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Copper(I)/Copper(II)-Assisted Tandem Catalysis: The Case Study of Ullmann/Chan–Evans–Lam N^1,N^3-Diarylation of 3-Aminopyrazole

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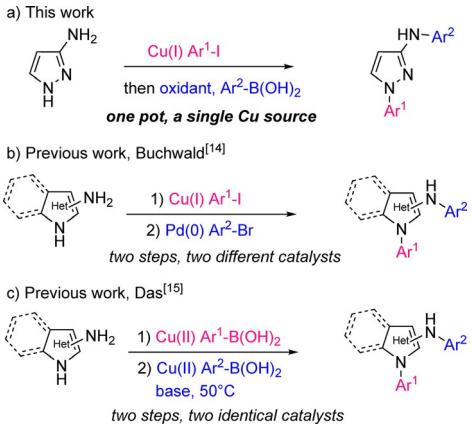
Unprecedented Cu^I/Cu^{II}-assisted tandem catalysis allowing an Ullmann/Chan–Evans–Lam sequence was achieved. This three-component, one-pot reaction triggered by a change in the oxidation state of the metal leads to the selective N^1,N^3-diarylation of 3-aminopyrazole. This new method should be a valuable tool for small-molecule drug discovery that requires suitable regio- and/or chemoselective strategies for the N-arylation of nitrogen-containing heterocycles.

Transition-metal-catalyzed domino reactions are powerful synthetic tools for sustainable organic chemistry, as they allow atom- and step-economical syntheses.[1] Among the various tandem catalysis methodologies,[2] assisted tandem catalysis has recently emerged as a potent strategy.[2c,3] This smart process relies on modification of the catalyst's activity during the course of the process, triggered in most cases by a change in the oxidation state of the metal. Mechanistically distinct reactions can thereby be mediated by a single metal source. To date, assisted tandem catalysis has solely been developed with the use of Ti,[4] Ru,[5] and Pd[6] complexes.

Within the transition-metal family, copper offers many advantages in that it is nontoxic, environmentally benign, rather cheap, and easy to handle. Thanks to the development of efficient catalytic systems over the last decade, copper-mediated cross-coupling reactions are today providing some of the most useful methods for the formation of aryl C–N, C–O, C–S, and C–C bonds.[7] In particular, Ullmann[8] and Chan–Evans–Lam (CEL)[9] couplings have become increasingly popular to afford N-arylated (hetero)aromatic amines, which are essential key building blocks for medicinal chemistry. Although copper-catalyzed domino reactions are receiving more attention these days,[10] there is, to our surprise, no report on Cu^I/Cu^{II} assisted tandem catalysis.

In this context, we sought to develop a one-pot N,N′-diarylation process relying on Cu^I-mediated Ullmann and Cu^{II}-catalyzed CEL reactions by using a single Cu source as the catalyst precursor and an oxidant as the in situ trigger. We envisioned that 3-aminopyrazole would be a unique model substrate to study this assisted tandem reaction (Scheme 1 a). Indeed, from a synthetic point of view, N-arylation of polynitrogenated heterocycles remains highly challenging owing to the possible formation of regioisomers and/or polyarylated products.[11–13] The selective N,N′-diarylation of such complex substrates was previously tackled by two groups: Buchwald in 2012 for 2-aminobenzimidazoles thanks to the complementarity of palladium and copper catalysts (Scheme 1 b),[14] and more recently, Das for a variety of aminoazoles by two successive Cu^{II} CEL couplings (Scheme 1 c).[15] However, these reactions were developed as two-step procedures. We report herein the successful achievement of our concept: the first example of a Cu^I/Cu^{II} assisted tandem process leading to the one-pot selective diarylation of 3-aminopyrazole.



Scheme 1. Strategies for the N,N′-diarylation of aminoazoles.

Efficient arylation of pyrazole and/or pyrazole derivatives has already been described through Ullmann[12] and Chan–Lam[13] couplings. However, the selective N^1-arylation of 3-aminopyrazole has received only very little attention, but it has been reported to proceed either under drastic conditions[12c] or to give products in moderate yields.[12d] We therefore undertook a screening of the solvent, base, and catalyst loading (see Table S A, Supporting Information) and found that the use of CuI (10 mol%), Cs_2CO_3 (1.0 equiv.), and 4-iodotoluene (1.5 equiv.) in 1-methylpyrrolidin-2-one (NMP) were optimal conditions to afford the desired N^1-arylated pyrazole in excellent yield.

We next explored the substrate scope with a variety of functionalized aryl iodides and iodo-substituted heterocycles (Table 1). Our optimized conditions proved to be efficient with

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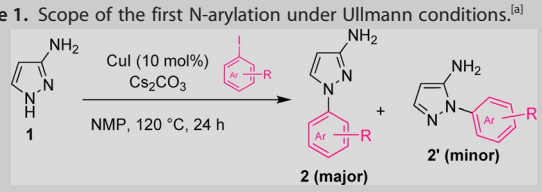
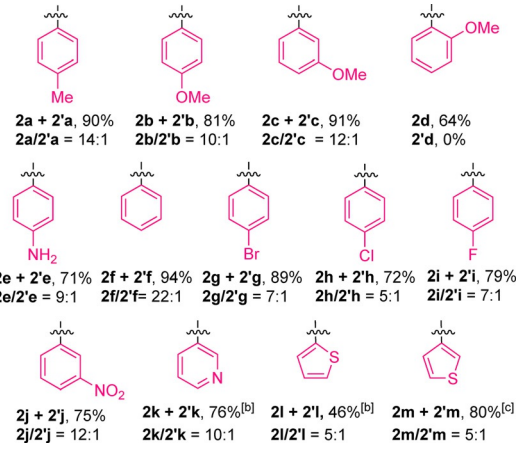
Table 1. Scope of the first N-arylation under Ullmann conditions.[a]



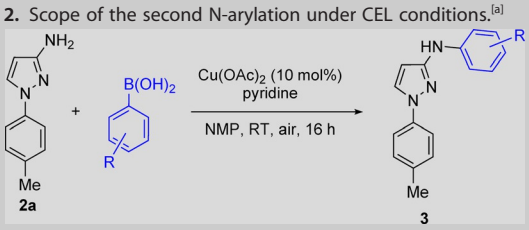


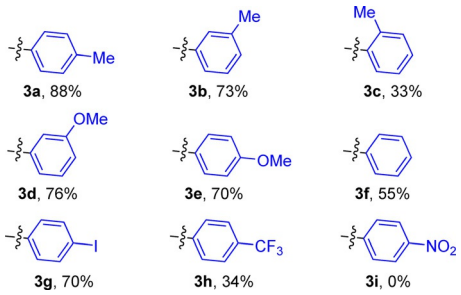
[a] Reaction conditions: **1** (1 mmol), aryl iodide (1.5 mmol), CuI (0.1 mmol), Cs_2CO_3 (1 mmol), NMP (3 mL), 120 °C, 24 h; yields refer to isolated products; ratio was determined by ^{1}H NMR spectroscopy. [b] 1,10-Phenanthroline (20 mol%) was added. [c] 1,1′-Bi-2-naphthol (20 mol%) was added.

electron-rich, electron-neutral, and electron-poor aryl iodides, and desired monoarylated pyrazoles **2a–j** were afforded in good to excellent yields ranging from 64 to 94% with high selectivities. Regioisomers **2** (major) and **2′** (minor) could be separated by column chromatography. Heteroaromatic coupling partners were the only ones to require the use of a ligand (see products **2k–m**). Interestingly, *ortho*-substituted product **2d** was exclusively formed without any trace amount of its **2′d** isomer, which suggests that N^1/N^2 selectivity is mostly governed by steric hindrance. Notably, these conditions are perfectly chemoselective, as no arylation of the exocyclic amine was observed.

We then focused on the subsequent CEL arylation of the exocyclic NH_2 group. Our objective of a domino process imposed to keep NMP as the solvent and to work under catalytic conditions. Using **2a** as the starting material, optimization of the reaction conditions (see Table S B) demonstrated that the use of $Cu(OAc)_2$ (10 mol%) with pyridine (11 mol%) afforded desired pyrazole **3a** in 87% yield. The substrate scope was next investigated with various boronic acids as coupling partners (Table 2). The reaction proved to be efficient with electron-rich and electron-neutral boronic acids, as well as with a *para*-iodo-derivative to afford diarylated products **3a–g** in good yields ranging from 55 to 88%. As expected, a few limitations were encountered for *ortho*-Me derivative **3c** (33%), as a result of steric hindrance, and for *para*-CF_3 derivative **3h** (34%) and *para*-NO_2 product **3i** (0%), as a result of a lack of reactivity.

Table 2. Scope of the second N-arylation under CEL conditions.[a]





[a] Reaction conditions: **2a** (0.5 mmol), arylboronic acid (1.15 mmol), $Cu(OAc)_2$ (0.05 mmol), pyridine (0.055 mmol), NMP (4 mL), RT, air, 16 h; yields refer to isolated products.

To develop the desired one-pot Ullmann/CEL sequence by using a single Cu source, we next tackled the feasibility of the Cu^{II}-catalyzed CEL reaction starting with CuI. Replacing $Cu(OAc)_2$ with CuI under our standard CEL conditions did not allow the formation of the desired product (Table 3, entry 1 vs. Table 2, **3a**). As oxidation of Cu^I to Cu^{II} by O_2 requires a proton source, the reaction was performed in the presence of AcOH (0.3 or 0.2 mol% without pyridine), but these conditions led to poor results (Table 3, entries 2 and 3). CEL coupling starting with Cu^I was finally achieved by the addition of $PhI(OAc)_2$ (0.2 mol%), which afforded **3a** in a good 74% yield (Table 3, entry 4).

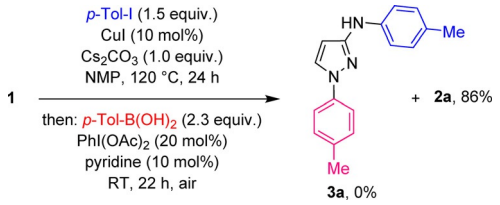
Table 3. CuI as a precatalyst for CEL coupling.[a]

Entry	[Cu]	Additive [(mol%)]	Yield[b] [%]
1	CuI	–	0
2	CuI	AcOH (0.3)	21
3[c]	CuI	AcOH (0.2)	21
4	CuI	$PhI(OAc)_2$ (0.2)	74

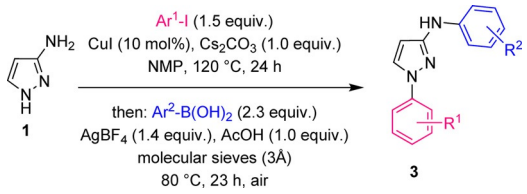
[a] Reaction conditions: **2a** (0.5 mmol), 4-TolB$(OH)_2$ (1.15 mmol), [Cu] (0.05 mmol), pyridine (0.055 mmol), NMP (4 mL), RT, air, 22 h. [b] Yields refer to isolated products. [c] Without pyridine.

A first attempt at the one-pot sequence was next undertaken by submitting **1** to our Ullmann conditions before 4-tolylboronic acid [4-TolB$(OH)_2$], $PhI(OAc)_2$, and pyridine were added (Scheme 2). After 22 h of stirring, the formation of **3a** could not be observed, whereas Ullmann adduct **2a** was isolated in 86% yield (see Table 1), which demonstrates thereby a complete inhibition of the CEL step.

We hypothesized that byproducts formed during the first arylation step or unreacted starting materials were responsible



Scheme 2. First one-pot N^1,N^3-diarylation attempt.



Scheme 3. One-pot N^1,N^3-diarylation.

Table 4. Inhibition of the second arylation step.[a]

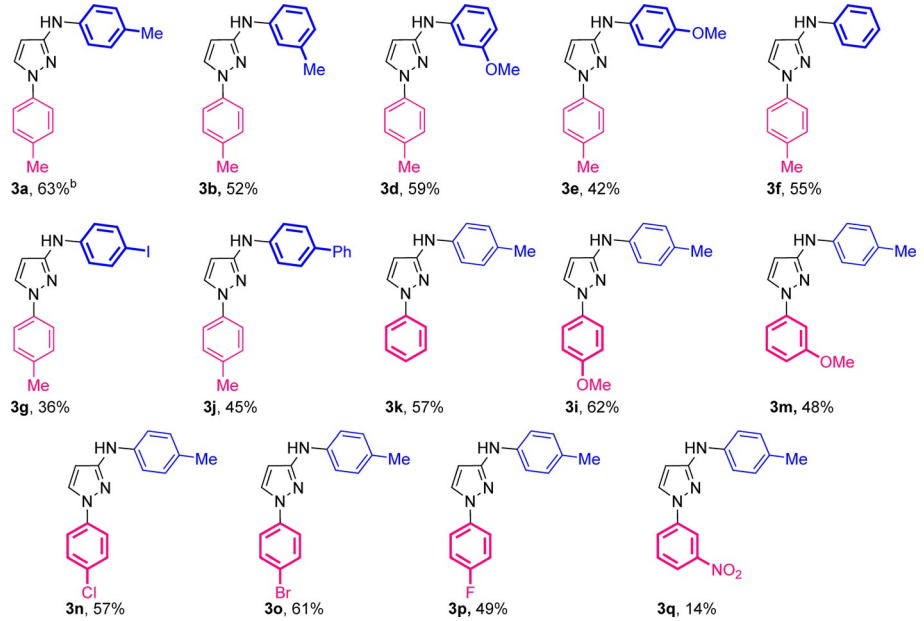
Entry	Additive [(equiv.)]	Yield[b] [%]
1	**1** (0.1)	84
2	4-iodotoluene (0.5)	85
3	Cs_2CO_3 (0.1)	72
4	$CsHCO_3$ (1.0)	43
5	CsI (1.0)	0
6	$CsHCO_3$ (1.0)/$PhCO_2H$ (1.0)	15
7[c]	$CsHCO_3$ (1.0)/$PhCO_2H$ (1.0)	84
8	CsI (1.0)/$AgBF_4$ (1.2)	59
9	CsI (1.0)/$AgBF_4$ (2.0)	9
10	CsI (1.0)/$AgBF_4$ (1.0)	29
11[c]	$CsHCO_3$ (1.0)/CsI (1.0) $PhCO_2H$ (1.0)/$AgBF_4$ (1.2)	73

[a] Reaction conditions: **2a** (0.5 mmol), 4-TolB$(OH)_2$ (1.15 mmol), $Cu(OAc)_2$ (0.05 mmol), pyridine (0.055 mmol), additive, NMP (4 mL), RT, air, 22 h. [b] Yields refer to isolated products. [c] Without pyridine, reaction temperature: 80 °C.

for the inhibition of the CEL reaction. Various control experiments were thus performed by separately adding each potential inhibitor to the second arylation reaction (Table 4). The addition of **1** or 4-iodotoluene had little impact on the reaction yield (Table 4, entries 1 and 2 vs. 88%, Table 2, **3a**). In contrast, the addition of Cs_2CO_3, $CsHCO_3$, and, unexpectedly, CsI was found to be deleterious to the reaction (Table 4, entries 3–5). Neutralization of $CsHCO_3$ was performed with $PhCO_2H$ in the absence of pyridine at 80 °C (Table 4, entries 6 and 7). The addition of a silver salt ($AgBF_4$, 1.2 equiv.) allowed the effect of CsI to be counteracted (Table 4, entries 8–10). Finally, running the reaction in the presence of both inhibitors ($CsHCO_3$, CsI) and both "antidotes" ($PhCO_2H$, $AgBF_4$) in the absence of pyridine at 80 °C allowed the catalytic activity to be recovered and smoothly afforded **3a** in 73% yield (Table 4, entry 11).

A final set of experiments was undertaken to refine the one-pot reaction conditions by varying the "antidotes" sources and amounts (see Table S C). $PhI(OAc)_2$ was found to be unnecessary in the presence of $AgBF_4$, with an optimal amount of 1.4 equivalents, and AcOH (1 equiv.) proved to be the best acid additive. Hence, **1** was submitted to our Ullman conditions for 24 h before 4-TolB$(OH)_2$, AcOH, and $AgBF_4$ were added to afford desired diarylated product **3a** in a good 63% yield (Scheme 3). The scope of the one-pot diarylation was finally examined (Scheme 3, Table 5). To our delight, a variety of substituted aryl iodides and boronic acids proved to be suitable coupling partners for 3-aminopyrazole (**1**). In a first set of experiments, the boronic acid was varied while keeping 4-iodotoluene as the partner for the Ullmann step. Yields of the domino sequence typically ranged from 45 to 63% for compounds **3a**, **3b**, **3d–f**, and **3j**, except for 4-iodo derivative **3g** (36% yield). Next, the aryl iodide was varied while keeping 4-TolB$(OH)_2$ as the partner for the CEL step. In this series, electron-neutral, electron-rich, and electron-poor aryl iodides also reacted smoothly to deliver **3k–p** in yields of 48–62%, except for the *meta*-nitro coupling partner (i.e., **3q**, 14% yield). Inter-

Table 5. Scope of the one-pot N^1,N^3-diarylation.[a]



[a] Reaction conditions: **1** (0.5 mmol), aryl iodide (0.75 mmol), CuI (0.05 mmol), $CsCO_3$ (0.5 mmol), NMP (1.5 mL), 120 °C, 24 h; then, $AgBF_4$ (0.7 mmol), acetic acid (0.5 mmol), arylboronic acid (1.15 mmol), 3 Å molecular sieves,[16] 80 °C, 23 h; yields refer to isolated products. [b] Without molecular sieves.

estingly, this domino sequence allowed the formation of *para*-chloro derivative **3n** and *para*-bromo derivative **3o**, which might be further functionalized through transition-metal catalysis. Noteworthy, during the course of this study the N^3-arylation of minor regioisomer **2′** (Table 1) was never observed.

In summary, we demonstrated that two successive Cu^I- and Cu^{II}-catalyzed C–N bond-formation events could be performed within a one-pot procedure by using a unique copper source. This is the first report of Cu^I/Cu^{II} assisted tandem catalysis triggered by a change in the oxidation state of the metal. This original process allows a one-pot Ullman/Chan–Evans–Lam sequence leading to the selective N^1,N^3-diarylation of 3-aminopyrazole and avoids the isolation and purification of the monoarylated intermediate. This new method should be a valuable tool for small-molecule drug discovery that requires suitable regio- and/or chemoselective strategies for N-arylation of nitrogen-containing heterocycles. In the course of this study, we also developed efficient ligandless catalyzed Ullman conditions for the selective N^1-arylation of 3-aminopyrazole and overcame the dramatic inhibition of Chan–Lam couplings through the use of $CsHCO_3$ and iodide.

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Keywords: aminoazoles · C–N coupling · copper · domino reactions · N-arylation

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