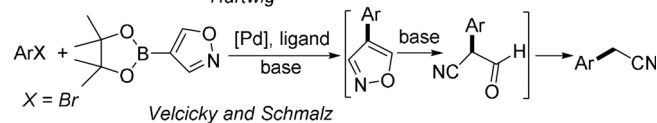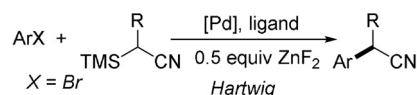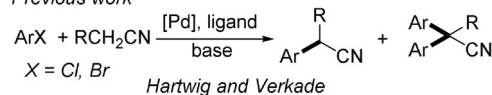# Assembly of α-(Hetero)aryl Nitriles via Copper-Catalyzed Coupling Reactions with (Hetero)aryl Chlorides and Bromides

Ying Chen, Lanting Xu, Yongwen Jiang, and Dawei Ma*

Abstract: *α-(Hetero)aryl nitriles are important structural motifs for pharmaceutical design. The known methods for direct synthesis of these compounds via coupling with (hetero)-aryl halides suffer from narrow reaction scope. Herein, we report that the combination of copper salts and oxalic diamides enables the coupling of a variety of (hetero)aryl halides (Cl, Br) and ethyl cyanoacetate under mild conditions, affording α-(hetero)arylacetonitriles via one-pot decarboxylation. Additionally, the CuBr/oxalic diamide catalyzed coupling of (hetero)aryl bromides with α-alkyl-substituted ethyl cyano-acetates proceeds smoothly at 60°C, leading to the formation of α-alkyl (hetero)arylacetonitriles after decarboxylation. The method features a general substrate scope and is compatible with various functionalities and heteroaryls.*

A considerable number of pharmaceutically important compounds contain α-(hetero)aryl nitriles as a basic structural motif[1] and they are valuable building blocks in organic synthesis. In particular, they have been frequently used as starting materials for preparing α-aryl amides and carboxylic acids, including manufacturing some non-steroidal anti-inflammatory drugs (NSAIDs).[2] Over the past two decades, many excellent methods for preparing α-aryl nitriles,[3–6] α-aryl carboxyl acids,[7] α-aryl esters[8] and amides[9] have been developed through different coupling approaches. Among them, metal-catalyzed coupling of aryl halides with nitriles is a promising one for large-scale synthesis because both coupling partners are conveniently available and cost effective. In this regard, the groups of Hartwig[3a] and Verkade[3b] have successfully achieved direct arylation of simple nitriles under the catalysis of palladium salts and sterically hindered phosphines (Figure 1). However, both mono-arylation and di-arylation occurred in most cases if primary nitriles were employed.[3a,b] To overcome this issue, Hartwig and Wu utilized α-silyl nitriles as the alternative coupling agents to achieve selective mono-arylation of acetonitrile and primary
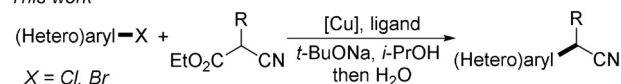

Figure 1. Assembly of α-(hetero)aryl nitriles via coupling (hetero)aryl halides with different surrogates of acetonitrile and primary nitriles.

nitriles,[3c] while Velcicky and co-workers employed isoxazole moiety as the precursor of cyanomethylene unit to obtain α-arylacetonitriles via a domino Suzuki coupling-isoxazole fragmentation process.[4] Although the reaction scope with Hartwig's method remains questionable as only one hetero-aryl bromide was examined,[3c] this reaction attracted immediate applications in drug discovery,[4a,10] implying that more practical methods for diversely assembling α-(hetero)aryl nitriles are highly desirable. We envisioned that ethyl cyanoacetate and its mono-substituted derivatives are more readily available surrogates of acetonitrile and primary nitriles, and therefore attempted for assembly of α-(hetero)-aryl nitriles through Cu-catalyzed arylation. The successful realization of this concept is disclosed here.

The metal-catalyzed coupling of aryl halides with ethyl cyanoacetate has received considerable attention during the past decades.[11–13] However, it remains to be developed for the practical applications in organic synthesis. For example, Cu-catalyzed arylation only worked well for aryl iodides,[11,12] while Pd-catalyzed version, albeit using rather expensive metal and ligands, is still problematic to most heteroaryl halides and α-alkyl substituted ethyl cyanoacetate.[13,5a] Thus, our primary goal was to develop a powerful catalytic system for Cu-catalyzed arylation with ethyl cyanoacetate and its derivatives. Based on our previous studies on oxalic diamides promoted Cu-catalyzed coupling reactions,[14] we decided to screen a series of oxalamide ligands using coupling of 4-chloroanisole and ethyl cyanoacetate as a model reaction. As demonstrated in Table 1, *N*-(2-methyl-naphthalen-1-yl)-*N'*-benzyl oxalamide (MNBO, **L1**), a ligand displayed excellent activity in amine arylation,[14e] was initially tested (entry 1). It was found that reaction occurred under the assistance of

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Table 1: Cu-catalyzed coupling of 4-chloroanisole with ethyl cyanoacetate under the assistance of different ligands.[a]

$X = Cl$, 5 mol% [Cu], 10 mol% **L**, 105 °C
$X = Br$, 0.5 mol% [Cu], 1 mol% **L**, 80 °C

L1: X = CH (MNBO)
L2: X = N (MNPMO)

L3

L4

L5 (APMO)

L6

L7

L8
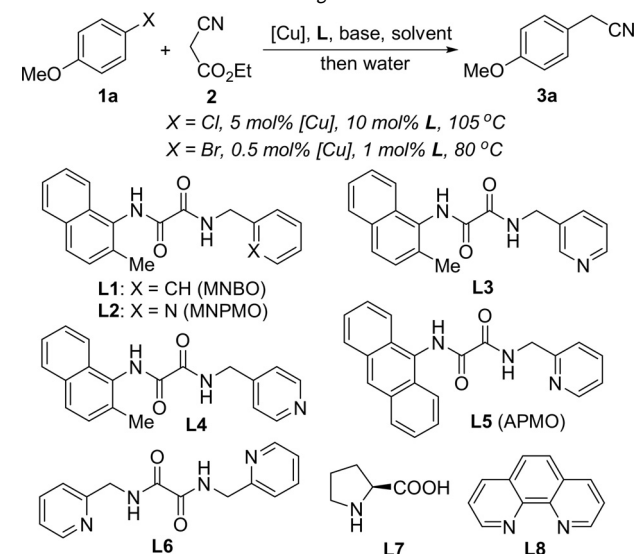
Entry	X	[Cu]	L	Base	Solvent	Yield [%][b]
1	Cl	CuI	L1	K$_3$PO$_4$	*i*-PrOH	7
2	Cl	CuI	L2	K$_3$PO$_4$	*i*-PrOH	17
3	Cl	CuI	L2	*t*-BuONa	*i*-PrOH	50
4	Cl	CuBr	L2	*t*-BuONa	*i*-PrOH	80
5	Cl	CuCl	L2	*t*-BuONa	*i*-PrOH	61
6	Cl	CuBr	L2	*t*-BuONa	EtOH	28
7	Cl	CuBr	L2	NaOH	EtOH	0
8	Cl	CuBr	L3	*t*-BuONa	*i*-PrOH	30
9	Cl	CuBr	L4	*t*-BuONa	*i*-PrOH	58
10	Cl	CuBr	L5	*t*-BuONa	*i*-PrOH	75
11	Cl	CuBr	L6	*t*-BuONa	*i*-PrOH	62
12	Cl	CuBr	L7	*t*-BuONa	*i*-PrOH	0
13	Cl	CuBr	L8	*t*-BuONa	*i*-PrOH	0
14	Br	CuBr	L2	*t*-BuONa	*i*-PrOH	70
15	Br	CuCl	L2	*t*-BuONa	*i*-PrOH	84
16	Br	CuCl	L2	K$_3$PO$_4$	*i*-PrOH	71
17	Br	CuCl	L2	K$_3$PO$_4$	EtOH	87
18	Br	CuCl	L2	K$_3$PO$_4$	dioxane	56

[a] Reaction conditions: for entries **1–13**: **1** (1.0 mmol), **2** (1.5 mmol), [Cu] (0.05 mmol), ligand (0.1 mmol), base (2.5 mmol), solvent (1.5 mL), 105 °C, 24 h; then water, 105 °C; For entries **14–18**: **1** (4.0 mmol), **2** (8.0 mmol), [Cu] (0.5 mol%), ligand (1.0 mol%), base (12.0 mmol), solvent (4.0 mL), 80 °C, 24 h, then H$_2$O (1.0 mL), 80 °C, 12 h. [b] The yield was determined by ¹H NMR analysis of crude products.

K$_3$PO$_4$ in 2-propanol at 105 °C. However, low conversion was observed and the desired α-aryl nitrile **3a** was obtained in 7% yield after decarboxylation. Changing the ligand to *N*-(2-methylnaphthalen-1-yl)- *N'*-(pyridin-2-ylmethyl)oxalamide (MNPMO, **L2**) gave an improved result (entry 2). Using this ligand we further screened several bases, copper salts and solvents, and found that *t*-BuONa was the best base (compare entries 2, 3 and 7), CuBr was the best catalyst precursor (compare entries 3–5), and 2-propanol was the better solvent than ethanol. Since **L2** showed better activity than **L1**, we wondered if its pyridine moiety can provide the additional coordination to copper, and thereby facilitating the catalytic cycle. Consequently, **L3** and **L4**, two simple analogues of **L2**, were also examined (entries 8 and 9). Their activity trend
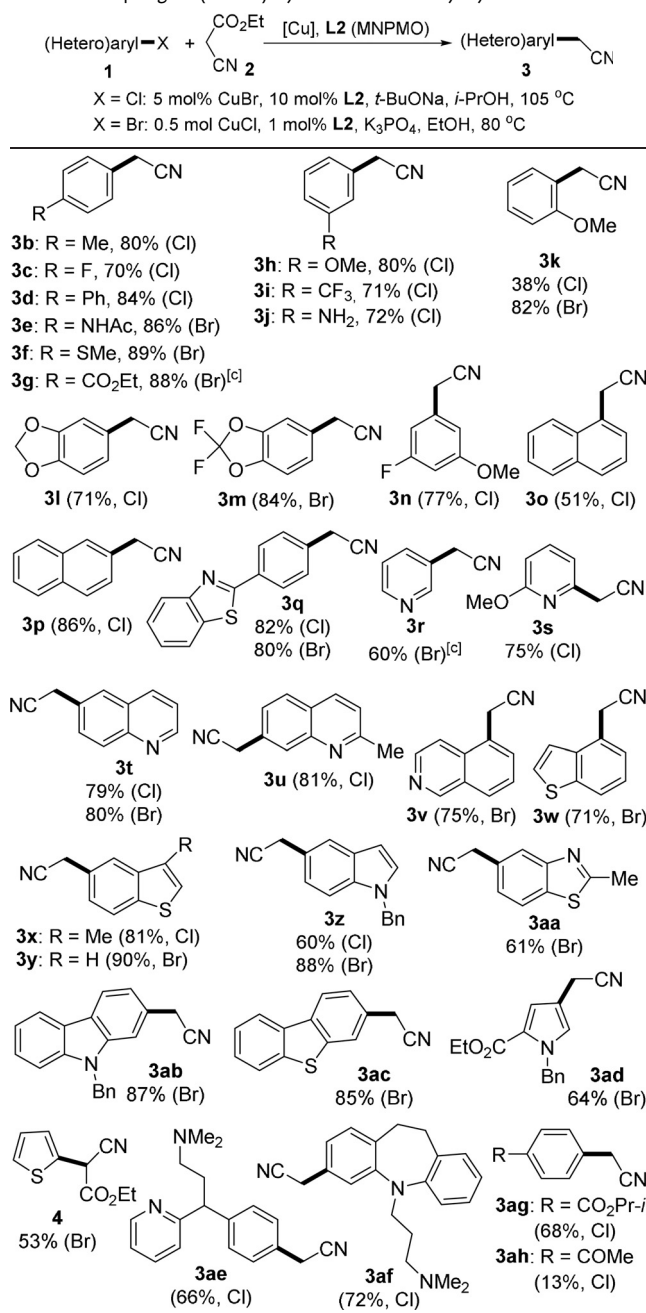
implied that the better performance of **L2** might result from relatively poor electron-donating ability of pyridin-2-yl methyl group, but not from the additional coordination to copper. Further evaluation revealed that changing the left part of the ligand **L2** to anthracenyl (**L5**, AMPO) and pyridin-2-ylmethyl (**L6**) also gave **3a** in reasonably high yields (entries 10 and 11), while ligands such as proline and 1,10-phenanthroline previously reported led to no conversion (entries 12 and 13).

In view of the above encouraging result, we examined whether the newly developed catalytic system is applicable for coupling of aryl bromides at low catalytic loading. Gratifyingly, under the catalysis of 0.5 mol% CuBr and 1 mol% **L2**, coupling of 4-bromoanisole and ethyl cyanoacetate proceeded smoothly at 80 °C to afford **3a** in 70% yield (entry 14). Changing the copper salt to CuCl led to the formation of **3a** in a better yield (entry 15). Further attempt indicated that combination of K$_3$PO$_4$ and ethanol gave a best result (compare entries 16–18).

We next examined the established conditions with a variety of (hetero)aryl chlorides and bromides. As summarized in Table 2, a series of aryl halides (Cl, Br) bearing either electron-donating or electron-withdrawing groups at the *para* and *meta*-position worked well, producing the corresponding α-aryl acetonitriles **3b**–**3j** in 70–89% yields. In case of ethyl 4-bromobenzoate as a substrate, the decarboxylation step should be carried out under acidic conditions to preserve the ester group in the structure (**3g**). Coupling with 2-chloroanisole gave **3k** in a poor yield, although a good result was observed in case of 2-bromoanisole as a coupling partner. This result indicated that the steric hindrance significantly influenced the coupling reaction with aryl chlorides. Further evidence was observed from the difference in coupling with 2-chloronathphlene (**3p**) and 1-chloronathphlene (**3o**). Additionally, three trisubstituted and two heterocycle-substituted aryl halides were applicable, delivering α-aryl acetonitriles **3l**–**3n** and **3q** in good yields.

Heteroaryl halides are recognized as difficult substrates under previous Pd- or Cu-catalyzed coupling conditions.[11–13] Fortunately, our new catalytic system addressed this long-standing problem. Under the standard conditions, coupling reaction of a range of heteroaryl halides (Cl, Br) proceeded smoothly, leading to the formation of α-heteroaryl acetonitriles **3r**–**3ad** in good to excellent yields. Noteworthy was that the common heterocycles such as pyridine (**3r**, **3s**), quinoline (**3t**, **3u**), isoquinoline (**3v**), benzothiophene (**3w**–**3y**), indole (**3z**), benzothizole (**3aa**), carbazole (**3ab**), dibenzothiophene (**3ac**) and pyrrole (**3ad**) were conveniently introduced by employing the corresponding heteroaryl halides. When 2-bromothiophene was used, coupling reaction took place to afford ester **4** in 53% yield. After its decarboxylation, we failed to isolate 2-(thiophen-2-yl)acetonitrile, mainly because of its low boiling point.

Furthermore, we found that the present method could be utilized for direct functionalization of known drugs bearing an aryl chloride unit. For example, coupling reaction with chlorpheniramine and clomipramine afforded **3ae** and **3af**, respectively. Additionally, an ester-embodied aryl chloride was applicable to afford **3ag** in 68% yield, while 1-(4-
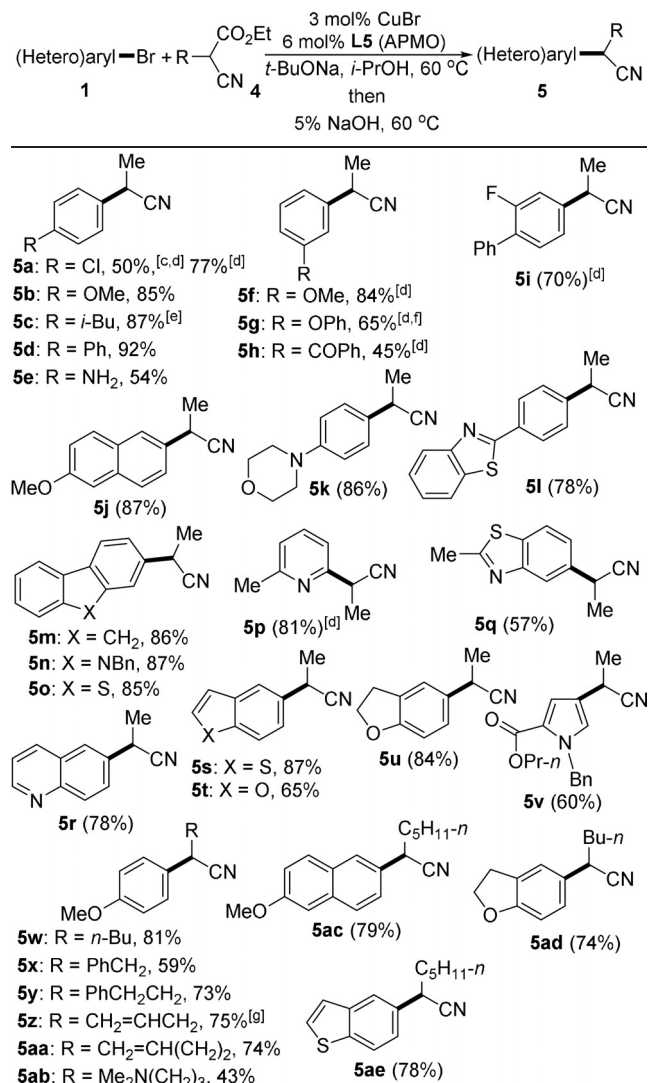
Table 2: Coupling of (hetero)aryl halides with ethyl cyanoacetate.[a,b]

X = Cl: 5 mol% CuBr, 10 mol% **L2**, t-BuONa, i-PrOH, 105 °C
X = Br: 0.5 mol CuCl, 1 mol% **L2**, K₃PO₄, EtOH, 80 °C

3b: R = Me, 80% (Cl)
3c: R = F, 70% (Cl)
3d: R = Ph, 84% (Cl)
3e: R = NHAc, 86% (Br)
3f: R = SMe, 89% (Br)
3g: R = CO₂Et, 88% (Br)[c]

3h: R = OMe, 80% (Cl)
3i: R = CF₃, 71% (Cl)
3j: R = NH₂, 72% (Cl)

3k
38% (Cl)
82% (Br)

3l (71%, Cl) **3m** (84%, Br) **3n** (77%, Cl) **3o** (51%, Cl)

3p (86%, Cl) **3q** 82% (Cl) 80% (Br) **3r** 60% (Br)[c] **3s** 75% (Cl)

3t 79% (Cl) 80% (Br) **3u** (81%, Cl) **3v** (75%, Br) **3w** (71%, Br)

3x: R = Me (81%, Cl)
3y: R = H (90%, Br)

3z 60% (Cl) 88% (Br)

3aa 61% (Br)

3ab Bn 87% (Br) **3ac** 85% (Br) **3ad** 64% (Br)

4 53% (Br) **3ae** (66%, Cl) **3af** (72%, Cl)

3ag: R = CO₂Pr-i (68%, Cl)
3ah: R = COMe (13%, Cl)

[a] Reaction conditions: for chlorides: **1** (1.0 mmol), **2** (1.5 mmol), CuBr (0.05 mmol), **L2** (0.1 mmol), t-BuONa (2.5 mmol), i-PrOH (1.5 mL), 105 °C, 24 h; then H₂O (1 mL), 105 °C, 12 h; for bromides: **1** (4.0 mmol), **2** (8 mmol), CuCl (0.02 mmol), **L2** (0.04 mmol), K₃PO₄ (12.0 mmol), EtOH (4.0 mL), 80 °C, 24 h; then H₂O (4 mL), 80 °C, 6–12 h. [b] Isolated yield. [c] Decarboxylation was conducted with 5 mL 2 N HCl, 80 °C, 12–36 h.

chlorophenyl)ethan-1-one gave the product **3 ah** in rather low yield. Taken together, we concluded that our method could be used for assembling a wide range of α-(hetero)aryl acetonitriles.

Considering that α-alkyl (hetero)arylacetonitriles are more important building blocks for drug synthesis, we next attempted the coupling reaction using α-alkyl substituted

ethyl cyanoacetates as the nucleophiles. As illustrated in Table 3, reaction of 2-bromoanisole and ethyl 2-cyanopropanoate under the catalysis of 3 mol% CuBr and 6 mol% **L2** occurred at 60 °C to afford **5 a** in 50% yield. A quick screening revealed that using **L5** (APMO) as a ligand significantly improved the yield (77%). The combination of CuBr and APMO was then tested for the reactions of a series of (hetero)aryl bromides and ethyl α-alkyl cyanoacetates. In general, decarboxylation took place spontaneously after coupling reaction occurred. However, incomplete decarboxylation was observed, particularly for those substrates possessing an electron-donating group. In such case, adding 5% NaOH and prolonging the heating gave the desired products in better yields. The generality of this reaction was quite

Table 3: Coupling of (hetero)aryl bromides with ethyl α-alkyl cyanoacetates.[a,b]

5a: R = Cl, 50%,[c,d] 77%[d]
5b: R = OMe, 85%
5c: R = i-Bu, 87%[e]
5d: R = Ph, 92%
5e: R = NH₂, 54%

5f: R = OMe, 84%[d]
5g: R = OPh, 65%[d,f]
5h: R = COPh, 45%[d]

5i (70%)[d]

5j (87%) **5k** (86%) **5l** (78%)

5m: X = CH₂, 86%
5n: X = NBn, 87%
5o: X = S, 85%

5p (81%)[d] **5q** (57%)

5r (78%) **5s**: X = S, 87% **5t**: X = O, 65% **5u** (84%) **5v** (60%)

5w: R = n-Bu, 81%
5x: R = PhCH₂, 59%
5y: R = PhCH₂CH₂, 73%
5z: R = CH₂=CHCH₂, 75%[g]
5aa: R = CH₂=CH(CH₂)₂, 74%
5ab: R = Me₂N(CH₂)₃, 43%

5ac (79%) **5ae** (78%) **5ad** (74%)

[a] Reaction conditions: **1** (2.0 mmol), **4** (4.0 mmol), CuBr (0.06 mmol), APMO (0.12 mmol), t-BuONa (4.0 mmol), i-PrOH (6.0 mL), 60 °C, 24 h; then 5% NaOH (2 mL), 60 °C, 4 h. [b] Isolated yield. [c] Using **L2** as the ligand. [d] Absence of 5% NaOH. [e] i-PrOH (2.0 mL). [f] i-PrOH (7.0 mL), 70 °C. [g] **4** (6.0 mmol), 80 °C, 24 h; then 5% NaOH (3.0 mL), 80 °C, 4 h.

satisfactory, as a number of functionalized aryl bromides and heteroaryl bromides were applicable for preparing α-methyl (hetero)arylacetonitriles **5a**–**5v**. Besides ethyl 2-cyanopropanoate, other more bulky analogues also worked well, affording **5w**–**5ad** in 43–81% yields. The olefin (**5z**, **5aa**) and amine (**5ab**) groups in the side chain did not alter the reaction process. Remarkably, some of our products were applicable for preparing non-steroidal anti-inflammatory drugs (NSAIDs),[15] which include Ibuprofen (from **5c**), Fenoprofen (from **5g**), Ketoprofen (from **5h**), Flurbiprofen (from **5i**), Naproxen (from **5j**), Cicloprofen (from **5m**), Indoprofen (from **5e**), Araprofen (from **5e**) and Alminoprofen (from **5e**). Thus, our method provided a facile and alternative entry to these known drugs and their analogues.

In conclusion, we have revealed that two pyridine-embodied oxalic diamides are powerful ligands for promoting Cu-catalyzed coupling reaction of (hetero)aryl halides with ethyl cyanoacetate and its α-mono-alkylated derivatives. Under the present conditions, readily available and inexpensive (hetero)aryl chlorides and bromides could be employed as the coupling partners for the first time. More importantly, a wide range of functionalized aryl and heteroaryl halides are applicable, thereby providing a convenient approach for preparing α-(hetero)aryl nitriles in a concise and diverse manner. Further application of these ligands in other coupling reactions are being explored in our laboratory, and the results will be disclosed in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anti-inflammatory drugs · C—C cross-coupling · copper · oxalamide ligands · α-(hetero)aryl nitriles

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