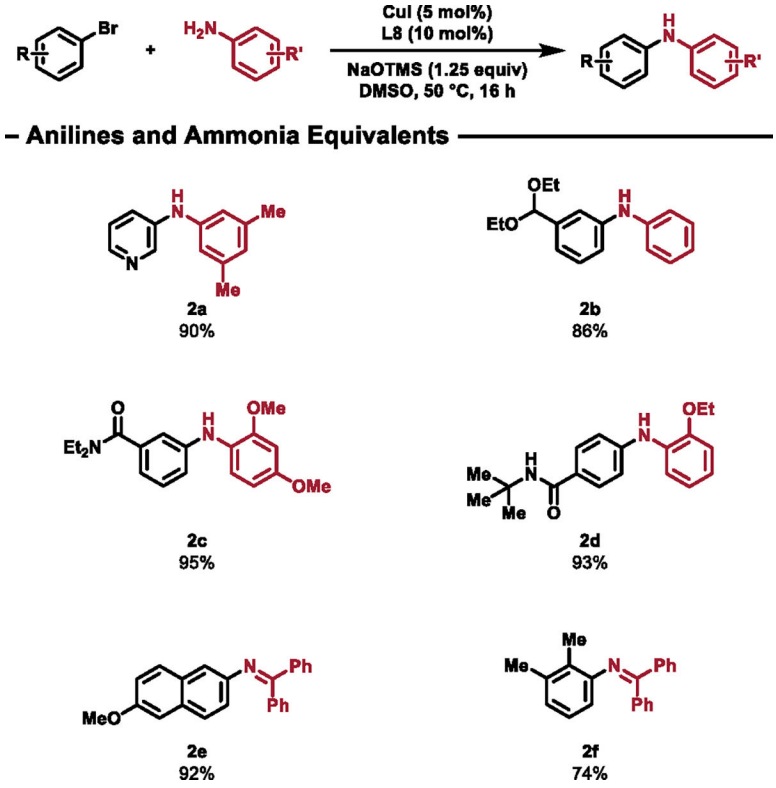
(A) General mechanism of C–N bond formation involving coordination of the amine to Cu before deprotonation. (B) General mechanism of C–O bond formation which we speculate does not involve a Cu-aided alcohol deprotonation. (C) Competition-style experiment to assess the inherent selectivity of coupling amino alcohols using either NaO*t*-Bu or NaOTMS as the base. (D) Scope of the chemoselective *N*- or *O*-arylation of amino alcohols. [a]Standard reaction conditions: 4-bromoanisole (0.10 mmol, 1.0 equiv), *n*-butanol (0.12 mmol, 1.2 equiv), amine (0.12 mmol, 1.2 equiv), Base (0.20 mmol, 2.0 equiv), CuI (5 mol %), **L8**

(10 mol %), DMSO (0.2 mL), 24 °C, 16 h. [b]Reaction temperature = 50 °C. [c]All yields represent the average of two isolated yields. Standard reaction conditions: aryl bromide (0.5 mmol), amino alcohol (0.6 mmol), NaO*t*-Bu or NaOTMS (0.625 mmol), CuI (5 mol %), **L8** (10 mol %), DMSO (1.0 mL), rt (NaO*t*-Bu) or 50 °C (NaOTMS), 16 h. [d]The amine of 6-aminohexanol was protected as a 2,5-dimethlypyrrole in order to facilitate formation of **4g**. [e]Product was isolated as the HCl salt.



Scheme 1. Substrate Scope of the Cu-Catalyzed Amination of Base-Sensitive Aryl Bromides[a,b,c,d]

[a]All yields represent the average of two isolated yields. Standard reaction conditions: aryl bromide (0.50 mmol), amine (0.6 mmol), NaOTMS (0.625 mmol), CuI (5 mol %), **L8** (10 mol %), DMSO (1.0 mL), 24 °C, 16 h. [b]Reaction temperature = 70 °C. [c]NaOTMS = 3 equiv. [d]Reaction temperature = 50 °C.



Scheme 2. Cu-Catalyzed Coupling of Aryl Bromides with Aniline Derivatives and Ammonia Equivalents[a]

[a]All yields represent the average of two isolated yields. Standard reaction conditions: aryl bromide (0.50 mmol), aniline derivative or benzophenone imine (0.60 mmol), NaOTMS (0.625 mmol), DMSO (1.0 mL), 50 °C, 16 h.