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# Cu-Catalyzed Couplings of Heteroaryl Primary Amines and (Hetero)aryl Bromides with 6-Hydroxypicolinamide Ligands

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**ABSTRACT:** A family of 6-hydroxypicolinamide ligands have been identified as effective supporting ligands for Cu-catalyzed couplings of heteroaryl bromides and chlorides with heteroaryl primary amines. The C−N couplings are carried out at 80−120 °C in DMSO or sulfolane using $K_2CO_3$ or $K_3PO_4$ as the base with 2−10 mol % CuI and supporting ligand. The strength of the base was found to have an impact on the chemoselectivity and rate. The use of $K_2CO_3$ as the base enabled selective C−N coupling of aryl bromides over aryl chlorides with 2−5 mol % Cu at 80−120 °C. With $K_3PO_4$ as the base, aryl chlorides are capable of undergoing C−N coupling, though 5−10 mol % Cu is required at 120−130 °C. Members of the ligand family are straightforward to prepare in one step from 6-hydroxypicolinic acid and the corresponding anilines.

**KEYWORDS:** *Cu-catalyzed C−N coupling, heteroaryl primary amines, (hetero)aryl bromides, 6-hydroxypicolinamides*



## INTRODUCTION

Metal-catalyzed cross-couplings are among the most frequently used methods for the assembly of pharmaceutical targets.[1] This methodology spans C−C, C−N, C−O, and C−S couplings, and of these, C−N couplings are often used for the preparation of clinically relevant drug candidates.[2] While Pd-catalyzed variants are the most frequently used because of their high efficiency and broad scope,[3] there is a need to develop comparable methods with nonprecious metals because of the increasing cost and limited supply of Pd. Cu is among the nonprecious metals capable of carrying out C−N couplings analogous to Pd.[4] Historically, Cu-catalyzed couplings have been developed using ligands derived from α-amino acids,[5] 1,2-diamines,[6] 1,3-dicarbonyls,[7] and other motifs[8] (Figure 1). More recently, Ma's group has advanced ligand design to the use of oxalamides[9] and amides derived from proline[10] (Figure 2). This family of ligands (Figure 2) has shown tremendous utility for C−N, C−O, and C−S couplings.[11,12]

A survey of C−N couplings carried out by Medicinal Sciences at Pfizer found that the vast majority involved heteroaryl halides and heteroaryl primary amines. There are few reports for this category of couplings,[13,14] and they have generally focused on coupling of anilines or primary amines with aryl halides. Most notable of these reports is the use of *N*,*N*′-bis(furan-2-ylmethyl)oxalamide (BFMO) as a ligand,[14] which was exemplified by Ma's group to be effective in Cu-catalyzed couplings of heteroaryl bromides with anilines and secondary amines. Of all of the couplings reported with BFMO as a ligand, there was only one example involving a heteroaryl primary amine.[14] Our ultimate goal was to identify the optimal ligand and a general set of conditions for the Cu-catalyzed couplings of heteroaryl bromides with heteroaryl primary amines.

## RESULTS AND DISCUSSION

The model system chosen for initial screening (Scheme 1) involved aryl bromide **1** and 2-aminopyridine (**2**).[1] The 2-aminopyridine moiety was selected because it is fairly common to assemble potential therapeutic agents with this functional group or closely related heterocycles. The substituted bromoarene **1** was selected for ease of monitoring the substrate and its derived impurities. The analytical responses measured included dehalogenation of the aryl bromide to give **4**, hydroxylation of the aryl bromide to form **5**, diarylation of the amine to afford **6**, and arylation of the supporting ligand.

After examination of a large number of ligands using 5−10 mol % CuI in DMSO with $K_3PO_4$ as the base at 120 °C, it was observed that BFMO and *N*,*N*′-bis(thiophen-2-ylmethyl)-oxalamide (BTMO)[15] were very difficult ligands to outperform (Table 1, entries 2 and 3). These Cu catalysts provided excellent reactivity and moderate selectivity for the desired monoarylated product **3** (~6:1 ratio of **3** to **6**). In comparison to BFMO and BTMO, dicarbonyl, diamine, salicylamide, amino acid, and amino alcohol ligands were relatively ineffective (Figure 3) on the basis of their inferior reaction rates and ultimately lower product conversions. Among the ligands examined that gave surprisingly poor results was **L21**. In this case, shifting the carbonyl group toward the periphery completely eliminated the reactivity. This suggests that maintaining a carbonyl for binding as a five-membered chelate in the catalytic cycle is important.[16,17] From a further survey of ligands, it became apparent that the catalyst maintained high activity when binding as a chelate through nitrogen, preferably through two amides. Regarding the ligands designed by Ma's group, the oxalamide moiety was the most critical design element. Other secondary binding features, such as a pendent furan or thiophene, had minor impacts on the reactivity and selectivity. The replacement of the furan-2-ylmethyl group with a hindered arene provided comparable reactivity (Table 1,

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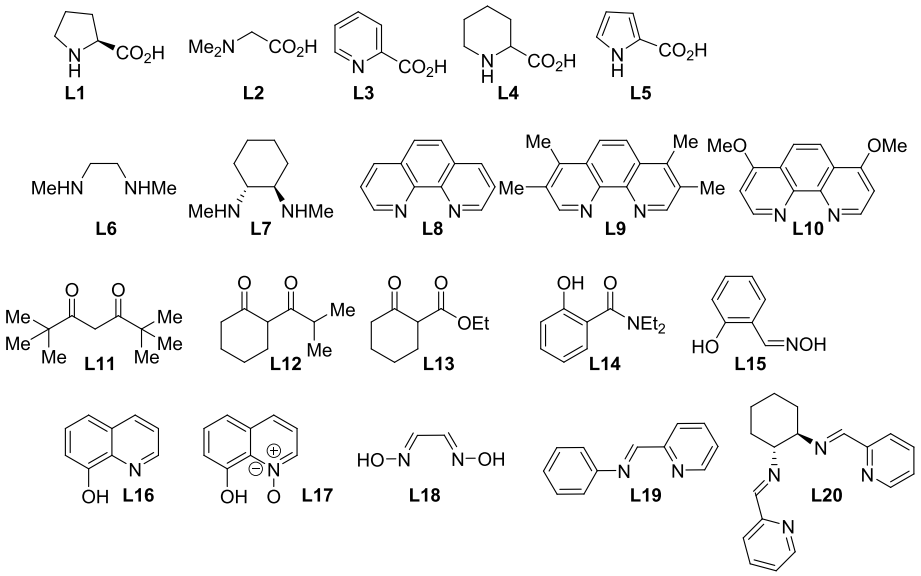



**Figure 1.** First generation of ligands employed in Cu-catalyzed couplings.

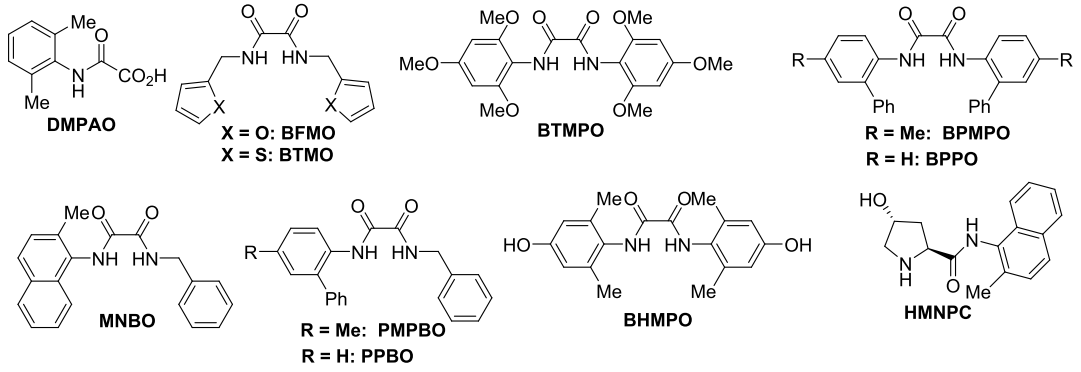
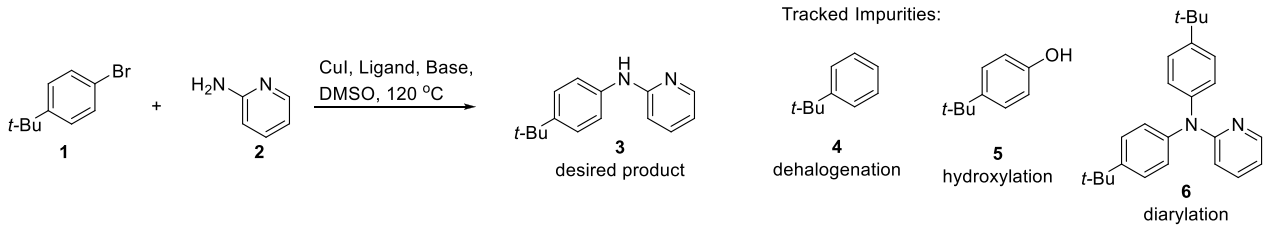



**Figure 2.** Second generation of ligands developed by Ma's group for Cu-catalyzed couplings.

**Scheme 1. Model C−N Coupling Studied with the Ligand Library**




entry 4), while less hindered aryl groups exhibited slightly reduced reactivity (Table 1, entry 5). The choice of the base was found to be critical as well. When $K_3PO_4$ was replaced with $K_2CO_3$, the oxalamide ligands (BFMO, BTMO, and *N*,*N*′-bis(2,4,6-trimethoxyphenyl)oxalamide (BTMPO)) possessed no reactivity for the coupling of **1** and **2**.

From the broad ligand screen, pyroglutamamides (such as **L35**, shown in Figure 4) emerged as efficient scaffolds for Cu catalysts. Pyroglutamamides had practical appeal as ligands because of their low cost. However, with weakly nucleophilic **2** as a substrate, N-arylation of the ligand pyrrolidinone moiety was highly competitive. The competitive arylation of **L35** led to catalyst deactivation and stalling of the reactions at partial conversion (Table 1, entry 6).[18] Increasing the ring size so that ligands were derived from 6-oxopipecolic acid (such as in **L36**) resulted in lower rates of competitive ligand arylation while maintaining relatively high reactivity for the desired coupling of **1** and **2** (Table 1, entry 7). Unfortunately, ligands derived from 6-oxopipecolic acid are not as practical to prepare as those derived from pyroglutamic acid because of the higher cost of the starting material. However, this provided a good lead for ligand design.

As an alternative to ligands possessing two amide donors, competitive reactivity was achieved when one of the two amides was replaced with a nitrogen heterocycle such as a pyridine (**L37**), indole, pyrrole, or benzimidazole. AbbVie disclosed the use of a picolinamide ligand (Figure 5) for the synthesis of dasabuvir, an HCV polymerase inhibitor[19] with a related C−N coupling. Following this precedent, picolinamide ligands such as **L37** were found to have sufficient reactivity but


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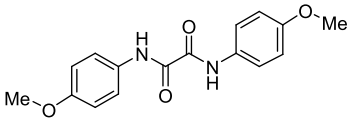
**Table 1. Comparison of Ligand Reactivities**[a,b]

| entry | ligand | 2 h IPC | 15 h IPC | 24 h IPC (% total impurities) |
|---|---|---|---|---|
| 1 | none | <1% | 6% | 9% |
| 2 | BTMO | 37% | 92% | 99% (19%) |
| 3 | BFMO | 39% | 99% | 99% (15%) |
| 4 | BTMPO | 35% | 97% | 99% (17%) |
| 5 | des-*ortho*-OMe BTMPO[c] | 13% | 80% | 99% (25%) |
| 6 | **L35** | 68% | 71% | 71% (12%) |
| 7 | **L36** | 75% | 99% | 99% (9%) |
| 8 | **L37** | 5% | 48% | 67% (28%) |
| 9 | **L38** | 14% | 47% | 48% (16%) |
| **10** | **L40** | **95%** | **99%** | **99% (1%)** |
| **11** | **L41** | **99%** | **99%** | **99% (7%)** |
| 12 | **L16** (8-hydroxyquinoline) | 8% | 37% | 70% |
| 13 | **L8** (phenanthroline) | <1% | 8% | 11% |
| 14 | **L6** (DMEDA) | <1% | 7% | 9% |

[a]Conditions: 5 mol % CuI, 10 mol % ligand, 1.5 equiv of $K_3PO_4$, 2 M DMSO relative to **1** (1 mmol), 1.1 equiv of **2**, 120 °C. [b]In-process control (IPC) reported as a conversion, excluding impurities or side products. [c]Structure of des-*ortho*-OMe-BTMPO:



possessed relatively poor selectivity for the desired product **3** versus diarylated product **6** (Table 1, entry 8).[20] The introduction of a methoxy group ortho to the pyridine (or pyrimidine) nitrogen improved selectivity for monoarylation (entry 9), but Cu complexes derived from **L37** or **L38** required 10 mol % Cu to achieve at least 90% conversion. It was then hypothesized that swapping the methoxy group for a hydroxy group would provide ligands with improved reactivity analogous to **L36** since this would enable the pyridine nitrogen to become an anionic donor. As expected, the 6-hydroxypicolinamides (**L40** and **L41**) were far superior ligands, providing more reactive Cu complexes with high selectivity for the desired monoarylated product **3**. Even more impressive was the observation that the hydroxypicolinamides (**L40** and **L41**) significantly surpassed the oxalamide ligands (BFMO, BTMO, and BTMPO) in terms of reactivity and selectivity.

The members of the family of 6-hydroxypicolinamide ligands **10** (Figure 6) were prepared in a single step by coupling of 6-hydroxypicolinic acid (**7**) with the corresponding anilines **8** by propylphosphonic anhydride (T3P) activation (Scheme 2). The amidation was significantly slower with more hindered and electron-deficient anilines. Upon completion of the amidation, heating with methanol hydrolyzed the remaining phosphonate species bound to the desired ligand. Usually the reaction was quenched with aqueous hydroxide followed by distillation to displace the THF and ethyl acetate with methanol. The phosphonate bound to the desired ligand (**9**) was visible by UPLC, allowing the phosphonate hydrolysis to be monitored. For most of the ligands, the hydrolysis required heating for 1−8 h in methanol under alkaline conditions. Once the hydrolysis was complete, the liberated ligand **10** was directly crystallized with the addition of water.

The family of 6-hydroxylpicolinamide ligands **10** displayed structure−activity relationships similar to those of Ma's oxalamide ligands (Table 2).[14,15,21] For the arylamide moiety, ortho substituents were essential to maintain a high level of activity. Preparing the parent 6-hydroxy-*N*-phenylpicolinamide (**L47**) from aniline provided significantly less reactivity than **L46** or **L43**. Introducing a second ortho substituent (**L40** and **L42**) further improved the reactivity and selectivity for the desired monoarylated product **3**. Electron-donating groups on the arylamide increased the reactivity (**L41**) while electron-withdrawing groups reduced it (**L45**). Despite the lower reactivity with **L45**, the model coupling reaction still managed to reach completion in a reasonable time frame and provided a relatively clean impurity profile. For the pyridyl ring, shifting the hydroxyl group to the 4-position and introducing a 6-methyl group or fused ring led to severe inhibition of the reactivity (**L48**). From this study, both **L40** and **L42** were deemed to be optimal as ligands for the coupling of **1** and **2**. However, **L40** was chosen for optimization studies and further

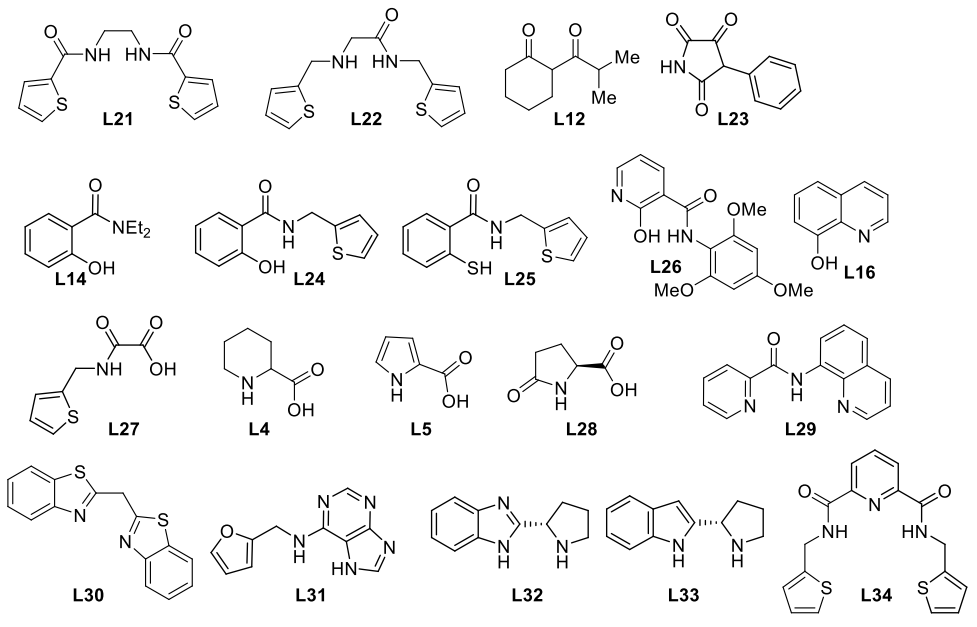



**Figure 3.** Ineffective ligands for the Cu-catalyzed coupling of **1** and **2**.



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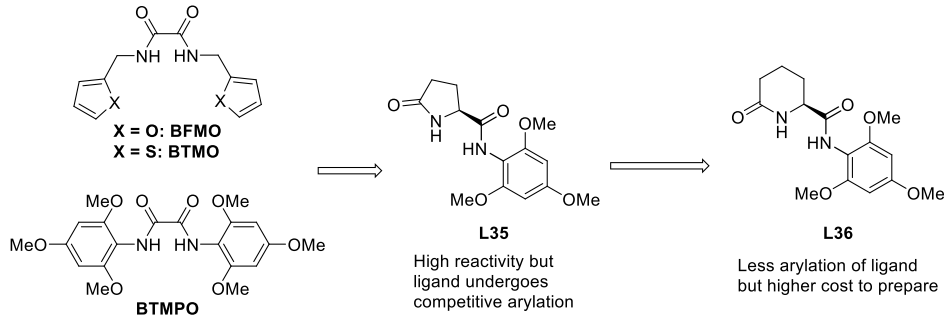



**Figure 4.** Early ligands examined for optimization of design.

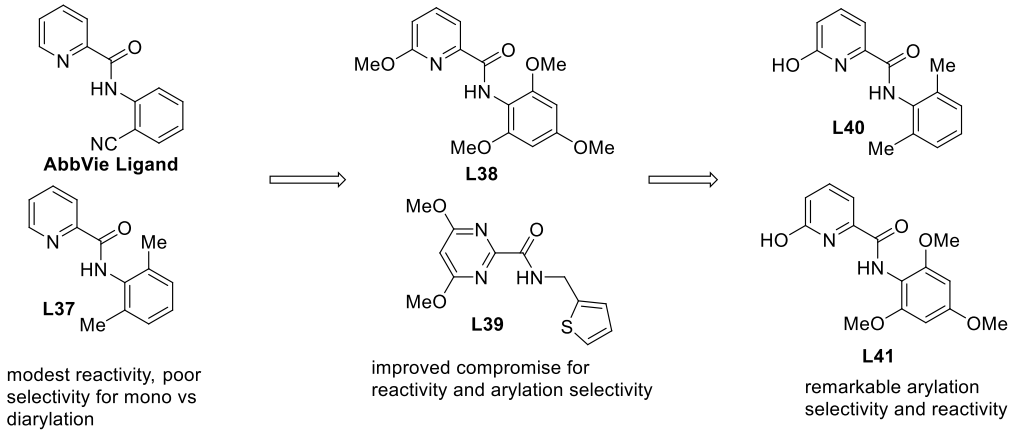



**Figure 5.** Further optimization of the ligand design.

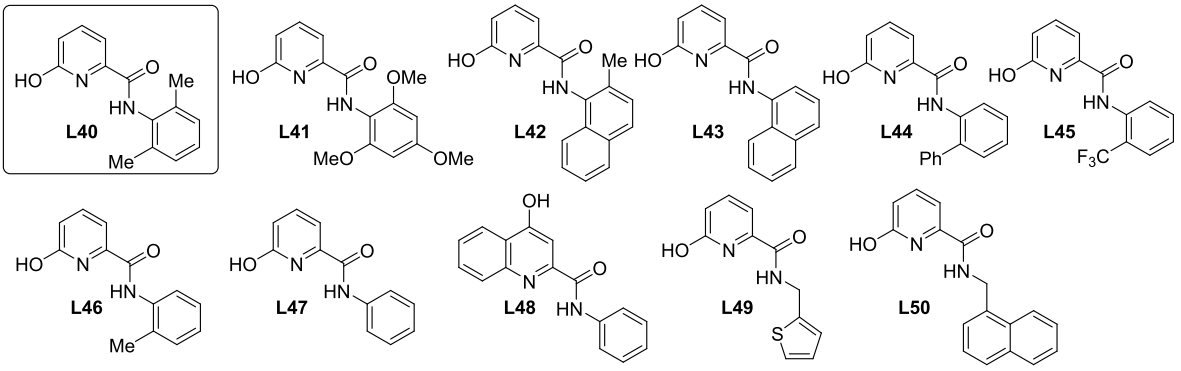
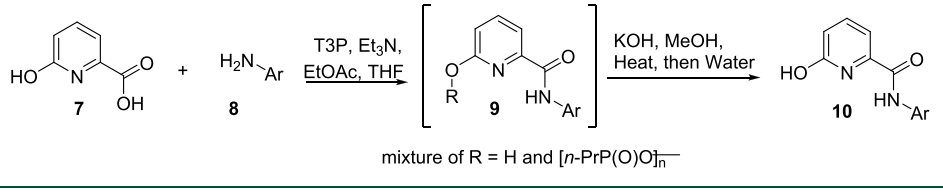



**Figure 6.** Library of 6-hydroxypicolinamide ligands **10**.

**Scheme 2. Preparation of 6-Hydroxypicolinamide Ligands**




development because of its preparation from inexpensive commodity chemicals.

**Optimization of the Reaction Conditions and Process Understanding.** Although the 6-hydroxypicolinamide ligands limited undesired diarylation (**6**) and dehalogenation (**4**), competitive hydroxylation of the aryl bromide (**5**) became more prevalent. The extent of hydroxylation was found to correlate directly to the level of water present in the reaction mixture. Spiking with higher levels of water led to corresponding higher levels of **5**. Because $K_3PO_4$ is highly hygroscopic, water was typically present when this base was used and led to significant levels of hydroxylation (5−10%) in early studies. To illustrate this further, the use of aqueous KOH (Table 3, entry 7) afforded **5** as the major product, suggesting that the catalyst could be efficiently used for hydroxylation if intended. With dry DMSO (≤0.05% water) and anhydrous $K_3PO_4$,[22] hydroxylation was not a significant issue (<1% **5**) and typically did not require additional



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**Table 2. Comparison of the Reactivities of 6-Hydroxypicolinamide Ligands 10[a,b]**

| entry | ligand | 2 h IPC | 15 h IPC (% total impurities) |
|---|---|---|---|
| 1 | **L40** | **93%** | **99% (1%)** |
| 2 | **L41** | 99% | 99% (7%) |
| 3 | **L42** | **99%** | **99% (1%)** |
| 4 | **L43** | 84% | 99% (4%) |
| 5 | **L44** | 65% | 95% (13%) |
| 6 | **L45** | 28% | 99% (4%) |
| 7 | **L46** | 85% | 99% (11%) |
| 8 | **L47** | 35% | 99% (16%) |
| 9 | **L48** | 1% | 16% |
| 10 | **L49** | 77% | 99% (11%) |
| 11 | **L50** | 40% | 79% (5%) |

[a]Conditions: 5 mol % CuI, 10 mol % ligand, 1.5 equiv of $K_3PO_4$, 2 M DMSO relative to **1** (1 mmol), 1.1 equiv of **2**, 120 °C. [b]In-process control (IPC) reported as a conversion, excluding impurities or side products.

**Table 3. Comparison of Bases Used in the Coupling of 1 and 2[a,c]**

| entry | base | 3 h IPC | 15 h IPC | 24 h IPC |
|---|---|---|---|---|
| 1 | $K_2CO_3$ | 51% | 99% (1%)[c] | 99% (1%)[c] |
| 2 | $Na_2CO_3$ | 11% | 30% | 38% |
| 3 | $Cs_2CO_3$ | 99% (13%)[c] | 99% (13%)[c] | 99% (13%)[c] |
| 4 | $K_3PO_4$ | 82% | 99% (1%)[c] | 99% (1%)[c] |
| 5 | $Na_3PO_4$ | 27% | 46% | 48% |
| 6 | KOH (pellets) | 25%[b] | 39%[b] | 39%[b] |
| 7 | aqueous KOH | 99% (76%)[c] | 99% (76%)[c] | 99% (76%)[c] |
| 8 | DBU | 30% | 40% | 40% |

[a]Conditions: 5 mol % CuI, 10 mol % **L40**, 1.5 equiv of base, 1 M in DMSO relative to **1** (1 mmol), 1.1 equiv of **2**, 120 °C. [b]A mixture of regioisomers was obtained. [c]In-process control (IPC) reported as a conversion, excluding impurities or side products; the extent of the hydroxylation impurity is reported as a percentage of the total product distribution.

precautions. With dry DMSO and substrates, $K_3PO_4$ and $K_2CO_3$ were found to be equivalent in maintaining low levels of competitive hydroxylation (<1%). When the solvent or substrates introduced significant levels of water (>0.2% by Karl Fischer analysis (KF) of the resulting reaction mixture), a practical solution to minimize the competitive hydroxylation was to conduct the couplings above the boiling point of water or to blend toluene with DMSO or sulfolane to facilitate removal of water by distillation.[23] The use of a 5:1 or 10:1 volume ratio of DMSO to toluene at 110−120 °C was ideal for minimizing hydroxylation in the presence of water.[24]

Of the inorganic bases, $K_3PO_4$ (Table 3, entry 4) demonstrated the highest reactivity other than $Cs_2CO_3$ (Table 3, entry 3) and aqueous KOH (Table 3, entry 7). Both $Cs_2CO_3$ and aqueous KOH had the liability of promoting competitive hydroxylation because of the presence of water in those reagents. While $Cs_2CO_3$ possessed high reactivity and could be potentially dried, it was considered less desirable for large-scale manufacture as cesium is a less abundant and more expensive heavy metal. As a viable alternative to $K_3PO_4$, $K_2CO_3$ (Table 3, entry 1) was effective with this ligand family **10** and could be useful for instances when a slightly milder base is required. While KOtBu or NaOtBu could be used as the base, they possess incompatibility with DMSO as a safety concern, especially with the relatively high temperatures required for the couplings.[25] As an alternative to DMSO, the alkoxide bases were evaluated in alcohol solvents but were still less reactive than $K_3PO_4$ under those conditions.

In general, potassium salts were more reactive than sodium salts. This trend was observed with carbonates (Table 3, entry 1 vs entry 2) and phosphates (Table 3, entry 4 vs entry 5) alike. Amine bases ($Et_3N$, $iPr_2NEt$, and TMEDA) were ineffective, but DBU (Table 3, entry 8) was able to promote the coupling relatively slowly, although the reaction appeared to stall at partial conversion. As an additional complication, DBU was observed to undergo coupling with the aryl bromide as a side reaction.[26]

The strength of the base was observed to influence both the reactivity and chemoselectivity. In this respect, $K_3PO_4$ provided more rapid catalysis than $K_2CO_3$, but $K_2CO_3$ provided selectivity toward exclusive coupling of aryl bromides over aryl chlorides. Early screening work with $K_3PO_4$ showed that aryl chlorides proceeded to couple at relatively low rates (48 h at 120−130 °C with 5−10 mol % Cu) compared with aryl bromides (2−6 h at 120 °C with 2−5 mol % Cu). Switching to the use of $K_2CO_3$ as the base ceased coupling with aryl chlorides entirely, even when chlorobenzene was used as a cosolvent.

Upon examination of solvents for the coupling reactions, DMSO, sulfolane, and other polar aprotic solvents were found to be ideal (Table 4, entries 1−3). The reaction was significantly slower when a large proportion of toluene or anisole was blended with DMSO.[27] Primary and secondary alcohols provided competitive levels of reactivity with the catalyst. Under some circumstances, primary alcohols were found to undergo competitive C−O coupling,[28] though

**Table 4. Comparison of Solvents Used in the Coupling of 1 and 2[a]**

| entry | solvent | 2 h IPC | 5 h IPC | 18 h IPC |
|---|---|---|---|---|
| 1 | DMSO | 58% | 99% | 99% (1%)[c] |
| 2 | sulfolane | 67% | 97% | 99% (2%)[c] |
| 3 | DMAC | 53% | 86% | 99% (1%)[c] |
| 4 | 1-butanol | 79% (9%)[c] | 99% (17%)[c] | 99% (17%)[c] |
| 5 | ethylene glycol | 85% (44%)[b] | 99% (67%)[b] | 99% (67%)[b] |
| 6 | 4-methyl-2-pentanol | 30% | 50% | 92% (10%)[c] |
| 7 | cyclohexanol | 98% | 99% (20%)[c] | 99% (20%)[c] |
| 8 | *tert*-amyl alcohol | 15% | 20% | 51% |

[a]Conditions: 5 mol % CuI, 10 mol % **L40**, 1.5 equiv of $K_3PO_4$, 2 M in solvent relative to **1** (1.0 mmol), 1.1 equiv of **2**, 120 °C; in-process control (IPC) reported as a conversion, excluding impurities or side products. [b]Extent of C−O coupling reported as a percentage of the product mixture. [c]Extent of total impurities reported as a percentage of the product distribution.


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secondary and tertiary alcohols did not. For the reaction conditions explored in Table 4, 1-butanol (entry 4) did not undergo ether formation. In contrast to 1-butanol, ethylene glycol (Table 4, entry 5) heavily favored C−O coupling under these conditions.[29] Tertiary alcohol solvents gave poor reactivity (Table 4, entry 8). Even though primary and secondary alcohols appeared to be ideal as solvents, generally more diarylation of the amine was observed compared with using polar aprotic solvents (DMSO, DMAC, or sulfolane); however, conditions could potentially be optimized to minimize this side reaction. With aryl chlorides as substrates, 1-butanol was generally more reactive than DMSO and, surprisingly, did not lead to any appreciable levels of side products, including C−O coupling (hydroxylation or ether formation).

The ligand to Cu molar ratio was found to have a profound impact on the reactivity and selectivity. As the ligand to Cu molar ratio was increased beyond 1:1, the reaction rate increased.[30] For example, a 1:1 ligand to Cu ratio at a Cu loading of 2.5 mol % gave 21% conversion to **3** after 6 h; the same transformation achieved 62% conversion with a 2:1 ligand to Cu ratio and >99% conversion with a 4:1 ligand to Cu ratio. In addition to its impact on the reaction rate, the ligand to Cu ratio influenced the extent of competing hydroxylation (formation of **5**). Maintaining the ligand to Cu ratio near 1:1 suppressed hydroxylation (Table 5, entries 1 and 2), but when the ligand to Cu ratio was increased to 2:1 and higher, hydroxylation became more problematic (Table 5, entries 3−5). The extent of competitive hydroxylation increased significantly with solvents possessing higher water levels and followed this same trend relating to the ligand to Cu molar ratio. For example, DMSO with >0.2% water by KF afforded 1−2% **5** at a 2:1 ligand to Cu ratio but 10−20% **5** at a 4:1 ligand to Cu ratio. As the overall reaction concentration for the coupling of **1** and **2** was increased, the reaction rate was observed to increase with similar product distributions. For optimal performance, the reaction concentration was typically maintained at 1−2 M and the ideal ligand to Cu molar ratio was typically in the range of 1.5:1 to 2:1.

**Table 5. Examination of the Ligand to CuI Molar Ratio**[a,b]

| entry | **L40**:CuI | 3 h IPC | 7 h IPC | 24 h IPC |
|---|---|---|---|---|
| 1 | 0.6:1 | 64% (<1%) | 72% (1%) | 77% (1%) |
| 2 | 1.3:1 | 66% (<1%) | 81% (1%) | 88% (1%) |
| 3 | 2:1 | 85% (1%) | 95% (3%) | 99% (4%) |
| 4 | 2:1[c] | 86% (2%) | 99% (1%) | 99% (3%) |
| 5 | 4:1 | 94% (5%) | 99% (5%) | 99% (5%) |

[a]Conditions: 4 mol % CuI, **L40** as indicated, 1 M in DMSO relative to **1** (1.0 mmol), 1.1 equiv of **2**, 1.5 equiv of $K_2CO_3$, and 0.10 equiv of sodium ascorbate. [b]In-process control (IPC) reported as a conversion, with the amount of **5** formed as a percentage of the product distribution reported in parentheses. [c]No sodium ascorbate was used.

Additives were examined to further understand their impact on the process. Introducing sodium ascorbate as an additive had a minimal effect on the reaction rate and purity profile for this set of substrates and conditions (Table 5, compare entries 3 and 4). Nevertheless, sodium ascorbate was included for this study to ensure reliable activation of the Cu catalyst for comparison of the kinetics and product distributions across all time points. When other substrates were explored, it was observed that electron-rich products possessing the 4-aminopyrazole moiety were capable of undergoing dimerization with Cu(II). In these cases, where Cu(II) must be present to enable dimerization,[31] the addition of sodium ascorbate was found to suppress this side reaction. When coupling reactions were initiated, frequently the reaction mixtures would transition through a green color at the start, suggesting the presence of Cu(II), and rapidly became a brown color shortly after heating.[32] The catalyst initiation proceeded well under nitrogen, but when couplings were conducted in vials without nitrogen inertion, the catalyst failed to initiate in some instances. In these rare cases, addition of sodium ascorbate enabled reliable catalyst activation.[33] In general, the addition of sodium ascorbate ensured that the reactions achieved maximum reaction rates more efficiently.[34]

The addition of KI to reactions allowed halogen exchange to proceed, converting the aryl bromide to the corresponding aryl iodide. When 0.50 equiv of KI was introduced into the reaction mixture, typically about 10−20% of the aryl bromide was converted to the aryl iodide as the aryl halides were consumed in the coupling. The addition of KI appeared to slow the reaction progress, and in cases where hydroxylation was highly competitive (such as coupling of aqueous ammonia or a secondary amine), it reduced the extent of hydroxylation by about 30−50%.[35] Using the corresponding aryl iodide had this same effect of slowing the reaction progress relative to the aryl bromide but gave the same product distribution as the aryl bromide.[36]

**Discussion of the Substrate Scope.** A variety of aryl and heteroaryl bromides were examined in the coupling with 2-aminopyridine (Figure 7) using 4 mol % CuI and 6 mol % **L40**. The couplings were generally carried out at 120−130 °C for efficiency, but in many cases the couplings of (hetero)aryl bromides could be conducted at 80−100 °C with longer reaction times. Unhindered bromides performed well, providing complete reactions within 4−12 h, while those possessing an ortho substituent typically did not proceed well in the coupling. For example, 4-bromochlorobenzene (**11f**) and 4-bromoanisole (**11k**) coupled cleanly, but the ortho-substituted isomers (**11g** and **11l**) failed to proceed in the coupling regardless of the base chosen. When the solvent was switched to 1-butanol, **11l** proceeded to couple more efficiently, reaching 42% conversion in 16 h and 76% conversion in 48 h with 4 mol % CuI at 120 °C. In the case of **11c**, coupling proceeded despite the *o*-pyrazole substituent, most likely because the pyrazole served as a directing group for Cu. A number of heterocycles such as 6-bromoquinoline (**11a**) coupled in good yield, but the isomer 8-bromoquinoline (**11b**) failed to couple well and favored hydroxylation. Highly electron-rich and unprotected substrates such as 3-iodoindazole and 6-bromoindazole failed to undergo coupling, most likely because of the deprotonation of the indazole nitrogen, which could impede oxidative addition or bind the Cu catalyst to form a stable complex.

Aryl chlorides coupled at a much lower rate than the corresponding aryl bromides. In general, the aryl chlorides did not appear to have the same tendency toward diarylation of the amine or competitive hydroxylation of the aryl halide. It was observed that switching the solvent from DMSO to 1-butanol provided a higher rate of catalysis for coupling of aryl chlorides with primary amines at 120 °C without any observed C−O coupling. Increasing the reaction temperature to 130 °C with DMSO or sulfolane as the solvent significantly increased the


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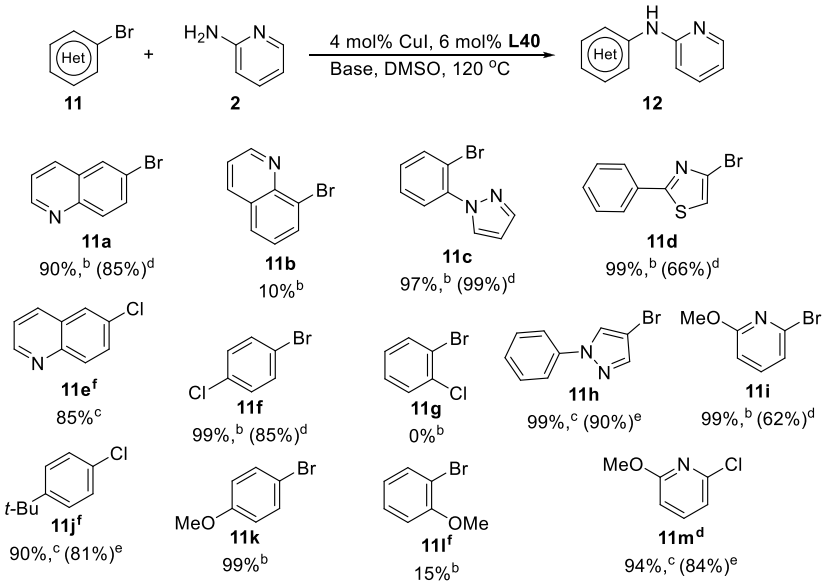


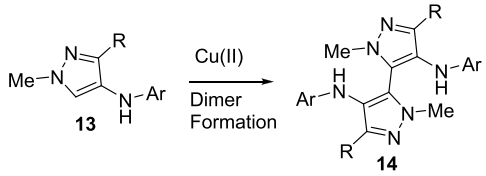

**Figure 7.** Couplings of 2-aminopyridine with various (hetero)aryl halides. Reaction conditions: 4 mol % CuI, 6 mol % **L40**, 1 M in DMSO, 1.5 equiv of $K_2CO_3$, 1.1 equiv of amine, 120 °C, 16 h. Notes: [b]HPLC/UPLC purity assay with $K_2CO_3$ as the base. [c]HPLC/UPLC purity assay with $K_3PO_4$ as the base. [d]Isolated yield with $K_2CO_3$ as the base. [e]Isolated yield with $K_3PO_4$ as the base. [f]Modified reaction conditions: 8 mol % CuI, 16 mol % **L40**, 2 M in DMSO, 1.5 equiv of $K_3PO_4$, 130 °C, 24 h.

reaction rate for aryl chlorides and other substrates that were less capable of undergoing oxidative addition with the Cu catalyst. When 8 mol % CuI and 16 mol % **L40** were used with 1.5 equiv of $K_3PO_4$ in DMSO, **11j** was able to achieve 66% conversion within 24 h and 90% conversion in 48 h. In comparison, chloropyridine **11m** was able to reach >90% conversion under these same conditions in 12−15 h with minimal side products (<1%). From this perspective, activated aryl chlorides seemed to be optimal substrates with reasonable reactivities and cleaner product profiles.

To demonstrate the efficiency of the process further, examples **11a** and **11h** were scaled up to 5 g using 2 mol % Cu and 4 mol % **L40**. In the case of **11a**, the reactions in DMSO and sulfolane were compared and achieved nearly identical reaction rates and impurity distributions.[37] For **11a**, the reaction stalled consistently at 50−60% conversion because of arylation of **L40**. Recharging the reaction mixture with another 4 mol % loading of **L40** allowed the reaction to reach >99% conversion within a few hours. This demonstrates the ability of recharging the ligand to Cu in the presence of the substrates and product to successfully reactivate the catalyst.[38] Upon reaction completion, the reaction mixtures were diluted with MeOH and aqueous ammonia to directly crystallize the desired products. Aqueous ammonia facilitated the removal of Cu during the crystallization. The ligand (**L40**) remained in the mother liquor or in an aqueous phase if a phase separation was performed for the workup. From this exercise, the products were isolated in good yields (76% and 90% for **12a** and **12h**, respectively).

Other heteroaryl amines were examined under similar conditions with a focus on aminopyrazoles. Couplings with highly electron-rich 4-amino-3-methoxymethylpyrazole were explored and were found to proceed rapidly with 2 mol % Cu. As the reactions approached completion, pyrazole dimers (**14**) consistently formed at levels ranging from 5% to 50% (Scheme 3). It was speculated that the presence of Cu(II) could promote the oxidative dimerization reaction of the aminopyrazole products.[39] The addition of sodium ascorbate at a level similar to the Cu loading was found to be sufficient to suppress this side reaction.

**Scheme 3. Dimer Formation of 4-Aminopyrazoles**




In general, the aminopyrazoles were prone to many side reactions, leading to lower yields in some cases (such as **13c**). Other than suppressing the dimerization of the pyrazoles with sodium ascorbate, the reaction conditions were not optimized. With the use of sodium ascorbate, a variety of heteroaryl bromides were coupled with 4-aminopyrazoles in modest to excellent yields (Figure 8). In the case of **13g**, the yield was lower because the ortho substituent impeded the catalysis.

This pyrazole dimerization side reaction was observed when 4-bromopyrazole derivatives (such as in example **11h** in Figure 7) were coupled with amines because this also furnished 4-(hetero)arylaminopyrazole products (**13**). In the case of coupling of **11h** with **2**, the addition of sodium ascorbate suppressed the observed dimerization to <1%. As an additional liability, dehalogenation was observed for **11h** as a major competing side reaction rather than hydroxylation, which had not been the case for any of the other substrates examined. Limiting the level of water to <0.1% seemed to minimize dehalogenation to <1%, analogous to hydroxylation which occurred with most other substrates. It was also found that the loading of sodium ascorbate was correlated to the extent of dehalogenation for coupling of substrate **11h**.

Couplings with 3-aminopyrazoles were found to be higher-yielding than those with 4-aminopyrazoles because these products did not undergo dimerization or other side reactions. The reactions were carried out with 4 mol % CuI and 6 mol % **L40** in DMSO with $K_2CO_3$ as the base (Figure 9). As observed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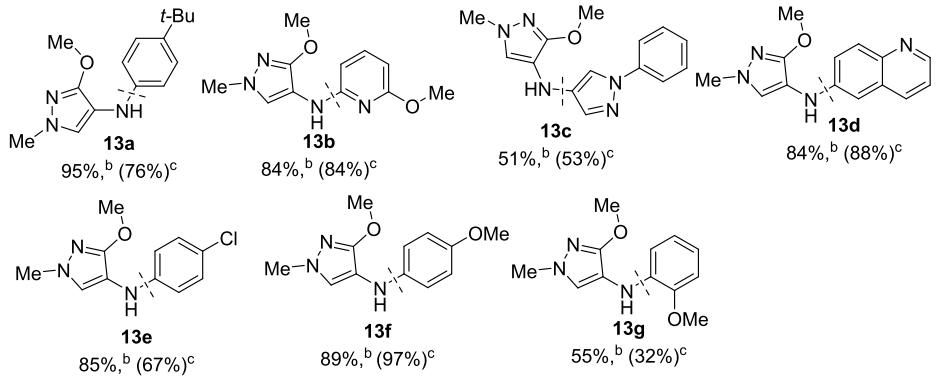


**Figure 8.** Couplings of (hetero)aryl bromides with 4-aminopyrazoles. Reactions conditions: 2 mol % CuI, 4 mol % **L40**, 1 M in DMSO, 2 equiv of $K_2CO_3$, 1.1 equiv of amine, and 0.10 equiv of sodium ascorbate at 80 °C (examples **13a**, **13d**, and **13e**) or 100 °C (examples **13b**, **13c**, **13f**, and **13g**). Notes: [b]HPLC/UPLC purity assay in the reaction mixture. [c]Isolated yield.

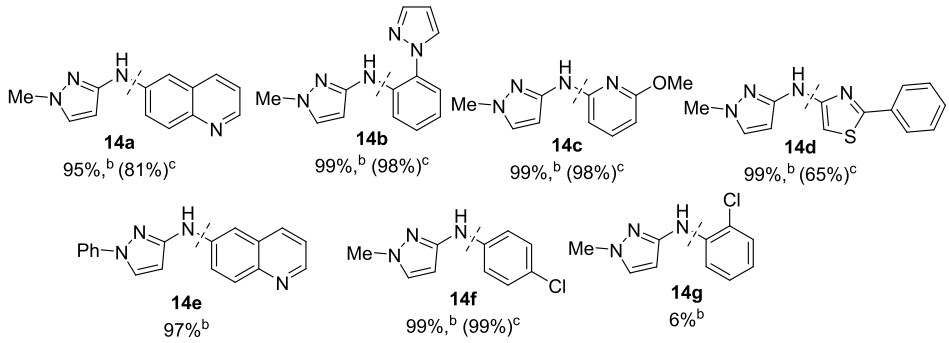


**Figure 9.** Couplings with 3-amino-*N*-methylpyrazole. Reaction conditions: 4 mol % CuI, 6 mol % **L40**, 1 M in DMSO, 1.5 equiv of $K_2CO_3$, 1.1 equiv of amine, 110 °C. Notes: [b]HPLC/UPLC purity assay. [c]Isolated yield.

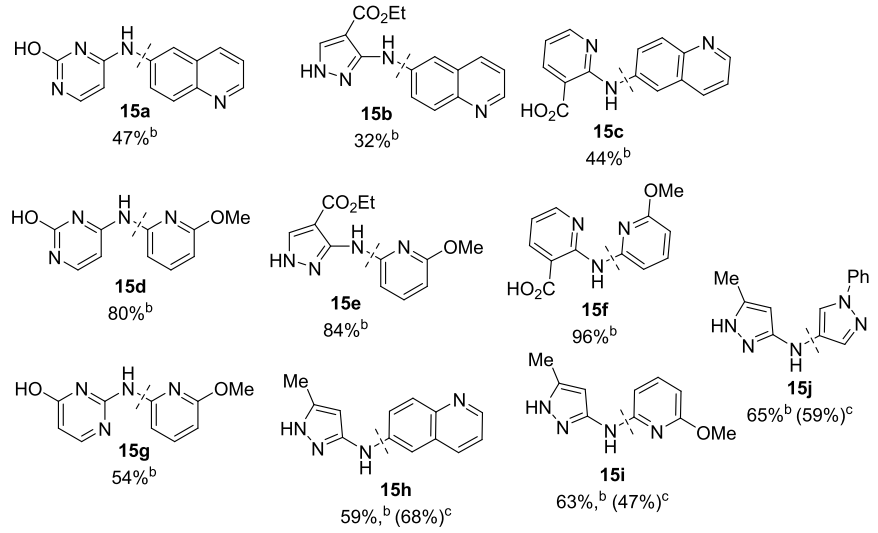


**Figure 10.** Other couplings of heteroaryl bromides with heteroaryl amines. Reaction conditions: 4 mol % CuI, 6 mol % **L40**, 1 M in DMSO, 1.5 equiv of $K_2CO_3$, 1.1 equiv of amine, 110 °C. Notes: [b]HPLC/UPLC purity assay. [c]Isolated yield.

with other substrate sets, aryl bromides with ortho substituents impeded catalysis (such as in **14g**) unless the ortho substituent was a directing group (such as in **14b**). Because $K_2CO_3$ was used as the base, **14f** was observed to form cleanly as the sole product with no competing coupling at the chloride.

A variety of other heteroaryl primary amines were examined in couplings, mainly with 6-bromoquinoline (**11a**) and 2-bromo-6-methoxypyridine (**11i**) (Figure 10). The highly activated substrate **11i** outperformed **11a** in each case. The reactions were much slower for the aminopyrimidines examined (**15a**, **15d**, and **15g**) because of the relatively poor nucleophilicity. For each of the pyrimidine couplings there was a strong preference for the C−N coupling over the potential C−O coupling, but the reactions achieved only modest conversions under these unoptimized conditions. In the cases with unprotected pyrazoles (**15b**, **15e**, and **15h**–**j**), competitive C−N coupling was observed to proceed at both nitrogens of the pyrazole ring. The typical isomer ratio was


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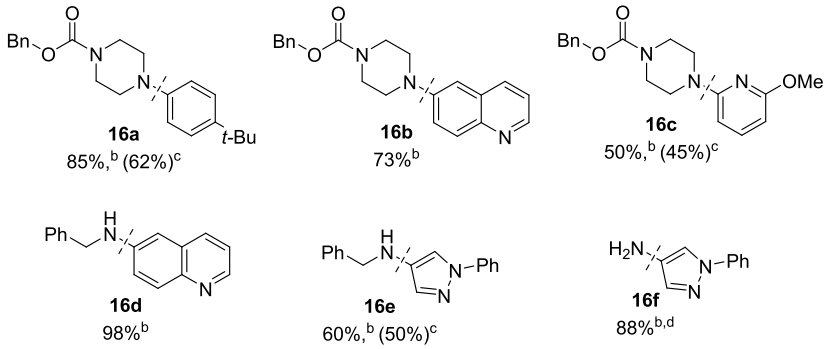


**Figure 11.** Couplings of alkyl amines and ammonia with (hetero)aryl bromides. Reaction conditions: 4 mol % CuI, 6 mol % **L40**, 1 M in DMSO, 1.5 equiv of $K_3PO_4$, 1.1 equiv of amine, 120 °C. Notes: [b]HPLC/UPLC purity assay. [c]Isolated yield. [d]Modified reaction conditions: 4 mol % CuI, 8 mol % **L40**, 1 M in DMSO, 1.5 equiv of $K_2CO_3$, 110 °C.

30:1:1, favoring the coupling at the desired primary amine rather than at the two pyrazole nitrogens. The unprotected pyrazoles had lower reaction rates and did not reach reaction completion, suggesting that protection or alkylation of the pyrazole is warranted for greater efficiency, as observed in other examples (Figures 8 and 9).

The scope of couplings with **L40** and CuI was briefly examined for primary and secondary alkyl amines (Figure 11). Couplings of (hetero)aryl bromides with benzylamine were complete in 1−2 h because of the high nucleophilicity. Couplings of aryl bromides with benzyloxycarbonyl (Cbz)-protected piperazine were also fairly rapid with $K_3PO_4$ as the base, but it was observed that hydroxylation with subsequent diaryl ether formation was highly competitive, which resulted in modest purity and yields for **16a−c**. Even though the couplings proceeded efficiently at 80 °C, this did not provide any benefit to the product distribution. Only when KI as was included as an additive was the level of hydroxylation reduced by about 50%. Coupling of Cbz-protected piperazine with aryl chloride **11j** to furnish **16a** was significantly slower than with the corresponding bromide (**1**) but was relatively clean with no significant C−O coupling (<1%) in sulfolane (99% conversion 48 h at 10 mol % Cu). This same transformation in DMSO had a similar reaction rate but formed 8% diaryl ether, similar to coupling with **1**. In contrast to what was observed with primary amines, the reaction between Cbz-protected piperazine and **11j** was much slower in 1-butanol (only 14% conversion over 20 h and 35% conversion after 48 h) and had competitive side reactions.

The coupling of ammonia with aryl halides has been demonstrated to be highly efficient with oxalamide ligands and other systems.[40] Bromination of arenes or heteroarenes followed by coupling with ammonia is a valuable alternative to nitration. In particular, nitration of pyrazoles and related heterocycles can produce potentially hazardous intermediates.[41] The coupling of **11h** with ammonia was demonstrated to afford **16f** with 88% purity using $K_2CO_3$ as the base in DMSO (1 M) at 110 °C over 24 h. The only impurity present with **16f** was the product of dehalogenation of **11h** (at a 12% level). Increasing the concentration of the substrates (2 M relative to **11h**) resulted in higher levels of dehalogenation and other side reactions for the coupling with ammonia. Dehalogenation seemed to be common problem for **11h** as a side reaction, and this was also observed in the coupling with benzylamine to yield **16e**. As observed in other examples with **11h**, increasing the loading of sodium ascorbate was correlated to an increase in dehalogenation for this substrate.

## CONCLUSIONS

A new family of 6-hydroxypicolinamide ligands was developed for the Cu-catalyzed coupling of heteroaryl bromides and heteroaryl primary amines. The reaction conditions were highly optimized for the coupling of 2-aminopyridine (**2**) with various heteroaryl bromides using CuI and **L40**. **L40** was selected for study because it provided high catalytic performance, delivered a clean product profile, and was practical to prepare. A number of key process parameters were identified that impact both the reaction rate and the product distribution. Among the most influential process parameters were the choice of solvent, base, reaction temperature, and concentration in addition to the ligand to Cu molar ratio. Even though DMSO was the most widely utilized solvent for the studies, sulfolane appeared to provide virtually identical performance and has better stability with base,[25] making it a more viable choice for process development. In a number of examples, 1-butanol and other alcohols were potential alternatives to polar aprotic solvents for these Cu-catalyzed C−N couplings. The use of sodium ascorbate provided more reliable activation of the catalyst, especially for experiments carried out in vials without nitrogen inertion. A variety of other heteroaryl amines were surveyed to illustrate the potential scope with this family of ligands. For the unoptimized substrates studied, additional development of reaction conditions could be carried out to improve the reaction profiles and increase the isolated yields. Reaction optimization should be possible through design of experiment (DoE) studies, which is likely to be necessary given the complexity of interactions among the various process parameters. Optimization of the ligand design for other applications is facilitated through the highly modular design and will be reported in due course.

## EXPERIMENTAL SECTION

**General.** All of the screening reactions were carried out in screw-capped glass vials without nitrogen inertion. For the substrate scope studies and scale-up trials (to prepare **12a** and **12h**), the reactions were conducted in dry reaction vessels under an atmosphere of dry nitrogen. All of the reagents and solvents were used as received without further purification unless otherwise specified.

***N*-(2,6-Dimethylphenyl)-6-hydroxypicolinamide (L40).** To a 100 mL reaction vessel were charged 6-hydroxypicolinic acid (10.0 g, 71.8 mmol), THF (100 mL), and triethylamine (30 mL, 216 mmol, 3 equiv) at 25 °C. This


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initially dissolved the picolinic acid, and a new, thicker white suspension formed. 2,6-Dimethylaniline (9.32 mL, 75.4 mmol, 1.05 equiv) was charged, and the resulting mixture was held at 25 °C; the charge of the aniline helped break up the slurry. To the reaction mixture was charged T3P (50 wt %) in ethyl acetate (60 mL, 100.6 mmol, 1.40 equiv) dropwise over 30 min. The exotherm was well-controlled by charging the T3P slowly. As the addition progressed, the reaction mixture became homogeneous. The mixture was held at 25 °C following addition for 30 min, warmed to 65 °C over 2 h, and held at 65 °C for 16 h. The jacket was heated to 85 °C to begin distillation, and the mixture was distilled to a volume of 80 mL with a pot temperature of ∼71 °C. The reaction mixture was cooled to 50 °C temporarily and quenched with water (40 mL) and aqueous 11.5 M KOH (10 mL, 115 mmol, 1.6 equiv) to adjust the pH to 10−11. The distillation was resumed under atmospheric conditions, and MeOH (80 mL) was charged in portions during the distillation (or as a constant-volume displacement). As the distillation continued, the pH dropped to 7 (volume at 120 mL). When a volume of about 110 mL was reached, the pH had dropped to 5−6. When a volume of about 100 mL was reached, crystals formed (UPLC tracking showed that the phosphonate hydrolysis had proceeded to completion over this time during the distillation) and had a pot temperature of 72−73 °C. To the mixture were charged water (30 mL) and MeOH (20 mL), which thickened the slurry. (Note: charging much more MeOH can start to redissolve the crystals). The reaction mixture was held at reflux for 1 h. The slurry was cooled to 20 °C over at least 2 h. The suspension thickened upon cooling. The slurry was held for 15 min at 20 °C. The crystals were filtered. The transfer was washed with 1:1 water/MeOH and dried with suction for 1 h. The crystals were transferred to a vacuum oven at 45 °C. **L40** (15.63 g, 90% yield) was isolated as white crystals (mp 235−237 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.18 (s, 6H), 6.79 (d, $J$ = 8.59 Hz, 1H), 7.10−7.17 (m, 3H), 7.35 (d, $J$ = 7.02 Hz, 1H), 7.75 (dd, $J$ = 8.59, 7.02 Hz, 1H), 9.84 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 18.6, 111.0, 117.2, 127.3, 128.3, 135.0, 135.8, 140.9, 145.0, 161.7, 162.8.

**6-Hydroxy-*N*-(2,4,6-trimethoxyphenyl)picolinamide (L41).** Prepared analogously to **L40** on the same scale of operations. **L41** (17.1 g, 78% yield) was isolated as purple crystals (mp 160−162 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.74 (s, 6H), 3.81 (s, 3H), 6.31 (s, 2H), 6.78 (d, $J$ = 8.59 Hz, 1H), 7.36 (d, $J$ = 5.85 Hz, 1H), 7.74 (t, $J$ = 7.81 Hz, 1H), 9.13 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.9, 56.2, 91.5, 107.1, 111.0, 117.2, 140.9, 145.0, 156.9, 160.1, 161.6, 162.8.

**6-Hydroxy-*N*-(2-methylnaphthalen-1-yl)picolinamide (L42).** Prepared analogously to **L40** on the same scale of operations. **L42** (15.2 g, 76% yield) was isolated as yellow crystals (mp 239−242 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.37 (s, 3H), 6.84 (d, $J$ = 8.59 Hz, 1H), 7.41−7.56 (m, 4H), 7.77−7.90 (m, 3H), 7.94 (d, $J$ = 7.31 Hz, 1H), 10.26 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 18.8, 113.0, 115.8, 123.3, 125.8, 126.9, 127.5, 128.4, 129.2, 130.9, 131.1, 132.8, 133.4, 136.3, 141.0, 162.0, 162.9.

**6-Hydroxy-*N*-(naphthalen-1-yl)picolinamide (L43).** Prepared analogously to **L40** on the same scale of operations. **L43** (15.6 g, 87% yield) was isolated as off-white crystals (mp 175−179 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.93 (d, $J$ = 8.59 Hz, 1H), 7.45−7.74 (m, 4H), 7.78−7.94 (m, 2H), 8.00 (d, $J$ = 7.81 Hz, 1H), 8.10 (d, $J$ = 7.61 Hz, 2H), 10.77 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 113.0, 116.0, 120.2, 122.0, 125.8, 126.2, 126.7, 126.8, 127.2, 129.0, 133.2, 134.2, 141.3, 146.4, 162.4, 163.1.

**6-Hydroxy-*N*-(*o*-tolyl)picolinamide (L46).** Prepared analogously to **L40** on the same scale of operations. **L46** (14.8 g, 90% yield) was isolated as white crystals (mp 190−192 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.34 (s, 3H), 6.88 (d, $J$ = 8.59 Hz, 1H), 7.08−7.16 (m, 1H), 7.25 (t, $J$ = 7.61 Hz, 1H), 7.29 (d, $J$ = 7.41 Hz, 1H), 7.52 (d, $J$ = 7.02 Hz, 1H), 7.84 (t, $J$ = 7.82 Hz, 1H), 7.92 (d, $J$ = 7.41 Hz, 1H), 10.01 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 18.0, 113.0, 115.8, 122.7, 125.3, 126.9, 130.0, 130.9, 136.3, 141.3, 146.4, 162.0, 162.9.

**6-Hydroxy-*N*-phenylpicolinamide (L47).** Prepared analogously to **L40** on the same scale of operations. **L47** (14.6 g, 95% yield) was isolated as white crystals (mp 269−272 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.83 (d, $J$ = 8.59 Hz, 1H), 7.14 (t, $J$ = 7.34 Hz, 1H), 7.34−7.45 (m, 3H), 7.75−7.82 (m, 3H), 10.23 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 100.1, 112.3, 116.9, 120.4, 124.5, 129.3, 138.6, 141.9, 162.0, 162.9.

**General Procedure for Coupling of Primary Amines with Heteroaryl Bromides.** To a 25 mL reaction tube were charged CuI (0.02−0.04 equiv) and **L40** (0.04−0.08 equiv) in DMSO (2−4 mL/g). After the mixture was held for at least 10 min at 25−35 °C, potassium carbonate or potassium phosphate (1.5 equiv) was charged. The reaction mixture was held at 25−30 °C for at least 10 min. To the reaction mixture was charged the heteroaryl bromide (5.00 mmol, 1 equiv) followed by the amine (5.50 mmol, 1.1 equiv). In cases with electron-rich heterocyclic amines, sodium ascorbate (0.10 equiv) was charged (it should also be used for reactions conducted without nitrogen inertion). The reaction mixture was heated to 120 °C and held until the reaction assay indicated >99% conversion. The reaction mixture was cooled to 50 °C. To the reaction mixture were charged aqueous ammonia (5 mL/g) and water (5 mL/g). For direct crystallization of the product, MeOH (2−3 mL/g) was charged, followed by aqueous ammonia (2−3 mL/g) and water (2−3 mL/g), and the mixture was held at 50−60 °C for 30−60 min and then cooled to room temperature to filter the crystals. For aqueous workup, ethyl acetate or toluene (10 mL/g) was charged to the aqueous mixture to extract the desired product. The layers were separated, and the organic phase was concentrated to either crystallize the desired product or purify the desired product by silica gel chromatography.

*N-(4-(tert-Butyl)phenyl)pyridin-2-amine (**3**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.27 (s, 9H), 6.69 (dd, $J$ = 6.83, 5.27 Hz, 1H), 6.80 (d, $J$ = 8.20 Hz, 1H), 7.28 (d, $J$ = 7.86 Hz, 2H), 7.50−7.58 (m, 3H), 8.11 (dd, $J$ = 4.88, 1.37 Hz, 1H), 8.89 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 31.8, 34.3, 110.8, 114.3, 118.5, 125.6, 137.6, 139.5, 143.2, 147.7, 156.6.

*Scale-Up of N-(Pyridin-2-yl)quinolin-6-amine (**12a**).* To a reaction vessel under nitrogen were charged CuI (97.2 mg, 0.02 equiv) and **L40** (242 mg, 0.04 equiv) in sulfolane (10 mL, ∼2 mL/g). This gave a light-brown suspension at first that became a solution eventually and was held for 20 min at 25−35 °C. To the reaction mixture were charged $K_2CO_3$ (5.24 g, 1.50 equiv), **11a** (5.20 g, 25.0 mmol), and 2-aminopyridine (2.59 g, 1.1 equiv, 27.5 mmol). The reaction mixture became a yellowish-brown color and was heated to 110−120 °C. Upon heating the reaction mixture turned a brown color. Heating was continued for about 4 h, at which point a reaction assay indicated that the reaction was 57% complete. The progress had stopped because of arylation of the ligand. Additional **L40**


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(242 mg, 0.04 equiv) was charged, and heating was resumed. After another 4 h of heating at 110−120 °C, a reaction assay indicated that the reaction was >99% complete. The reaction mixture was cooled to 60 °C. To the reaction mixture was charged MeOH (20 mL, ∼4 mL/g) followed by aqueous ammonia (20 mL, ∼4 mL/g) and water (20 mL, ∼4 mL/g). The reaction mixture was held at 55−60 °C for 1 h and then cooled to 22 °C over 1 h. The slurry was held at 22 °C for 2 h and then filtered. The transfer was washed with 2:1 water/MeOH and dried in a vacuum oven at 45 °C for 16 h. **12a** (4.20 g, 76% yield) was isolated as light-tan crystals (mp 159−162 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.84 (dd, $J$ = 6.63, 5.46 Hz, 1H), 6.96 (d, $J$ = 8.20 Hz, 1H), 7.42 (dd, $J$ = 8.20, 4.29 Hz, 1H), 7.64 (t, $J$ = 7.70 Hz, 1H), 7.83 (dd, $J$ = 8.98, 2.34 Hz, 1H), 7.91 (d, $J$ = 9.37 Hz, 1H), 8.20 (d, $J$ = 7.80 Hz, 1H), 8.23−8.31 (m, 1H), 8.52 (d, $J$ = 1.95 Hz, 1H), 8.68 (br d, $J$ = 2.73 Hz, 1H), 9.43 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 111.7, 111.8, 115.4, 122.0, 124.0, 129.4, 129.7, 135.2, 137.9, 140.2, 144.2, 147.8, 147.9, 156.1.

*N-(2-(1H-Pyrazol-1-yl)phenyl)pyridin-2-amine (**12c**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.52 (t, $J$ = 2.15 Hz, 1H), 6.74−6.80 (m, 2H), 7.14 (td, $J$ = 7.71, 1.37 Hz, 1H), 7.36 (t, $J$ = 7.42 Hz, 1H), 7.50−7.57 (m, 2H), 7.83 (d, $J$ = 1.56 Hz, 1H), 8.06−8.11 (m, 2H), 8.19 (d, $J$ = 1.95 Hz, 1H), 9.12 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 106.9, 110.0, 115.2, 122.3, 122.4, 124.2, 127.7, 130.3, 131.0, 133.7, 137.7, 140.6, 147.6, 155.2.

*2-Phenyl-N-(pyridin-2-yl)thiazol-4-amine (**12d**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.79 (dd, $J$ = 6.44, 5.66 Hz, 1H), 7.04 (d, $J$ = 8.20 Hz, 1H), 7.46−7.55 (m, 2H), 7.55−7.63 (m, 1H), 7.68 (s, 1H), 7.92 (dd, $J$ = 7.81, 1.56 Hz, 2H), 8.21 (dd, $J$ = 5.07, 1.56 Hz, 1H), 10.14 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 95.7, 110.8, 114.6, 125.6, 129.2, 130.0, 133.1, 137.1, 147.1, 151.0, 154.3, 163.3.

*N-(4-Chlorophenyl)pyridin-2-amine (**12f**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.76 (dd, $J$ = 6.63, 4.68 Hz, 1H), 6.82 (d, $J$ = 8.20 Hz, 1H), 7.28 (d, $J$ = 8.98 Hz, 2H), 7.57 (td, $J$ = 7.80, 1.95 Hz, 1H), 7.73 (d, $J$ = 8.59 Hz, 2H), 8.16 (dd, $J$ = 4.68, 1.56 Hz, 1H), 9.16 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 111.0, 114.6, 119.2, 128.3, 129.1, 137.3, 140.7, 147.1, 155.5.

*Scale-Up of N-(1-Phenyl-1H-pyrazol-4-yl)pyridin-2-amine (**12h**).* To a reaction vessel under nitrogen were charged CuI (77.5 mg, 0.02 equiv) and **L40** (194 mg, 0.04 equiv) in DMSO (10 mL, ∼2 mL/g). This gave a light-brown solution that was held for 10 min at 25−35 °C. To the reaction mixture were charged $K_3PO_4$ (6.50 g, 1.50 equiv), **11h** (4.70 g, 20.0 mmol), and 2-aminopyridine (2.07 g, 1.1 equiv, 22.0 mmol). The reaction mixture became a green color and was heated to 110−120 °C. Upon heating the reaction mixture turned a brown color. After about 1 h of heating, sodium ascorbate (99 mg, 0.025 equiv) was charged to the reaction mixture. Heating was continued for about 4 h, at which point a reaction assay indicated that the reaction was >99% complete. The reaction mixture was cooled to 60 °C. To the reaction mixture was charged MeOH (20 mL, ∼4 mL/g) followed by aqueous ammonia (20 mL, ∼4 mL/g) and water (40 mL, ∼8 mL/g). The reaction mixture was held at 60−65 °C for 1 h and then cooled to 22 °C over 1 h. The slurry was held at 22 °C for 1 h and then filtered. The transfer was washed with 2:1 water/MeOH and dried in a vacuum oven at 45 °C for 16 h. **12h** (4.26 g, 90% yield) was isolated as light-tan crystals (mp 108−110 °C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.67 (t, $J$ = 6.24 Hz, 1H), 6.75 (d, $J$ = 8.59 Hz, 1H), 7.26 (t, $J$ = 7.02 Hz, 1H), 7.48 (t, $J$ = 7.41 Hz, 2H), 7.49−7.54 (m, 1H), 7.77 (s, 1H), 7.78 (d, $J$ = 8.4 Hz, 2H), 8.18 (dd, $J$ = 5.07, 1.56 Hz, 1H), 8.64 (s, 1H), 9.04 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 109.5, 113.2, 115.6, 117.6, 125.4, 126.4, 129.5, 133.1, 137.0, 139.9, 147.6, 155.3.

*6-Methoxy-N-(pyridin-2-yl)pyridin-2-amine (**12i**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.86 (s, 3H), 6.26 (d, $J$ = 7.80 Hz, 1H), 6.85 (dd, $J$ = 7.41, 4.68 Hz, 1H), 7.21 (d, $J$ = 8.20 Hz, 1H), 7.55 (t, $J$ = 8.00 Hz, 1H), 7.65 (ddd, $J$ = 8.59, 7.02, 1.95 Hz, 1H), 7.81 (d, $J$ = 8.59 Hz, 1H), 8.21 (dd, $J$ = 5.07, 1.17 Hz, 1H), 9.54 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 53.1, 100.4, 103.2, 111.7, 115.8, 137.5, 140.3, 147.4, 152.7, 154.2, 162.4.

*N-(4-(tert-Butyl)phenyl)-3-methoxy-1-methyl-1H-pyrazol-4-amine (**13a**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.29 (s, 9H), 3.74 (br s, 3H), 3.92 (s, 3H), 4.60−4.95 (br s, 1H), 6.60−6.77 (m, 2H), 7.14−7.24 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 31.5, 33.9, 39.2, 56.2, 108.7, 113.0, 125.9, 126.6, 141.1, 144.3, 157.8.

*6-Methoxy-N-(3-methoxy-1-methyl-1H-pyrazol-4-yl)-pyridin-2-amine (**13b**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.74 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 5.76 (br s, 1H), 6.08 (dd, $J$ = 14.05, 7.80 Hz, 2H), 7.35 (t, $J$ = 7.81 Hz, 1H), 7.51 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.1, 53.3, 56.3, 98.4, 98.7, 107.3, 125.0, 139.9, 155.5, 155.9, 163.6.

*3-Methoxy-1-methyl-N-(1-phenyl-1H-pyrazol-4-yl)-1H-pyrazol-4-amine (**13c**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.72 (s, 3H), 3.95 (s, 3H), 7.10 (s, 1H), 7.19−7.25 (m, 1H), 7.37−7.47 (m, 3H), 7.50 (s, 1H), 7.57−7.68 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.1, 56.3, 113.2, 115.7, 118.2, 123.2, 125.6, 129.3, 131.9, 133.1, 140.3, 155.8.

*N-(3-Methoxy-1-methyl-1H-pyrazol-4-yl)quinolin-6-amine (**13d**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.79 (s, 3H), 3.93 (s, 3H), 5.21 (br s, 1H), 6.80−6.86 (m, 1H), 7.16−7.32 (m, 3H), 7.89 (d, $J$ = 7.41 Hz, 1H), 7.93 (d, $J$ = 8.98 Hz, 1H), 8.63 (dd, $J$ = 8.63, 4.29 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.3, 56.3, 105.0, 107.4, 120.8, 121.3, 127.6, 129.8, 130.2, 134.1, 143.4, 145.1, 146.5, 158.2.

*N-(4-Chlorophenyl)-3-methoxy-1-methyl-1H-pyrazol-4-amine (**13e**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.75 (s, 3H), 3.91 (s, 3H), 6.62 (d, $J$ = 8.59 Hz, 2H), 7.11 (d, $J$ = 8.59 Hz, 2H), 7.18 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.2, 56.2, 107.6, 114.4, 122.8, 127.5, 128.9, 145.6, 158.1.

*3-Methoxy-N-(4-methoxyphenyl)-1-methyl-1H-pyrazol-4-amine (**13f**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.73 (s, 3H), 3.75 (s, 3H), 3.92 (s, 3H), 4.69 (s, 1H), 6.64−6.72 (m, 2H), 6.73−6.81 (m, 2H), 7.15 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.2, 55.8, 56.3, 109.5, 114.7, 114.7, 126.4, 140.9, 152.7, 157.7.

*3-Methoxy-N-(2-methoxyphenyl)-1-methyl-1H-pyrazol-4-amine (**13g**).* $^1$H NMR (400 MHz $CDCl_3$): $\delta$ 3.75 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.95−5.87 (br s, 1H), 6.66−6.75 (m, 2H), 6.78−6.86 (m, 2H), 7.20 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 39.2, 55.4, 56.2, 108.0, 109.7, 111.1, 117.5, 121.0, 126.7, 136.5, 146.6, 157.9.

*N-(1-Methyl-1H-pyrazol-3-yl)isoquinolin-7-amine (**14a**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.80 (s, 3H), 5.90 (d, $J$ = 2.34 Hz, 1H), 7.34 (dd, $J$ = 8.20, 4.29 Hz, 1H), 7.56 (dd, $J$ = 9.37, 2.73 Hz, 1H), 7.57 (d, $J$ = 2.34 Hz, 1H), 7.83 (d, $J$ = 8.98 Hz, 1H), 7.89 (d, $J$ = 2.34 Hz, 1H), 8.05 (d, $J$ = 8.20, 1H), 8.57 (dd, $J$ = 4.29, 1.56 Hz, 1H), 8.87 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 38.5, 94.0, 106.5, 121.4, 122.1, 129.3, 129.5, 131.1, 133.9, 141.6, 142.9, 146.2, 150.7.


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*N-(2-(1H-Pyrazol-1-yl)phenyl)-1-methyl-1H-pyrazol-3-amine (**14b**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.74 (s, 3H), 5.92 (d, $J$ = 2.34 Hz, 1H), 6.58 (t, $J$ = 2.15 Hz, 1H), 6.87−6.91 (m, 1H), 7.24−7.31 (m, 1H), 7.42 (dd, $J$ = 8.00, 1.37 Hz, 1H), 7.55 (d, $J$ = 2.34 Hz, 1H), 7.84−7.88 (m, 1H), 7.87−7.88 (m, 1H), 8.25 (d, $J$ = 2.73 Hz, 1H), 8.75 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 38.4, 94.7, 106.8, 116.0, 118.6, 123.5, 126.1, 128.1, 131.0, 131.4, 136.6, 140.5, 149.6.

*6-Methoxy-N-(1-methyl-1H-pyrazol-3-yl)pyridin-2-amine (**14c**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.72 (s, 3H), 3.82 (s, 3H), 6.07 (d, $J$ = 7.80 Hz, 1H), 6.39 (d, $J$ = 2.34 Hz, 1H), 6.68 (d, $J$ = 7.80 Hz, 1H), 7.43 (t, $J$ = 7.81 Hz, 1H), 7.49 (d, $J$ = 1.95 Hz, 1H), 9.16 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 38.2, 52.9, 95.2, 98.0, 100.7, 130.6, 139.9, 149.3, 153.8, 162.7.

*N-(1-Methyl-1H-pyrazol-3-yl)-2-phenylthiazol-4-amine (**14d**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.74 (s, 3H), 5.80 (d, $J$ = 1.95 Hz, 1H), 7.06 (s, 1H), 7.43−7.52 (m, 4H), 7.89 (dd, $J$ = 8.00, 1.37 Hz, 2H), 9.42 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 38.3, 91.1, 92.5, 125.5, 129.2, 129.9, 131.0, 133.2, 150.5, 153.2, 163.5.

*N-(4-Chlorophenyl)-1-methyl-1H-pyrazol-3-amine (**14f**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.74 (s, 3H), 5.75 (d, $J$ = 2.34 Hz, 1H), 7.19 (d, $J$ = 8.98 Hz, 2H), 7.35 (d, $J$ = 8.98 Hz, 2H), 7.51 (d, $J$ = 1.95 Hz, 1H), 8.58 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 38.3, 93.5, 116.0, 120.9, 128.4, 131.0, 142.6, 150.8.

*N-(5-Methyl-1H-pyrazol-3-yl)quinolin-6-amine (**15h**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.22 (s, 3H), 5.72 (s, 1H), 7.33 (dd, $J$ = 8.39, 4.10 Hz, 1H), 7.55 (dd, $J$ = 8.98, 2.34 Hz, 1H), 7.80 (d, $J$ = 8.98 Hz, 1H), 7.91−7.98 (m, 1H), 8.05 (d, $J$ = 7.80 Hz, 1H), 8.56 (dd, $J$ = 4.29, 1.56 Hz, 1H), 8.72−8.81 (m, 1H), 11.78 (br s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 10.7, 93.2, 106.5, 121.4, 122.1, 129.2, 129.5, 133.9, 138.4, 141.8, 142.8, 146.1, 151.1.

*6-Methoxy-N-(5-methyl-1H-pyrazol-3-yl)pyridin-2-amine (**15i**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.28 (s, 3H), 3.92 (s, 3H), 6.01 (s, 1H), 6.20 (d, $J$ = 7.80 Hz, 1H), 6.53 (d, $J$ = 7.80 Hz, 1H), 7.09−7.23 (br s, 1H), 7.42 (t, $J$ = 7.80, 1H), 9.64−9.93 (br s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 11.9, 53.4, 93.9, 99.8, 100.3, 140.2, 142.0, 148.4, 153.4, 163.4.

*5-Methyl-N-(1-phenyl-1H-pyrazol-4-yl)-1H-pyrazol-3-amine (**15j**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.25 (s, 3H), 5.59 (s, 1H), 6.38−6.80 (br s, 1H), 7.19−7.26 (m, 1H), 7.41 (t, $J$ = 8.00 Hz, 2H), 7.59 (s, 1H), 7.66 (dd, $J$ = 8.78, 0.98 Hz, 2H), 8.07 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 11.2, 91.6, 115.6, 118.3, 125.6, 128.5, 129.2, 132.9, 140.3, 140.7, 153.6.

*Benzyl 4-(4-(tert-Butyl)phenyl)piperazine-1-carboxylate (**16a**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.24 (s, 9H), 3.04−3.08 (m, 4H), 3.54 (br s, 4H), 5.12 (s, 2H), 6.88 (d, $J$ = 7.68 Hz, 2H), 7.24 (d, $J$ = 8.59 Hz, 2H), 7.32−7.40 (m, 5H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 31.8, 34.1, 43.9, 49.3, 66.8, 116.4, 126.1, 128.1, 128.4, 128.9, 137.3, 142.3, 149.1, 154.9.

*Benzyl 4-(6-Methoxypyridin-2-yl)piperazine-1-carboxylate (**16c**).* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.51−3.57 (m, 4H), 3.61−3.67 (m, 4H), 3.87 (s, 3H), 5.18 (s, 2H), 6.12 (d, $J$ = 7.81 Hz, 1H), 6.17 (d, $J$ = 8.20 Hz, 1H), 7.29−7.49 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 43.5, 45.0, 53.0, 67.2, 98.3, 98.8, 127.9, 128.0, 128.5, 136.6, 140.2, 155.3, 157.9, 163.1.

*N-Benzyl-1-phenyl-1H-pyrazol-4-amine (**16e**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.15 (d, $J$ = 6.24 Hz, 2H), 5.32 (t, $J$ = 6.24 Hz, 1H), 7.17 (t, $J$ = 7.41 Hz, 1H), 7.23 (t, $J$ = 7.02 Hz, 1H), 7.29−7.36 (m, 3H), 7.38−7.44 (m, 4H), 7.67 (d, $J$ = 7.80 Hz, 2H), 7.75 (s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 49.9, 110.5, 116.9, 124.7, 126.7, 127.6, 128.2, 129.3, 131.2, 136.5, 140.0, 140.2.

*1-Phenyl-1H-pyrazol-4-amine (**16f**).* $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.19 (br s, 2H), 7.19 (t, $J$ = 7.38 Hz, 1H), 7.27 (s, 1H), 7.42 (t, $J$ = 7.81 Hz, 2H), 7.68 (d, $J$ = 9.37, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 112.6, 117.5, 125.2, 129.8, 133.2, 134.0, 140.6.

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### Notes

The authors declare no competing financial interest.

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(16) For the oxalamide ligands it has been suggested by computational and structure−activity relationship studies that one of the amides can switch binding from the amide nitrogen to the carbonyl oxygen as needed during the catalytic cycle. See: Chan, V. S.; Krabbe, S. W.; Li, C.; Sun, L.; Liu, Y.; Nett, A. J. Identification of an Oxalamide Ligand for Copper-Catalyzed C−O Couplings from a Pharmaceutical Compound Library. *Chem. Cat Chem.* **2019**, DOI: 10.1002/cctc.201900393.

(17) This binding mode for oxalamide−Cu complexes has been observed in single-crystal X-ray structures. See: Zilic, D.; Rakvin, B.; Milic, D.; Pajic, D.; Dilovic, I.; Cametti, M.; Dzolic, Z. Crystal Structures and Magnetic Properties of a Set of Dihalobridged Oxalamidato Copper(II) Dimers. *Dalton Trans.* **2014**, *43*, 11877−11887.

(18) Ligand arylation was found in this case and in other examples to be a competitive process throughout the reaction time frame. The rate of ligand arylation was found to be dependent on the nature of the aryl halide, amine, and ligand involved, in addition to the reaction conditions. It was noted that certain substrates tended to promote ligand arylation to a greater extent than others.

(19) (a) Krueger, A. C.; et al. Aryl Uracil Inhibitors of Hepatitis C Virus NS5B Polymerase: Synthesis and Characterization of Analogs with a Fused 5,6-Bicyclic Ring Motif. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3487−3490. (b) Barnes, M. D.; Shekhar, S.; Dunn, T. B.; Barkalow, J. H.; Chan, V. S.; Franczyk, T. S.; Haight, A. R.; Hengeveld, J. E.; Kolaczkowski, L.; Kotecki, B. J.; Liang, G.; Marek, J. C.; McLaughlin, M. A.; Montavon, D. K.; Napier, J. J. Discovery and Development of Metal-Catalyzed Coupling Reactions in the Synthesis of Dasabuvir, an HCV-Polymerase Inhibitor. *J. Org. Chem.* **2019**, *84*, 4873−4892.

(20) For diarylation impurity **6**, **L37** provided nearly equal amounts of two regioisomers of **6** (which would include arylation of the pyridine nitrogen), while the more hindered 6-hydroxypicolinamides **L40** and **L41** produced only one major isomer of **6** as an impurity (most likely the isomer shown).

(21) As observed with Ma's reports, hindered aryl amides and more electron-rich amides provided more efficient catalysis. On the basis of the structure−activity relationship of the picolinamide ligands, coordination of Cu most likely occurs much of the time through the two nitrogens of the ligands.

(22) We found that free-flowing Redi-Dri reagent-grade anhydrous $K_3PO_4$ from Sigma (product no. RDD019) provided optimal results regarding water level minimization.



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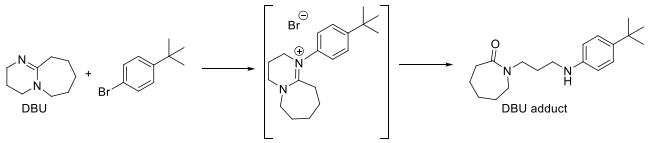
(23) Water was removed by distillation, which reduced the operating volume, though toluene could be replaced to maintain a constant volume during the distillation if desired. For trials on a small scale, this was done by allowing water to distill from vials through a small orifice in the lid, such as a disposable needle inserted into a rubber seal of the lid.

(24) From a processing perspective, it could be ideal to distill the toluene at the start of the process in the absence of the Cu catalyst and, once the water is removed by distillation, to add the Cu catalyst to the reaction mixture and continue heating in the absence of elevated levels of water.

(25) (a) Wang, Z.; Richter, S. M.; Gates, B. D.; Grieme, T. A. Safety Concerns in a Pharmaceutical Manufacturing Process Using Dimethyl Sulfoxide (DMSO) as a Solvent. *Org. Process Res. Dev.* **2012**, *16*, 1994−2000. (b) Yang, Q.; Cabrera, P. J.; Li, X.; Sheng, M.; Wang, N. X. Safety Evaluation of the Copper-Mediated Cross-Coupling of 2-Bromopyridines with Ethyl Bromodifluoroacetate. *Org. Process Res. Dev.* **2018**, *22*, 1441−1447. (c) Wang, Z.; Richter, S. M.; Bellettini, J. R.; Pu, Y.-M.; Hill, D. R. Safe Scale-Up of Pharmaceutical Manufacturing Processes with Dimethyl Sulfoxide as the Solvent and a Reactant or a Byproduct. *Org. Process Res. Dev.* **2014**, *18*, 1836−1842.

(26) DBU was found to undergo coupling with the aryl bromide and after workup hydrolyzed to give the adduct shown below:




(27) Using toluene or anisole as a minor solvent component with DMSO or sulfolane did not lead to significant erosion in the reaction rate, but when toluene or anisole was used as the main solvent by volume, the reaction rate decreased substantially, such that a reaction that was typically complete in 3−6 h now required 24−30 h.

(28) Primary alcohols coupled readily with aryl halides under certain reaction conditions, especially those involving KOtBu in the alcohol. Cu-catalyzed C−O couplings with **10** and related ligands will be reported in due course.

(29) 1-Butanol was observed to undergo significant C−O coupling with **1** under more dilute conditions with higher amounts of $K_3PO_4$. In contrast, *sec*-butanol performed more closely to cyclohexanol, with high reactivity and relatively high amounts of diarylated amine but no sign of C−O coupling. Under the conditions of Table 4, 1-butanol showed no C−O coupling but did undergo significant diarylation to yield **6** as a major impurity. Additional optimization will be required to increase the efficiency of C−O couplings with this ligand family **10**. It is likely that at lower temperatures and through the use of sodium ascorbate to allow facile catalyst activation, 1-butanol could be used efficiently with fewer side reactions.

(30) This reactivity trend correlating to the ligand to Cu ratio varied in magnitude with different substrate combinations. While this effect was almost absent in some cases, in others the rate enhancement was amplified dramatically.

(31) It has been shown that Cu(II) salts can be present in cross-couplings. See: (a) Sambiagio, C.; Munday, R. H.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Picolinamides as Effective Ligands for Copper-Catalysed Aryl Ether Formation: Structure-Activity Relationships, Substrate Scope and Mechanistic Investigations. *Chem. - Eur. J.* **2014**, *20*, 17606−17615. (b) Sherborne, G. J.; Adomeit, S.; Menzel, R.; Rabeah, J.; Brückner, A.; Fielding, M. R.; Willans, C. E.; Nguyen, B. N. Origins of High Catalyst Loading in Copper(I)-Catalysed Ullmann-Goldberg C−N Coupling Reactions. *Chem. Sci.* **2017**, *8*, 7203−7210.

(32) These observations relating to Cu(II) are consistent with those previously reported for Cu-catalyzed C−N couplings in ref 31.

(33) Catalyst activation appeared to be more problematic with substrates capable of chelating Cu, most likely rendering a relatively stable Cu(II) complex. The use of sodium ascorbate facilitated activation of the catalyst in these instances.

(34) Various Cu salts were examined, and even though some salts were slower to initiate catalysis, they all provided similar conversions and product distributions. With the addition of sodium ascorbate, minimal differences were observed among Cu salts. For example, $Cu_2O$ was consistently slow to initiate catalysis compared with CuI, but when sodium ascorbate was added, the reaction immediately proceeded at a rate similar to that with CuI.

(35) Phase-transfer reagents ($Bu_4NI$, $Bu_4NBr$, $Bu_4NCl$, and $Bu_4NBF_4$) were examined and had minimal positive effect on the reaction rate. Only sodium ascorbate appeared to influence the reaction rate in instances where the presence of unproductive Cu(II) may have a greater tendency to impede the catalyst activation and reaction rate or product distribution.

(36) Surprisingly, use of the aryl iodide in place of the aryl bromide did not improve the product distribution in cases where the addition of KI to the aryl bromide appeared to do so.

(37) The coupling with **11a** was found to be highly sensitive to the concentration of the Cu catalyst relative to the substrates. Impurities were minimized at a concentration of 1 M. At 2 M, diarylation of the amine began to predominate. At 0.5 M, dehalogenation and hydroxylation began to be more competitive with the desired coupling.

(38) This observation suggests that the order of addition may not matter in many cases. Typically, the ligand and CuI were combined in the solvent prior to addition of any substrates to ensure optimal formation of the catalyst. Trials in which the CuI and ligand were added to the substrates last provided comparable results, suggesting that the order of addition may not matter. It is suspected that with strongly binding substrates the premixing of the ligand and CuI may be more important, but this has not been observed.

(39) Oxidative dimerization of (hetero)arenes promoted by Cu has been studied. See: (a) Morgan, B. J.; Xie, X.; Phuan, P.-W.; Kozlowski, M. C. Enantioselective synthesis of Binaphthyl Polymers Using Chiral Asymmetric Phenolic Coupling Catalysts: oxidative Coupling and Tandem Glaser/Oxidative Coupling. *J. Org. Chem.* **2007**, *72*, 6171−6182. (b) Do, H.-Q.; Daugulis, O. An Aromatic Glaser-Hay Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 17052−17053. (c) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Somete, T.; Mori, A. Oxidative Dimerization of Azoles via Copper(II)/Silver(I)-Catalyzed CH Homocoupling. *Tetrahedron Lett.* **2010**, *51*, 850−852. (d) Li, Y.; Jin, J.; Qian, W.; Bao, W. An Efficient and Convenient Cu(OAc)2/Air Mediated Oxidative Coupling of Azoles via C-H Activation. *Org. Biomol. Chem.* **2010**, *8*, 326−330. (e) Zhu, M.; Fujita, K.; Yamaguchi, R. Efficient Synthesis of Biazoles by Aerobic Oxidative Homocoupling of Azoles Catalyzed by a Copper(I)/2-Pyridonate Catalytic System. *Chem. Commun.* **2011**, *47*, 12876−12878. (f) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234−6458.

(40) (a) 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. (b) Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. *Org. Lett.* **2017**, *19*, 2809−2812. (c) Schranck, J.; Tlili, A. Transition-Metal-Catalyzed Monoarylation of Ammonia. *ACS Catal.* **2018**, *8*, 405−418. (d) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. Amination of Aryl Halides Using Copper Catalysis. *Tetrahedron Lett.* **2001**, *42*, 3251−3254. (e) Xia, N.; Taillefer, M. A Very Simple Copper-Catalyzed Synthesis of Anilines by Employing Aqueous Ammonia. *Angew. Chem., Int. Ed.* **2009**, *48*, 337−339. (f) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. CuI/4-Hydro-L-Proline as a More Effective Catalytic System for Coupling of Aryl Bromides with N-Boc Hydrazine and Aqueous Ammonia. *J. Org. Chem.* **2009**, *74*, 4542−4546.

(41) 4-Nitropyrazoles have the potential to be explosive compounds. Halogenation and coupling with ammonia (or a surrogate) provides a viable alternative to avoid this issue.



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