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Practical Cu-catalyzed amination of functionalized heteroaryl halides

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Abstract—The amination of a variety of highly functionalized heterocyclic bromides has been accomplished using a CuI/proline catalyst system. The current study significantly expanded the scope of the reaction by using examples relevant to drug discovery programs and has demonstrated reaction rate acceleration using microwave heating.

Metal catalyzed C–N bond formation reactions of aromatic compounds have made tremendous advances in the past decade.[1] Landmark innovations from the Hartwig[2] and Buchwald[3] groups have continued to inspire researchers to discover milder and more selective conditions for a diverse array of substrates. Heteroaromatic amines are ubiquitous in biologically active molecules.[4] Historically, this class of compounds has been prepared using either nucleophilic aromatic substitution reactions or potentially dangerous and sometimes unselective nitration chemistry. The use of metal catalyzed C–N bond formation reactions allows chemists to view various heteroaryl halides, which are widely commercially available, as viable synthons.

Over the course of several drug discovery programs, we found a need to prepare a variety of N-substituted nicotinamides such as **1a** (Table 1) for SAR studies. After surveying the literature on C–N coupling methods for heteroaryl compounds,[5] we noticed that there were very few examples of heteroaromatic substrates containing unprotected amide NH groups. Moreover, it does not appear that there is a general metal/ligand combination that is amenable to parallel synthesis of diverse classes of heterohalides and amines.

We used the coupling of **1** and morpholine as a test case and examined a number of literature methods using a variety of state of the art ligands for both Pd and Cu.[6] Selected results are summarized in Table 1. It quickly became apparent that the CuI/proline method reported by Ma[7] consistently outperformed all the other methods.

To optimize this reaction, we examined the conditions in more detail, and the selected examples are summarized in Table 2. A number of *N*,*O*-bidentate ligands were tested along with other condition changes such as catalyst amounts and different bases. The time of reaction was held constant using a timer to turn off the heating source.

The conversion of each reaction was analyzed by LC/MS. For most of the reactions, four main products were observed: the desired product; starting material; debromination product; and product derived from ligand addition. Among the amino acid ligands tested, pipecolinic acid and azetidine-2 carboxylic acid gave comparable conversions (entry 2 vs 3). Reactions with dimethylglycine and *N*-methyl proline were slower, giving slightly lower yields as compared to proline (entries 1 and 7) but gave no ligand addition product. Proline proved to be the optimal ligand in terms of rate and yield. The reaction can be pushed to completion by doubling the catalyst amount (Table 2 entry 8 vs Table 1 entry 5). We found that the reaction can be accelerated by microwave heating, which significantly reduces the reaction time (entry 8 vs 9).[8] We attempted to overcome the slower rate of reaction with dimethylglycine or *N*-methyl proline by heating the reactions in the microwave reactor at higher

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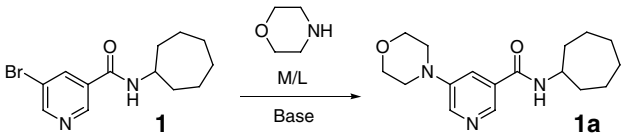
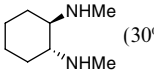
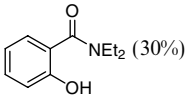
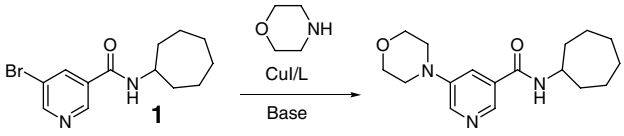
Table 1. Metal catalyzed amination of **1**

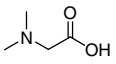
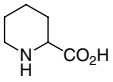
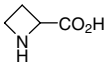
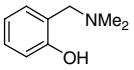
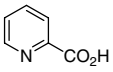
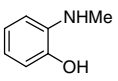


Entry	Catalyst, conditions[b]	Ligand	% conversion (dp/sm/de-Br)[c]
1[a]	$Pd_2(dba)_3$ (5%), K_3PO_4, toluene	x-Phos[d] (20%)	30/45/25
2[a]	$Pd_2(dba)_3$ (5%), K_3PO_4, toluene	q-Phos[e] (20%)	25/60/15
3[a]	CuI (10%), K_3PO_4, toluene	 (30%)	5/50/45
4[a]	CuI (10%), K_3PO_4, DMF	 (30%)	10/70/20
5	CuI (10%), K_2CO_3, DMSO	Proline (20%)	50/40/5/5[f]

[a] See Ref. 6.
[b] Base (3 equiv), 110 °C.
[c] Conversions were determined based on LC/MS results. dp = desired product, sm = starting material, de-Br = debrominated product.
[d] x-Phos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl.
[e] q-Phos: pentaphenylferrocenyl di-*tert*-butylphosphine.
[f] Product derived from ligand addition.

Table 2. Optimization of Cu catalyzed amination

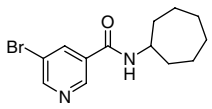
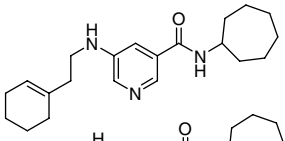
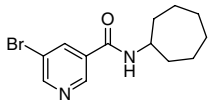
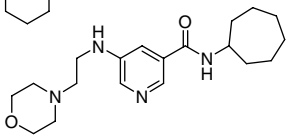
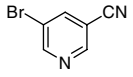
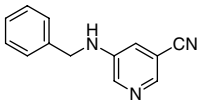
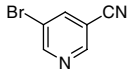
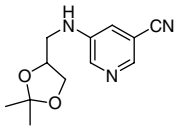
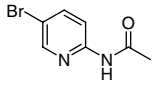
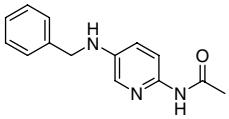
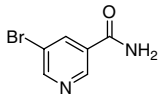
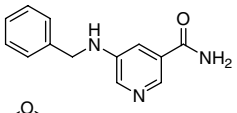
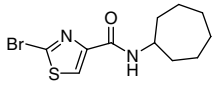
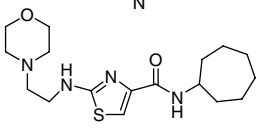
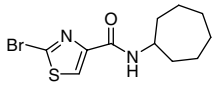
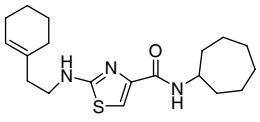
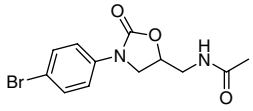
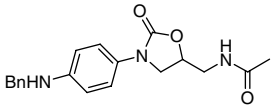
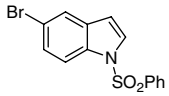
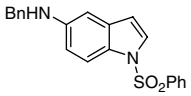


Entry	Reaction conditions[a]	Ligand	% conversion (dp/sm/de-Br/ligand adduct)[b]
1	A		45/50/5/0
2	A		30/35/20/15
3	A		30/30/25/15
4	A		10/20/50/20
5	A		5/95/0/0
6	A		15/70/5/10
7	A	*N*-Methyl proline	40/50/10/0
8	B	Proline	80/0/5/15
9	C	Proline	75/0/15/10
10[c]	C	Proline	75/0/15/10

[a] Condition A: **1** (0.2 mmol), morpholine (1.5 equiv), CuI (10%), ligand (20%), K_2CO_3 (3 equiv), DMSO (1 mL), 120 °C, 15 h. Condition B: **1** (0.2 mmol), morpholine (2.0 equiv), CuI (20%), ligand (40%), K_2CO_3 (3 equiv), DMSO (1 mL), 120 °C, 15 h. Condition C: **1** (0.2 mmol), morpholine (2.0 equiv), CuI (20%), ligand (40%), K_2CO_3 (3 equiv), DMSO (1 mL), microwave heating at 140 °C, 30 min.
[b] Conversion based on LC/MS.
[c] Reaction performed on 1 mmol scale.

temperatures (>170 °C), but an increased amount of the debromination product was noticed. Among the common inorganic bases surveyed, K_3PO_4 and Na_2CO_3 gave poorer yields, and Cs_2CO_3 gave comparable results

Table 3. C–N formation of heteroaryl bromides with aliphatic primary amines

Entry	Het-Br		Product	Yield isolated/HPLC (%)
1[a]		**1**		50/65
2[b]		**1**		56/70
3[a]		**2**		70/90
4[b]		**2**		33/50
5[b]		**3**		55/75
6[b]		**4**		60/80
7[b]		**5**		70/80
8[b]		**5**		70/80
9[a]		**6**		65/80
10[a]		**7**		65/75

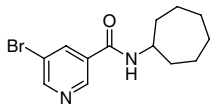
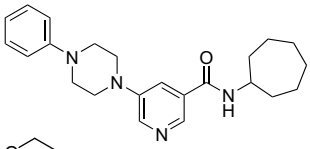
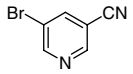
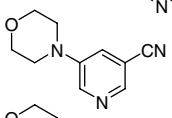
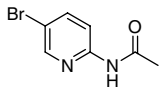
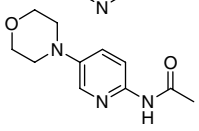
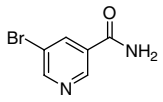
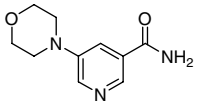
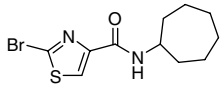
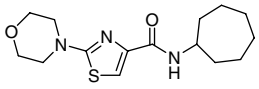
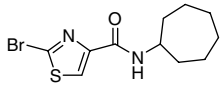
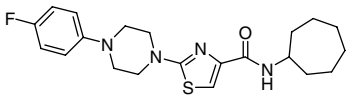
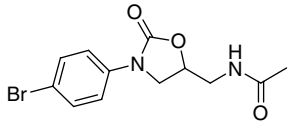
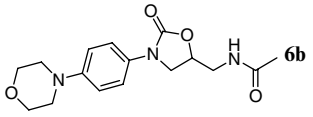
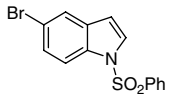
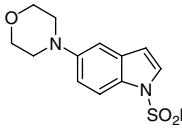
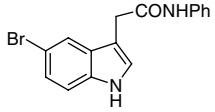
[a] Reaction performed on 0.2 mmol scale using condition 1.
[b] Reaction performed on 0.33 mmol scale using condition 2.

to K_2CO_3. DMSO was the preferred solvent not only because it gave consistently good reaction yields, but it was also highly compatible with our high-throughput reversed-phase HPLC purification systems.[9] The isolated yields using either condition B or C are generally between 60% and 70%, and the reaction has been scaled (1 mmol) with reproducible results (entry 10).

In addition to **1**, we demonstrated the utility of the Cu/proline amination system on various highly functionalized heterocyclic bromides and amine nucleophiles. We tested the reaction on substrates with functional groups commonly encountered in medicinal chemistry such as cyanides (**2**), primary and secondary amides (**3**–**6**), carbamates (**6**), 5-membered heterocycles (**5**), 6-membered heterocycles (**1**–**4**), and indoles (**7**). Table 3 shows the results from primary amines. Reactions generally gave good conversion and acceptable isolated yields using either conventional heating (condition 1) or microwave heating (condition 2).

Good conversion was achieved on substrate **3** which is a potential metal chelator (entry 5). Multifunctional oxazolidinone **6** (entry 9) underwent coupling without the need for an additional protecting group on the amide nitrogen. This result is noticeably different from previous work using this type of substrate and Pd as catalyst where amide NH protection is required.[5e]

Table 4. C–N formation of heteroaryl bromides with cyclic aliphatic secondary amines

Entry	Het-Br		Product	Yield isolated/HPLC (%)
1[a]		**1**		42/60
2[a]		**2**		65/90
3[b]		**3**		58/70
4[b]		**4**		52/80
5[a]		**5**		65/75
6[b]		**5**		50/85
7[a]		**6**	 **6b**	72/85
8[a]		**7**		66/70
9[c]		**8**		No product

[a] Reaction performed on 0.2 mmol scale using condition 1.
[b] Reaction performed on 0.33 mmol scale using condition 2.
[c] Reaction performed using condition 1 and morpholine as amine nucleophile.

Control reaction of thiazole substrate **5** without Cu gave <10% coupled product. Lower isolated yields were either due to water solubility of the products which were lost during extractive work up or material loss on HPLC purification.[9] Side product from ligand addition was less than 5% when primary amines are used as nucleophiles.

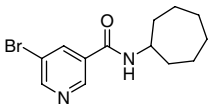
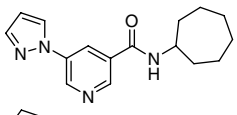
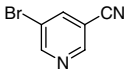
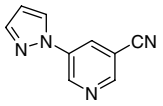
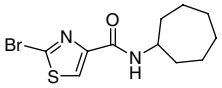
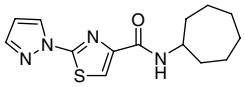
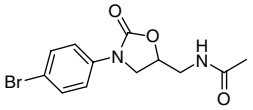
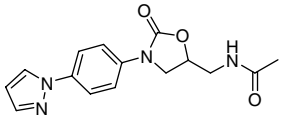
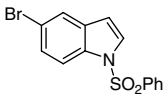
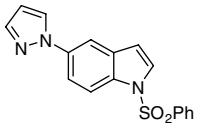
Table 4 summarizes the results from C–N coupling of heteroaryl bromides with cyclic aliphatic secondary amines. Similar to primary amines, the yields were good, but the rate of reaction is slower than primary amines. Compound **6b** (entry 7) is structurally similar to the commercially marketed antibiotic Linezolid[10] which was synthesized via a multi-step sequence using traditional nucleophilic aromatic substitution. With the current method, one would have greater access to structural analogues for SAR studies through C–N coupling on unprotected substrates such as **6**. Indoles with an unprotected heterocyclic NH such as **8** (entry 9) or the structurally simpler 5-bromoindole did not work in our hands.

We also attempted using acyclic secondary amines as nucleophiles, but the reactions invariably failed or at best formed less than 20% of the desired product.

Table 5 shows the results of coupling reactions with pyrazole as the nucleophile. The reactivity of pyrazole is similar to that of secondary amines, and generally good yields were obtained.

Aniline and other aromatic amines such as 2-aminothiazole are poor nucleophiles for this reaction. Low conversions were observed and significant debromination occurred in all the examples. Specifically, when bromides **1**, **6**, and **7** were reacted with aniline, product yields were 20%, 38%, and 25%, respectively. No product was recovered from the reaction with bromide **5**.

Table 5. C–N formation of heteroaryl bromides with pyrazole

Entry	Het-Br		Product	Yield isolated/HPLC (%)
1[a]		**1**		72/80
2[b]		**2**		30/80
3[a]		**5**		65/75
4[a]		**6**		70/80
5[a]		**7**		68/75

[a] Reaction performed on 0.2 mmol scale using condition 1.
[b] Reaction performed on 0.33 mmol scale using condition 2.

In conclusion, we have demonstrated the expanded scope and utility of CuI/proline catalyzed amination reactions on functionalized heterocyclic bromides with various types of amine nucleophiles often encountered in a drug discovery program. The current method is performed using a mild base that is compatible with many functional groups, and the polar solvent medium used in the reaction greatly facilitates the purification of products especially when reversed-phase HPLC is used. Although the catalyst loading is relatively high, both the metal and the ligand are inexpensive and readily available. Unlike many of the Pd catalyzed reactions which use non-polar phosphine ligands, amino acid ligands are easily separated from the product mixture through simple aqueous workup. Finally, we have also revealed some of the limitations of the current catalyst system when aryl amines and acyclic secondary amines are used as nucleophiles. We hope that our current results will stimulate further research and lead to improvements to this crucial bond forming reaction.

Experimental

Condition 1. Heteroaryl bromide (0.2 mmol), CuI (7.6 mg, 0.04 mmol), proline (9.2 mg, 0.08 mmol), and K_2CO_3 (83 mg, 0.6 mmol) were placed in a 5 mL microwave tube capped with a rubber septum. The tube was placed under vacuum and refilled with argon three times. Amine (0.4 mmol) and degassed DMSO (1 mL) were added to the tube and the rubber septa was quickly replaced with a microwave tube cap. The reaction was heated in an oil bath at 120 °C for 15 h before it was cooled, diluted with EtOAc, and filtered through a pad of Celite. The EtOAc was removed on a rotary evaporator. The residual DMSO solution was diluted with 1 mL of MeOH, and the solution was purified through reversed phase HPLC using 0.1% TFA in water and CH_3CN as eluent. The desired fractions were evaporated in a SpeedVac, and the purified products were subjected to ^1H NMR, ^{13}C NMR, HRMS, and IR analyses.

Condition 2. Heteroaryl bromide (0.33 mmol), CuI (13 mg, 0.067 mmol), proline (15.5 mg, 0.134 mmol), K_2CO_3 (140 mg, 1.00 mmol) and amine (0.673 mmol) were combined in a microwave tube fitted with a septum. The tube was evacuated and then filled with nitrogen several times. DMSO (1.5 mL) was added, and the septum was replaced with a crimped septum cap. The reaction mixture was heated in a microwave at 140 °C for 30 min. The reaction mixture was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was extracted again with EtOAc (2 mL). The combined organic washes were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography (Biotage 40S, 50% EtOAc/hexane then EtOAc). The purified product was subjected to the standard characterizations as described above.

Acknowledgments

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Supplementary data

Detailed experimental procedures and ^1H and ^{13}C NMR spectra of the synthesized compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.119.

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8. All microwave reactions were performed using a Personal Chemistry Emrys™ Optimizer in a septa capped 0.50–2 mL Biotage™ microwave vial with magnetic stirring. Power required to maintain target temperature was controlled by Emrys™ Optimizer Software.
9. Samples were purified by preparative HPLC on a Waters Nova-Pak HR C18 6 μm 60 Å Prep-Pak cartridge column (40 mm × 100 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 70 mL/min (0–0.5 min 10% A, 0.5–12.0 min linear gradient 10–95% A, 12.0–15.0 min 95% A, 15.0–17.0 min linear gradient 95–10% A). Samples were injected in 2.5 mL of DMSO/MeOH (1:1).
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