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Copper-promoted *ortho*-directed C–H amination of 2-arylpyridines with NH-heterocycles†

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Copper-mediated C–N coupling of azaheterocycles with aryl C–H bonds has been realized for the synthesis of N-(hetero)arylated heteroarenes. This method is characterized by high regioselectivity, atom economy and a wide substrate scope of 2-arylazines and azaheterocycles. The corresponding C–N coupling products were shown to undergo further transformation to synthesize more complex molecules.

Nitrogen-containing compounds have been widely employed in the synthesis of biologically active molecules, natural products, and pharmaceutical compounds (Fig. 1).[1] Over the past few decades, significant advancements have been made in transition-metal catalyzed C–H bond functionalization, due to its high efficiency and atom economy, and the absence of the need for pre-treatment of raw materials.[2] This approach has been instrumental in the synthesis of numerous complex heterocyclic compounds.

Nitrogen heterocycles have been employed extensively as a directing group in C–H activation reactions, facilitating the formation of C–C, C–O, C–N, and C–X bonds.[3] The formation of C–N bonds has been demonstrated using anilines, aryloxycarbamates, aryl azides, and sulfoximines as the coupling partners (Scheme 1, eqn (1)).[4] In addition, there have been various copper-promoted C–H aminations directed by other chelators (Scheme 1, eqn (2)).[5] Furthermore, stable pyrazole could be employed as a coupling partner in a C–H activation system,[6] facilitating the creation of additional heterocyclic frameworks with potential biological activity.

In this study, we developed a simple copper(II)-mediated amination of 2-arylpyridines with stable pyrazole, resulting in the generation of polycyclic complex nitrogen-containing molecules (Scheme 1, eqn (3)).

The investigation started with 2-phenylpyridine (**1a**) and 1*H*-pyrazole (**2a**) as model substrates to optimize the reaction conditions (Table 1). The azolation of substrate **1a** with pyrazole proceeded with 8% yield using a simple monodentate directing group (entry 1). It is important to note that the addition of an acid can increase the solubility of **2a** and have a significant effect on the system. Following the screening process, it was found that the most suitable equivalent of MesCOOH was 1.5 (entries 2–4). The effect of other copper salts on the reaction was then tested and it was found that only $Cu(OAc)_2$ was able to mediate the reaction. Substitution of $Na_2S_2O_8$ with alternative oxidants, including oxone, $(NH_4)_2S_2O_8$ and an Ag salt, resulted in varying yields, with AgF showing the highest yield (entries 7–9). Further solvent screening showed that the yield could be increased to 61% with *m*-xylene or 62% with HFIP (entries 9–13). In addition, the yield could be slightly increased by adjusting the concentration (entry 14). The reaction showed increased activity when a mixed solvent of *m*-xylene and HFIP was used. Furthermore, by screening the ratio of the two solvents, the yield of **3aa** was increased to 73%. More favorable results were obtained when the equivalent of **2a** was increased to 5 equivalents (entry 16). It is noteworthy that this azolation process could be carried out under milder conditions, leading to the synthesis of **3aa** in

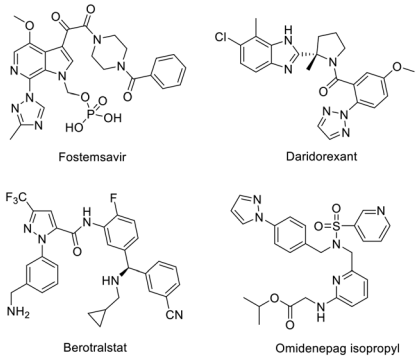

Fig. 1 Examples of newly approved drugs containing N-(hetero)arylated azaheterocycles.

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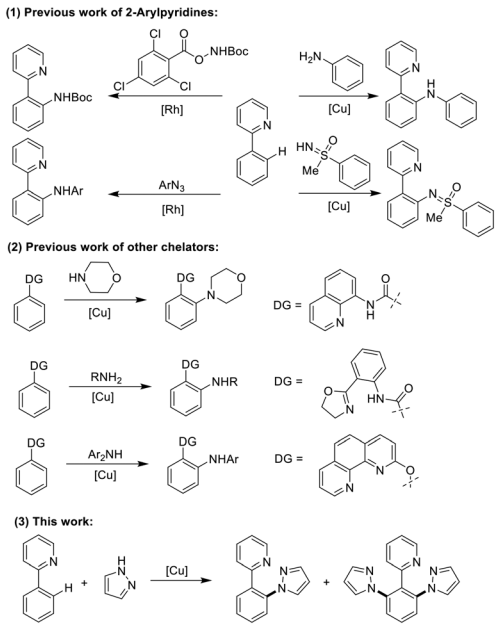
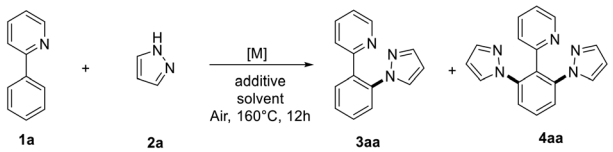


Scheme 1 Background and summary of metal-catalyzed and metal-mediated amination of the C(sp^2)–H bond.

90% yield at 130 °C. The use of a catalytic amount of a copper salt resulted in low conversions (entry 18), indicating that the process is dependent on the presence of a copper salt (entry 19). Furthermore, the silver salt was identified as a crucial component of this system (entry 20).

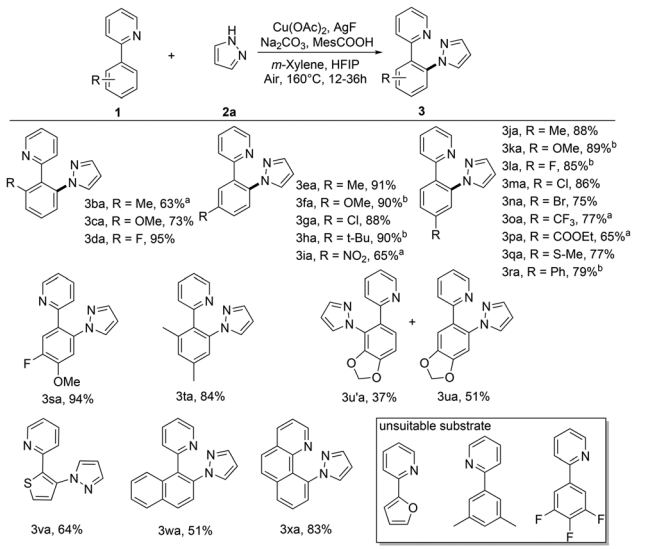
After determining the optimized reaction conditions, we explored the substrate range of 2-arylpyridines **1**, as shown in Scheme 2. The corresponding products **3** were obtained in moderate to good yields using 2-arylpyridines with different substituents. It was observed that electron-donating substituents on the aryl ring of 2-phenylpyridine were more compatible with this protocol and gave higher yields compared to substrates containing electron-withdrawing substituents such as **3ka** and **3oa**. Scheme 2 shows that the groups at the *ortho*-position of the phenyl ring resulted in a lower yield due to high steric hindrance (**3ba** and **3ca**). When the substrate had a *meta*-substituent, the less sterically hindered C–H bond was selectively functionalized (**3ea–3ia**) and *meta*-substituted groups reduced the disubstituted by-product, resulting in good yields. The azolation of **1ua** with an acetal group at the *meta*- and *para*-positions was less regioselective due to high reaction activity. Progress can still be made by changing the benzene ring to other ring systems such as thiophene (**3va**), a naphthalene ring (**3wa**) and a fused ring (**3xa**).

Table 1 Optimization of reaction conditions[a]



		Additive			Yield[b] (%)	
Entry	[Cu]	Oxidant	Acid	Solvent	**3aa**	**4aa**
1	$Cu(OAc)_2$	$Na_2S_2O_8$	—	Toluene	8	—
2[c]	$Cu(OAc)_2$	$Na_2S_2O_8$	MesCOOH	Toluene	37	<10
3	$Cu(OAc)_2$	$Na_2S_2O_8$	MesCOOH	Toluene	50	<10
4[d]	$Cu(OAc)_2$	$Na_2S_2O_8$	MesCOOH	Toluene	45	<10
5	$CuCl_2$	$Na_2S_2O_8$	MesCOOH	Toluene	—	—
6	$Cu(acac)_2$	$Na_2S_2O_8$	MesCOOH	Toluene	—	—
7	$Cu(OAc)_2$	Oxone	MesCOOH	Toluene	56	<10
8	$Cu(OAc)_2$	$(NH_4)_2S_2O_8$	MesCOOH	Toluene	39	<10
9	$Cu(OAc)_2$	AgF	MesCOOH	Toluene	58	<10
10	$Cu(OAc)_2$	AgF	MesCOOH	TFE	53	<10
11	$Cu(OAc)_2$	AgF	MesCOOH	HFIP	62	15
12	$Cu(OAc)_2$	AgF	MesCOOH	*o*-Xylene	47	<10
13	$Cu(OAc)_2$	AgF	MesCOOH	*m*-Xylene	61	<10
14[e]	$Cu(OAc)_2$	AgF	MesCOOH	*m*-Xylene	65	<10
15[e]	$Cu(OAc)_2$	AgF	MesCOOH	*m*-Xylene : HFIP = 1 : 2	73	11
16[e,f]	$Cu(OAc)_2$	AgF	MesCOOH	*m*-Xylene : HFIP = 1 : 2	82	8
17[e,f,g]	$Cu(OAc)_2$	AgF	MesCOOH	*m*-Xylene : HFIP = 1 : 2	90	8
18[e,f,h]	$Cu(OAc)_2$	AgF	MesCOOH	*m*-Xylene : HFIP = 1 : 2	10	—
19[e,f]	—	AgF	MesCOOH	*m*-Xylene : HFIP = 1 : 2	NR	—
20[e,f]	$Cu(OAc)_2$	—	MesCOOH	*m*-Xylene : HFIP = 1 : 2	15	—

[a] Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2a** (0.3 mmol), Cu salt (1.5 equiv.), Na_2CO_3 (2 equiv.), oxidant (1.5 equiv.), MesCOOH (1.5 equiv.) in toluene (1 mL) at 160 °C under air for 12 h. [b] Isolated yields. [c] MesCOOH (0.5 equiv.). [d] MesCOOH (2.5 equiv.). [e] Solvent = 1.5 mL in total. [f] **2a** (5 equiv.). [g] 130 °C for 36 h. [h] $Cu(OAc)_2$ (0.3 equiv.).



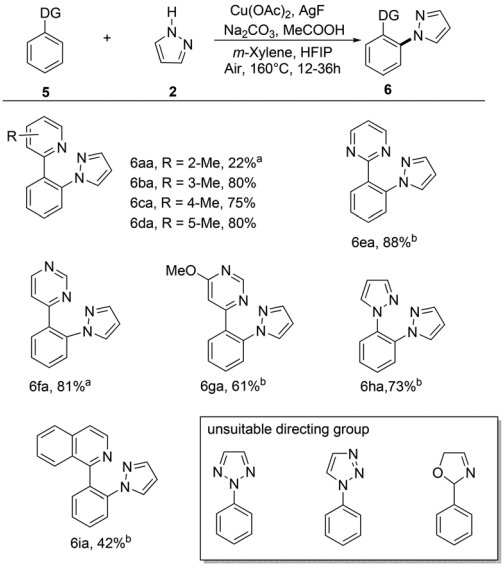
Scheme 2 Substrate scope of 2-aryl pyridines **1** for compound **3**. Reaction conditions unless otherwise specified: **1** (0.1 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (1.5 equiv.), AgF (2.0 equiv.), Na_2CO_3 (2.0 equiv.) and MesCOOH (1.5 equiv.) in *m*-xylene : HFIP = 1 : 2 (total 1.5 mL) at 160 °C for 12 h under an air atmosphere. [a] 36 h. [b] Reacting at 130 °C for 36 h.

We then focused on the substrate region of the directing groups (Scheme 3). To investigate the reaction site, we substituted methyl at various positions on the pyridine ring to give the corresponding products (**6aa–6da**). These products were combined with the reaction results of various substituted substrates on the benzene ring. It was concluded that the azolation process takes place at the adjacent position of the benzene ring. The reaction properties of pyrimidines as the leading group were found to be good, giving the desired compounds **6ea–6ga** with yields of 61%–88%. Similarly, the use of pyrazole **5h** as the directing group gave the corresponding product with a yield of 73%. However, isoquinoline was found to be a less active directing group for the azolation process, resulting in a yield of only 42% for the product **6ia**.

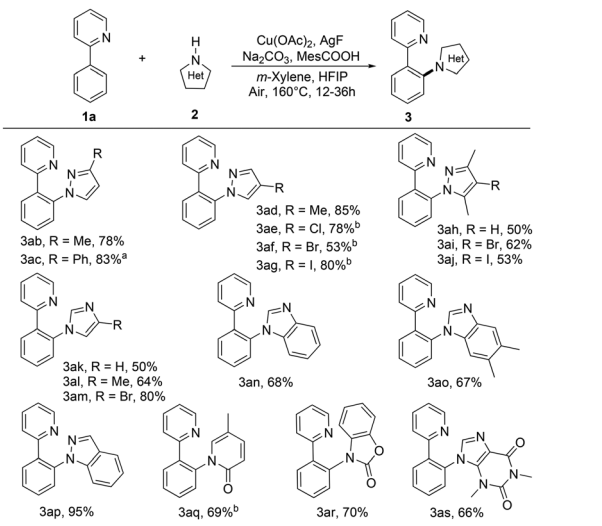
Scheme 4 shows the feasibility of a series of azoles **2**. The experiments showed that the reaction was successful with substrates such as pyrazole (**3ab–3aj**), imidazole (**3ak–3am**), benzimidazole (**3an** and **3ao**), indazole (**3ap**), 5-methylpyridin-2(1*H*)-one (**3aq**), 2-benzoxazolinone (**3ar**) and theophylline (**3as**). The reaction was successful with both electron-withdrawing and electron-donating groups, leading to compound **3** in moderate to high yields. However, it was found that certain heterocyclic systems such as triazole, pyrrole and indole did not undergo complete transformation.

To further explore the potential for conversion of these products, halogen-containing product molecules (**3na** and **3ag**) were subjected to the Suzuki coupling[7] (Scheme 5a) and the Sonogashira coupling[8] (Scheme 5b). The resulting compounds **7** and **8** were obtained in yields of 90% and 77%, respectively. As planned, **3xa** was subjected to C–H alkylation using a pyrazole as the directing group in the presence of $[Cp^*RhCl_2]_2$, $AgSbF_6$ and PivOH at 120 °C (Scheme 5c).[9]

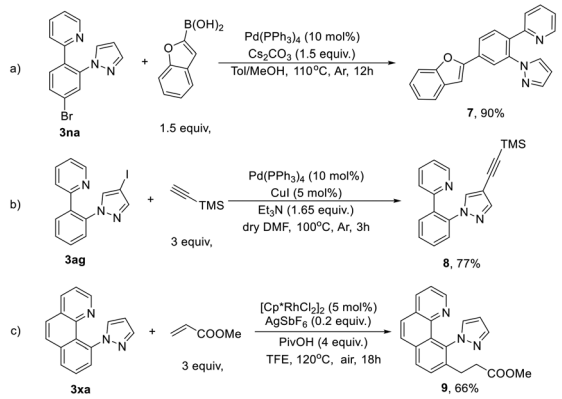
In order to elucidate the underlying experimental mechanism, radical scavenging experiments were conducted utilizing 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and butylated hydroxytoluene (BHT) (Scheme 6a), which served to suppress



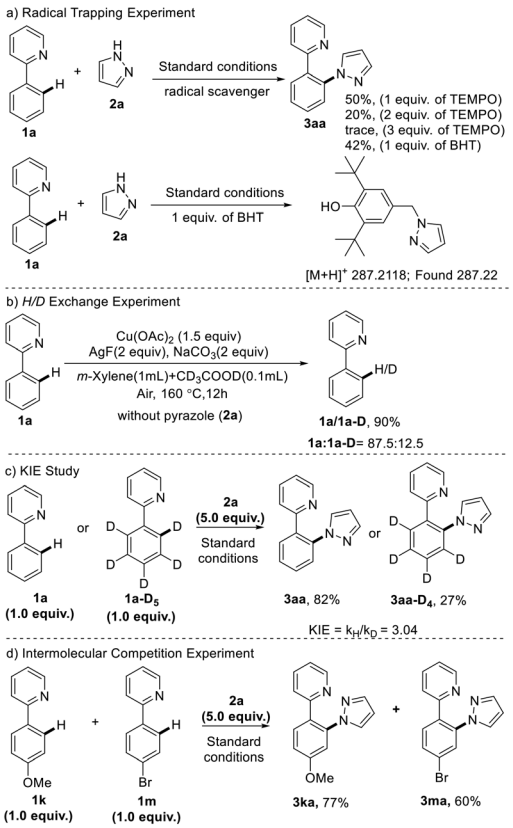
Scheme 3 Substrate scope of directing groups. Reaction conditions unless otherwise specified: **5** (0.1 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (1.5 equiv.), AgF (2.0 equiv.), Na_2CO_3 (2.0 equiv.) and MesCOOH (1.5 equiv.) in *m*-xylene : HFIP = 1 : 2 (total 1.5 mL) at 160 °C for 12 h under an air atmosphere. [a] Reacting for 36 h, then adding [Cu] (1.5 equiv.) and [Ag] (2 equiv.), and reacting for another 36 h. [b] Reacting for 36 h.



Scheme 4 Substrate scope of azoles **2** for compound **3**. Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (1.5 equiv.), AgF (2.0 equiv.), Na_2CO_3 (2.0 equiv.) and MesCOOH (1.5 equiv.) in *m*-xylene : HFIP = 1 : 2 (total 1.5 mL) at 160 °C for 12 h under an air atmosphere. [a] Reacting at 130 °C for 36 h. [b] Reacting for 36 h.

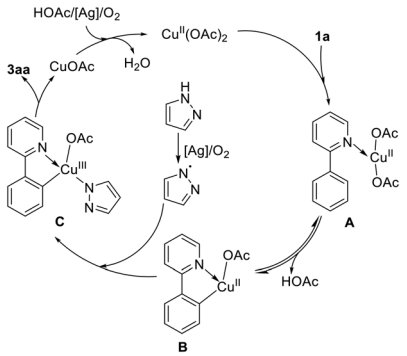


Scheme 5 Synthetic transformations.



Scheme 6 Preliminary mechanistic investigation.

this system. Furthermore, an adduct of BHT and pyrazole **2a** was identified by LC-MS (Scheme 6a). Subsequently, deuterium labelling experiments were conducted (Scheme 6b), resulting in the observation of 12.5% deuterium at both *ortho*-positions under the standard conditions in the absence of **2a**. This indicates that the C–H activation process is reversible. Moreover, a kinetic isotope effect (KIE) of 3.04 was observed for **3aa** or **3aa-D4** in a parallel experiment (Scheme 6c), which suggests that the initial *ortho* C–H bond cleavage may be the rate-determining step. Furthermore, the observed preference



Scheme 7 Proposed reaction mechanism.

for substrates with a high electronic density over those with a low electronic density (Scheme 6d) provides further evidence that the initial *ortho* C–H bond cleavage may be the rate-determining step.

A plausible reaction mechanism is presented in Scheme 7, based on the mechanistic study and previous research.[10] The formation of intermediate **A** is initiated by the chelation of **1a** and Cu(II), which is then converted to intermediate **B** through a reversible C–H bond cleavage. The pyrazole radical, generated from pyrazole in the presence of the silver salt, attacks intermediate **B** to give the Cu(III) intermediate **C**. Intermediate **C** then undergoes reductive elimination to give the product **3aa** and Cu(I). Subsequently, the active catalyst is regenerated by the oxidizing agent, such as a silver salt or oxygen.

Conclusions

In conclusion, the copper-mediated amination of 2-arylpyridines and heteroarenes has been successfully achieved with high regioselectivity. The synthesis of over thirty complex heterocyclic compounds has been achieved through the use of C–H activation to form a C–N bond. Further derivative reactions are currently being conducted in our laboratory.

Conflicts of interest

There are no conflicts of interest to declare.

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