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# Mild and efficient ligand-free copper-catalyzed condensation for the synthesis of quinazolines

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ABSTRACT

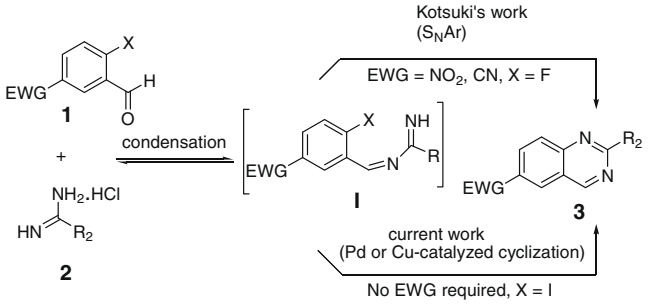
Condensation of *o*-iodobenzaldehydes **1a–c** with amidine hydrochlorides **2a–p** under ligand-free copper-catalyzed Ullmann N-arylation conditions afforded the corresponding quinazolines **3a–r** in good to excellent yields.



Quinazolines have attracted considerable interest because of their potential therapeutic properties as anticancer agents,[1] NF-κB nuclear translocation inducers,[2] ALK5 inhibitors,[3] and cannabinoid-1 inverse agonists.[4] Numerous synthetic methodologies to prepare quinazolines are known, however they suffer from drawbacks such as requiring activating groups,[5] harsh reaction conditions,[6] multistep synthesis[7], and expensive catalysts.[8] Recently, Kotsuki et al. reported a one-step synthesis of quinazolines by the condensation of *o*-fluorobenzaldehydes with amidine hydrochlorides (Scheme 1).[5] Although practical, this method is limited in scope to *o*-fluorobenzaldehydes which possess cyano- and nitro-activating groups that facilitate the intramolecular nucleophilic aromatic substitution ($S_NAr$). Therefore, a more general method for the rapid synthesis of quinazoline analogs remains highly desirable. Our analysis of Kotsuki's synthetic protocol led us to postulate that the cyclization step could be accomplished via either a Buchwald–Hartwig amination[9] or an Ullmann N-arylation reaction[10] (Scheme 1). This modification would offer an opportunity to expand the scope of this methodology to substrates other than cyano- and nitro-activated *o*-fluorobenzaldehydes. Herein, we disclose the ligand-free copper-catalyzed condensation of *o*-iodobenzaldehydes with amidine hydrochlorides for the synthesis of quinazolines.[11]

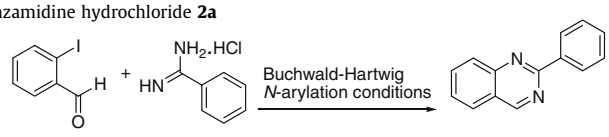
We began our investigation with *o*-iodobenzaldehyde **1a** and benzamidine hydrochloride **2a** as the model substrates to explore the palladium-catalyzed cyclization reaction (Table 1).[9] The initial attempt using conditions that were developed for N-arylation of amidoximes with aryl halides[9a] afforded only a 15% yield of quinazoline **3a** (Table 1, entry 1). A series of common palladium-catalyzed N-arylation conditions were also evaluated. However, none of these conditions offered any improvement in yield.

We next investigated the copper-catalyzed Ullmann N-arylation reaction to promote the cyclization step. Using the conditions developed by Ma and co-workers,[10a] we obtained a 34% yield of **3a** from the reaction of *o*-iodobenzaldehyde **1a** with benzamidine hydrochloride **2a** in the presence of CuI, *N*-methylglycine L**1**, and $K_2CO_3$ in DMSO at 60 °C for 18 h (Table 2, entry 1). Raising the reaction temperature from 60 °C to 100 °C (entry 2) led to a decrease in




**Scheme 1.** Comparison of Kotsuki's quinazolines synthesis and the current work.

**Table 1**
Screening of Buchwald–Hartwig N-arylation reaction of *o*-iodobenzaldehyde **1a** with benzamidine hydrochloride **2a**




**1a** **2a** **3a**

| Entry | Catalyst | Ligand | Base | Solvent | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | Xantphos | $Cs_2CO_3$ | Dioxane | 15 |
| 2 | $Pd_2(dba)_3$ | (*o*-biPh)-P(*t*-Bu)$_2$ | KO*t*-Bu | Toluene | Trace |
| 3 | $Pd_2(dba)_3$ | IPr·HCl[b] | KO*t*-Bu | Dioxane | nd |
| 4 | $Pd(OAc)_2$ | Xantphos | $Cs_2CO_3$ | Dioxane | 7 |

[a] Yield determined by HPLC.
[b] IPr·HCl: 1,3-bis(2,6-di-isopropylphenyl)imidazolium chloride.

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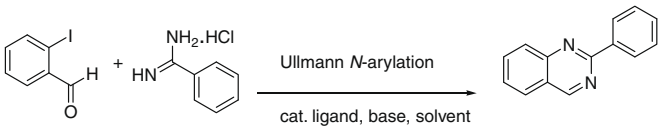
**Table 2**
Optimization of the copper-catalyzed Ullmann condensation of *o*-iodobenzaldehyde **1a** with benzamidine hydrochloride **2a**




**1a** **2a** **3a**

| Entry | Catalyst | Ligand | Base | Solvent | Temperature (°C) | Yield of **3a**[a] (%) |
|---|---|---|---|---|---|---|
| 1 | CuI | L**1** | $K_2CO_3$ | DMSO | 60 | 34 |
| 2 | CuI | L**1** | $K_2CO_3$ | DMSO | 100 | 27 |
| 3 | CuI | L**1** | $K_2CO_3$ | DMF | 60 | 28 |
| 4 | CuI | L**1** | $K_2CO_3$ | DMAC | 60 | 25 |
| 5 | CuI | L**1** | $K_2CO_3$ | Dioxane | 60 | 5 |
| 6 | CuI | L**1** | $K_2CO_3$ | NMP | 60 | Trace |
| 7 | CuI | L**1** | $K_2CO_3$ | MeOH | 60 | 40 |
| **8** | **CuI** | **L1** | **$K_3PO_4$** | **MeOH** | **60** | **74** |
| 9 | CuI | L**1** | $K_3PO_4$ | EtOH | 60 | 41 |
| 10 | CuI | L**1** | $K_3PO_4$ | *n*-PrOH | 60 | 46 |
| 11 | CuI | L**1** | $K_3PO_4$ | *i*-PrOH | 60 | 37 |
| **12** | **CuI** | — | **$K_3PO_4$** | **MeOH** | **60** | **86** |
| 13 | CuBr | — | $K_3PO_4$ | MeOH | 60 | 86 |
| 14 | CuCl | — | $K_3PO_4$ | MeOH | 60 | 73 |
| 15 | CuOAc | — | $K_3PO_4$ | MeOH | 60 | 86 |
| 16 | $Cu_2O$ | — | $K_3PO_4$ | MeOH | 60 | 52 |
| 17 | CuI | — | $Na_2CO_3$ | MeOH | 60 | 35 |
| **18** | **CuI** | — | **$Cs_2CO_3$** | **MeOH** | **60** | **93** |
| 19 | CuI | — | $Et_3N$ | MeOH | 60 | Trace |

Bold entries highlights the importance findings of each step of the optimization.
[a] Yield determined by HPLC.

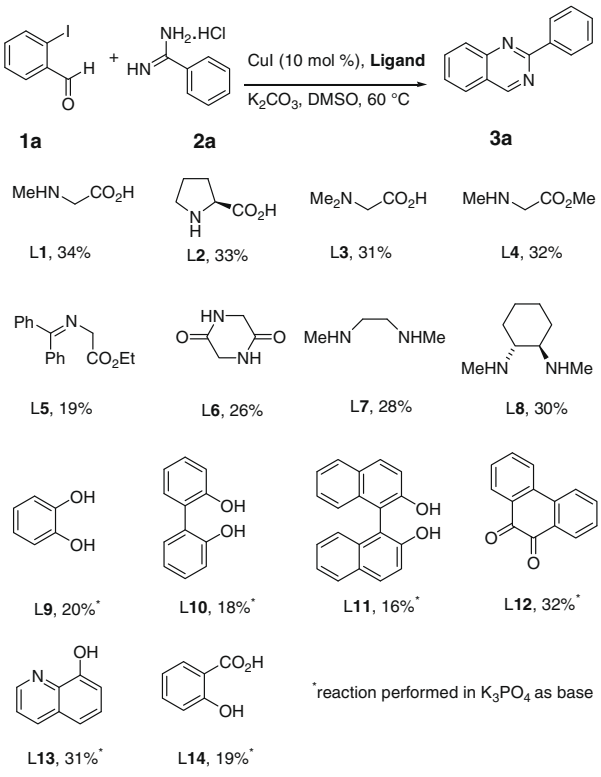
yield from 34% to 27%. As the copper-catalyzed Ullmann N-arylation afforded an improved yield of quinazoline **3a**, we decided to focus on optimizing these reaction conditions using CuI as the catalyst with the temperature set at 60 °C.

We first examined the effect of ligand. The ligand selection for our screening was based on commercial availability and literature precedent for promoting N-arylation of aryl halides in the presence of weak bases with DMSO as a solvent. It was found that several ligands afforded a similar yield of quinazoline **3a**. However, our first choice of ligand, *N*-methylglycine L**1**, provided the best yield of quinazoline **3a** (Scheme 2).

Next, we evaluated the effect of solvent by screening a variety of polar, nonpolar, and protic solvents. The reaction in methanol with $K_2CO_3$ as the base slightly improved the yield of quinazoline **3a** (Table 2, compare entries 1 and 7). The yield of **3a** was improved to 74% when $K_3PO_4$ was used as the base (entry 8). We also screened other protic solvents using $K_3PO_4$ as the base. However, none of these solvents provided a better yield of quinazoline **3a** than methanol. Thus, methanol was selected as the reaction solvent for additional optimization studies.

The key breakthrough in our search for the optimal reaction conditions occurred when we studied the ligand-free copper-catalyzed reaction in methanol in the presence of $K_3PO_4$. These conditions gave quinazoline **3a** in 86% yield (entry 12). This result is consistent with the well documented utility of aryl iodides as substrates in Ullmann-type reactions conducted under ligand-free conditions.[12]

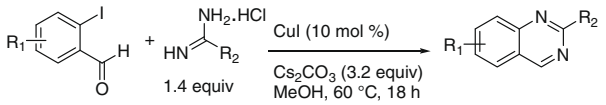
We then examined a series of catalysts, under ligand-free conditions, using methanol as the solvent and $K_3PO_4$ as the base. It was found that CuI, CuBr, and CuOAc afforded similar yields of quinazoline **3a** (entries 12, 13, and 15). Further tweak of the reaction parameters identified 10 mol % of CuI with 1.4 equiv of benzamidine hydrochloride **2a** and 3.2 equiv of $Cs_2CO_3$ in methanol at 60 °C as the best conditions for the preparation of quinazoline **3a** from *o*-iodobenzaldehyde **1a** and benzamidine hydrochloride **2a**. These reaction conditions afforded quinazoline **3a** in 93% yield (entry 18).




**Scheme 2.** Ligand screening for the Ullmann N-arylation reaction of *o*-iodobenzaldehyde **1a** with benzamidine hydrochloride **2a**.

Using the optimized reaction conditions,[13] we evaluated the scope of the ligand-free copper-catalyzed condensation reaction with various amidine hydrochlorides **2a–n**. The results are summarized in Table 3. In general, a variety of substituted benzamidine hydrochlorides with functional groups such as methoxy, fluoro,

**Table 3**
Ligand-free copper-catalyzed Ullmann condensation of *o*-halobenzaldehydes **1a–c** with various amidine hydrochlorides **2a–p**




**1a–c** **2a–p** **3a–r**

| Entry | $R_1$ | $R_2$ | Product **3** | Yield[a] (%) |
|---|---|---|---|---|
| 1 | H | Ph | **3a** | 89 |
| 2 | H | 4-Me–Ph | **3b** | 89 |
| 3 | H | 4-MeO–Ph | **3c** | 61 |
| 4 | H | 4-F–Ph | **3d** | 82 |
| 5 | H | 4-$CF_3$–Ph | **3e** | 70 |
| 6 | H | 4-Cl–Ph | **3f** | 66 |
| 7 | H | 4-Pyridine | **3g** | 80 |
| 8 | H | 2-Me–Ph | **3h** | 86 |
| 9 | H | 2-MeO–Ph | **3i** | 86 |
| 10 | H | 2-Pyridine | **3j** | 59 |
| 11 | H | 3-Me–Ph | **3k** | 94 |
| 12 | H | 3-MeO–Ph | **3l** | 83 |
| 13 | H | 3-$NO_2$–Ph | **3m** | 83 |
| 14 | H | Pyridimine-5-carboximidamide | **3n** | 53 |
| 15 | H | MeO–C(=NH)$NH_2$·HCl | **3o** | 71 |
| 16 | H | Cyclopropane–C(=NH)$NH_2$·HCl | **3p** | 87 |
| 17 | 4,5-$(MeO)_2$ | Ph | **3q** | 85 |
| 18 | 4-F | Ph | **3r** | 62[b] |

[a] Yield of isolated products.
[b] 24% of 7-methoxy-2-phenylquinazoline was isolated as a side product.

trifluoromethyl, and heterobenzamidine hydrochlorides were found to be compatible with the reaction conditions. In all cases, the desired quinazolines **3a–n** were obtained in good to excellent yields. *O*-Methylisourea hydrochloride **2o** and cyclopropanecarboximidamide hydrochloride **2p** also participated in the reaction to provide the corresponding quinazolines **3o**,**p** in good yields (entries 15 and 16).

Electron-donating and electron-withdrawing substituents on *o*-iodobenzaldehydes were also tolerated. 4,5-Dimethoxy-2-iodobenzaldehyde afforded a very good yield of quinazoline **3q** (entry 17), while 4-fluoro-2-iodobenzaldehyde gave **3r** in a lower yield of 62% (entry 18) due to the concomitant formation of 7-methoxy-2-phenylquinazoline via an $S_NAr$ displacement of the fluorine substituent by methanol. With *o*-bromobenzaldehyde as the substrate, a dramatically lower yield (5%) was observed for the formation of **3a**. Raising the reaction temperature from 60 °C to 100 °C improved the yield from 5% to 30%, while increasing the temperature further to 110 °C resulted in a decrease in yield to 13%.

In conclusion, we have developed an efficient, ligand-free, copper-catalyzed Ullmann condensation for the synthesis of a variety of quinazolines from *o*-iodobenzaldehydes in good to excellent yields. One-pot conditions as well as the mild reaction conditions make this methodology an attractive alternative for the synthesis of this class of molecules.

## Acknowledgment

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13. *Typical experiment of the ligand-free copper-catalyzed condensation reaction*: *Compound* **3a**. To a reaction tube were added copper iodide (16.4 mg, 0.086 mmol), cesium carbonate (899 mg, 2.76 mmol), benzamidine hydrochloride **2a** (189 mg, 1.2 mmol), *o*-iodobenzaldehyde **1a** (200 mg, 0.86 mmol), and methanol (2 mL). The reaction mixture was purged with nitrogen and heated at 60 °C overnight. Upon cooling to rt, 0.5 mL of water and 5 mL of EtOAc were added to the reaction mixture, which was vortexed thoroughly.[14] The mixture was filtered through a Celite cartridge and the cartridge was washed three times with EtOAc. The filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel using ethyl acetate–hexanes (0:100–30:70) to afford **3a** in 89% yield (158 mg).
14. The reaction mixture can also be quenched with water. The aqueous layer was extracted three times with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo.