# Iron/Copper-Cocatalyzed Ullmann N,O-Arylation Using $FeCl_3$, CuO, and *rac*-1,1′-Binaphthyl-2,2′-diol

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**Abstract:** We have developed an efficient and inexpensive bimetallic catalyst $FeCl_3$, CuO, and *rac*-BINOL that could promote N,O-arylation of aliphatic, arylamines, and phenols. The cross-coupling reaction conditions have high tolerance of various functional groups. This versatile and efficient iron/copper-cocatalyst can widely be used in the synthesis of the compounds containing (aryl)C–N or (aryl)C–O(aryl) bond.

**Key words:** copper, iron, cross-coupling, N-arylation, O-arylation

Although copper-catalyzed Ullmann reactions have been developed for more than one hundred years,[1] their applications are limited because of the harsh reaction conditions such as high temperatures, the usual requirement of stoichiometric amounts of copper catalysts, long reaction times, and low yields.[2] In recent years, copper-catalyzed Ullmann reactions show renaissance because of the discovery of new copper sources, bases, ligands, and other additives. Highly efficient ligands for copper-catalyzed arylations have been reported, including aliphatic diamines,[3] 1,10-phenanthroline and its derivatives,[4] ethylene glycol,[5a] 1,1,1-tris(hydroxymethyl)ethane,[5b] diethylsalicylamide,[5c] amino acids,[6] oxime-type and Schiff base ligands,[7] thiophene-2-carboxylate,[8] bidentate phosphines,[9a] diphosphinidenecyclobutene,[9b] diazaphospholane,[10] cyclic β-diketone,[11a] β-ketone ester,[11b] diphenyl pyrrolidine-2-phosphonate,[12a] pyrrolidine-2-phosphonic acid phenyl monoester,[12b] and BINOL (1.1′-binaphthyl-2.2′-diol)[12c–12e] for N-arylation of amines and amides; 1-naphthoic acid,[13a] 2,2,6,6-tetramethylheptane-3,5-dione,[13b] *N,N*-dimethylglycine,[6d] 8-hydroxyquinoline,[13c] neocuproine,[13d] salicylaldoxime (Salox),[13e] 1,1,1-tris-(hydroxymethyl)ethane,[5b] and aminophosphonic acid derivatives[12b,13f] for O-arylation of substituted phenols or alcohols. Iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones.[14] Iron-catalyzed arylation has made great progress,[15] but only a few examples for N-arylation of amines by using iron alone or associated with copper as the catalysts were reported.[16] In this paper, we have developed an inexpensive and readily available catalyst $FeCl_3$, CuO, and BINOL to construct C(aryl)–N and C(aryl)–O bonds from aryl iodides and bromides.

After the optimization process of solvents, ligands, and catalysts, the following cross-coupling reactions were carried out under our standard conditions – 10 mol% $FeCl_3$ and 10 mol% CuO as the cocatalyst, 20 mol% *rac*-BINOL as the ligand relative to aryl halides, DMF as the solvent, and $Cs_2CO_3$ as the base.

The iron/copper cocatalyzed N-arylation of aliphatic amines was explored under our standard conditions.[17] As shown in Table 1, the coupling reactions were performed well for all the substrates examined, and the desired arylamines were obtained in good yields. Aryl halides containing electron-withdrawing group showed higher reactivity than those containing electron-donating group. Although aryl iodides containing electron-donating group and aryl bromides gave slightly lower reaction yields, they could provide higher yields when temperature was raised. For aryl halides, coupling of iodobenzenes containing bromine or chlorine selectively took place on the C–I bond (entries 15–18) using 1.2 equivalents of aliphatic amines as partners.

We also attempted the cross-coupling reactions of aryl halides with arylamines.[17] As shown in Table 2, we found that $FeCl_3$, CuO, and *rac*-BINOL could promote the conversion of the substrates to the corresponding arylamines, and aryl bromides containing an electron-withdrawing group on the benzene ring afforded better results. Aryl iodides showed higher reactivity than aryl bromides in the coupling reaction. For example, coupling of 1-bromo-4-iodobenzene with indole (entry 21) yielded the target product **5n** containing bromine on the benzene ring.

The standard reaction conditions were also suitable for O-arylation.[18] As shown in Table 3, aryl iodides gave good yields. However, aryl bromides were slightly inferior substrates (entries 11 and 13). Fortunately, addition of two equivalents of KI in the reaction system could improve the yields of the target products (entries 12, 14–17). Similarly, aryl halides containing an electron-withdrawing group showed higher reactivity than those containing an electron-donating one, and the substituted phenols containing an electron-rich group gave higher yields than those containing an electron-deficient one.

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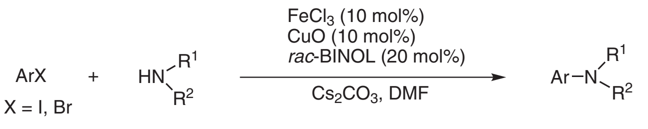
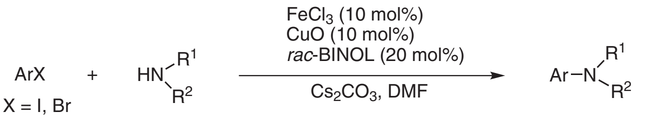
**Table 1** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Aliphatic Amines[a]

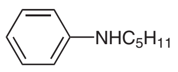
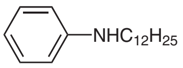
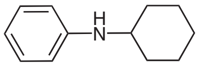
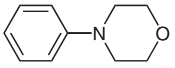
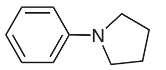
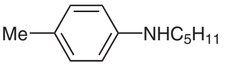
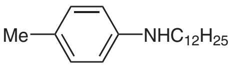
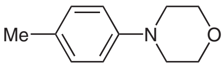
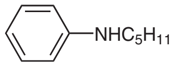
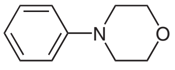
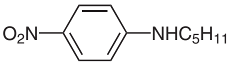
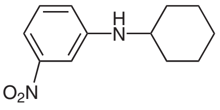
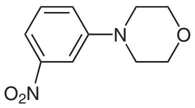
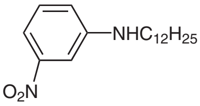
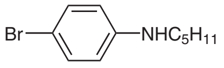
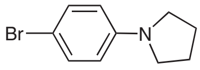
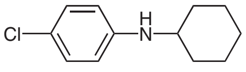
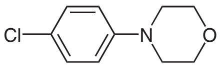


**1** **2** **3**

**Table 1** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Aliphatic Amines[a] (continued)



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

| Entry | Aryl halide | Product | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | PhI<br>**1a** | <br>**3a** | 80 | 12 | 84 |
| 2 | **1a** | <br>**3b** | 90 | 12 | 76 |
| 3 | **1a** | <br>**3c** | 80 | 12 | 89 |
| 4 | **1a** | <br>**3d** | 90 | 12 | 85 |
| 5 | **1a** | <br>**3e** | 90 | 12 | 83 |
| 6 | TolI<br>**1b** | <br>**3f** | 90 | 12 | 73 |
| 7 | **1b** | <br>**3g** | 90 | 12 | 72 |
| 8 | **1b** | <br>**3h** | 100 | 12 | 75 |
| 9 | PhBr<br>**1c** | <br>**3a** | 100 | 12 | 76 |
| 10 | **1c** | <br>**3d** | 100 | 24 | 82 |
| 11 | 4-$O_2NC_6H_4Br$<br>**1d** | <br>**3i** | 90 | 12 | 86 |
| 12 | 3-$O_2NC_6H_4Br$<br>**1e** | <br>**3j** | 90 | 12 | 88 |
| 13 | **1e** | <br>**3k** | 100 | 12 | 89 |
| 14 | **1e** | <br>**3l** | 100 | 24 | 81 |
| 15 | 4-$BrC_6H_4I$<br>**1f** | <br>**3m** | 80 | 12 | 87 |
| 16 | **1f** | <br>**3n** | 90 | 12 | 85 |
| 17 | 4-$ClC_6H_4I$<br>**1g** | <br>**3o** | 90 | 12 | 88 |
| 18 | **1g** | <br>**3p** | 80 | 12 | 90 |

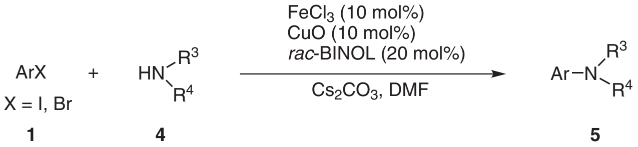
[a] Reaction conditions: aryl halide (1.0 mmol), aliphatic amine (1.2 mmol), ligand (0.2 mmol), $Cs_2CO_3$ (2 mmol), DMF (2 mL) under $N_2$. Amount of catalyst relative to aryl halide.

[b] Isolated yield.

In summary, we have developed an efficient and inexpensive bimetallic catalyst $FeCl_3$, CuO, and *rac*-BINOL that could promote N,O-arylation of aliphatic, arylamines, and phenols, and the cross-coupling reactions could tolerate many functional groups. This versatile and efficient iron/copper-cocatalyst can widely be used in the synthesis of the compounds containing the (aryl)C–N or (aryl)C–O(aryl) bond. Other synthetic applications of this catalyst are now in progress.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

**Table 2** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Arylamines[a]



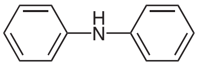
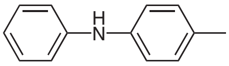
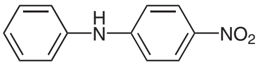
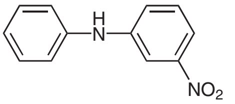
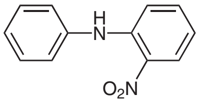
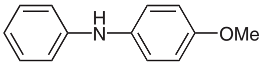
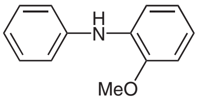
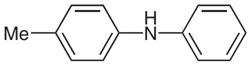
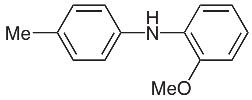
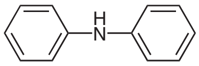
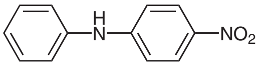
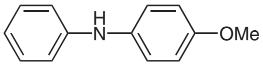
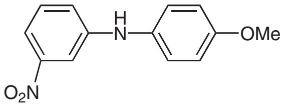
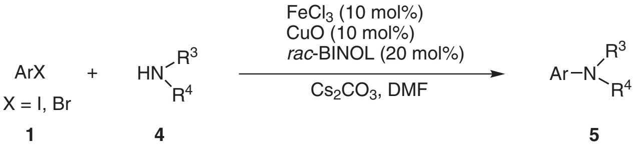
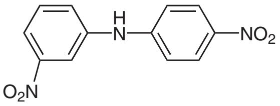
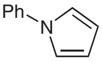
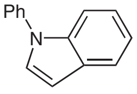
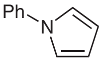
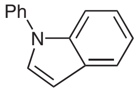
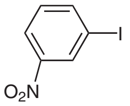
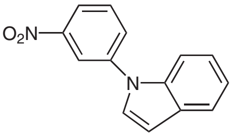
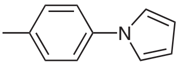
| Entry | Aryl halide | Product | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | <br>**5a** | 100 | 24 | 78 |
| 2 | **1a** | <br>**5b** | 80 | 12 | 68 |
| 3 | **1a** | <br>**5c** | 100 | 12 | 85 |
| 4 | **1a** | <br>**5d** | 80 | 12 | 81 |
| 5 | **1a** | <br>**5e** | 90 | 12 | 89 |
| 6 | **1a** | <br>**5f** | 90 | 12 | 85 |
| 7 | **1a** | <br>**5g** | 80 | 12 | 80 |
| 8 | **1b** | <br>**5b** | 90 | 12 | 79 |
| 9 | **1b** | <br>**5h** | 90 | 12 | 82 |
| 10 | **1c** | <br>**5a** | 110 | 12 | 76 |
| 11 | **1c** | <br>**5c** | 110 | 24 | 82 |
| 12 | **1c** | <br>**5f** | 110 | 24 | 81 |
| 13 | **1e** | <br>**5i** | 100 | 12 | 86 |

**Table 2** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Arylamines[a] (continued)

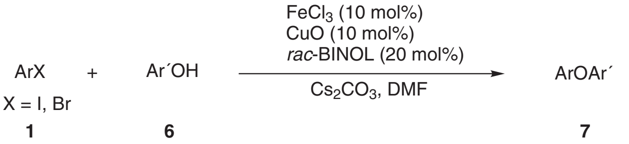


| Entry | Aryl halide | Product | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 14 | **1e** | <br>**5j** | 110 | 12 | 84 |
| 15 | **1a** | <br>**5k** | 90 | 12 | 78 |
| 16 | **1a** | <br>**5l** | 90 | 12 | 89 |
| 17 | **1c** | <br>**5k** | 110 | 24 | 75 |
| 18 | **1c** | <br>**5l** | 110 | 24 | 82 |
| 19 | <br>**1h** | <br>**5m** | 100 | 12 | 89 |
| 20 | **1f** | <br>**5n** | 90 | 12 | 84 |

[a] Reaction conditions: aryl halide (1.0 mmol), arylamine (1.2 mmol), ligand (0.2 mmol), $Cs_2CO_3$ (2 mmol), DMF (2 mL) under $N_2$. Amount of catalyst relative to aryl halide.

[b] Isolated yield.

**Table 3** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Phenols[a]



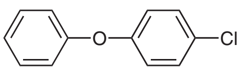
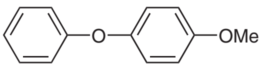
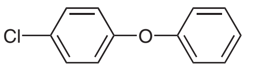
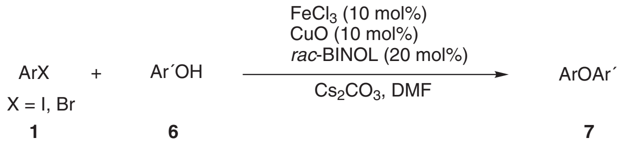
| Entry | Aryl halide | Product | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | <br>**7a** | 110 | 12 | 83 |
| 2 | **1a** | <br>**7b** | 110 | 12 | 84 |
| 3 | **1g** | <br>**7a** | 110 | 24 | 87 |

**Table 3** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Phenols[a] (continued)



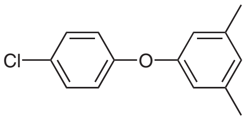
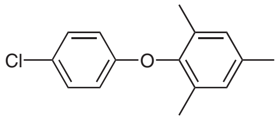
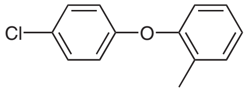
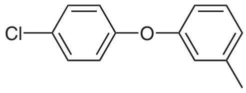
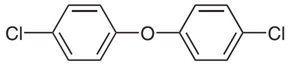
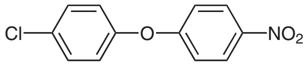
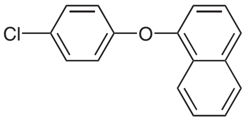
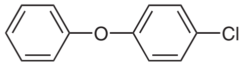
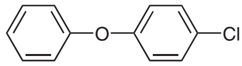
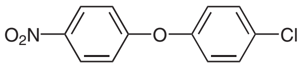
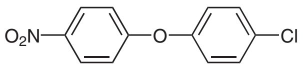
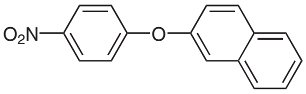
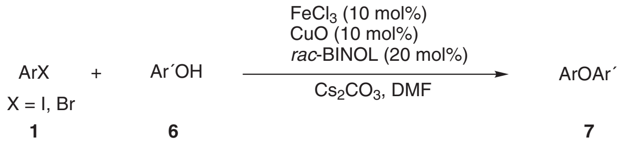
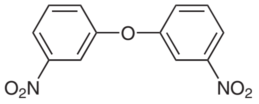
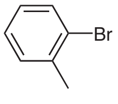
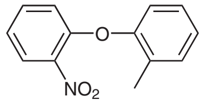
| Entry | Aryl halide | Product | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 4 | **1g** |  <br>**7c** | 110 | 12 | 78 |
| 5 | **1g** |  <br>**7d** | 120 | 24 | 71 |
| 6 | **1g** |  <br>**7e** | 110 | 24 | 80 |
| 7 | **1g** |  <br>**7f** | 110 | 12 | 80 |
| 8 | **1g** |  <br>**7g** | 110 | 12 | 84 |
| 9 | **1g** |  <br>**7h** | 100 | 12 | 89 |
| 10 | **1g** |  <br>**7i** | 120 | 12 | 78 |
| 11 | **1c** |  <br>**7a** | 120 | 24 | 60 |
| 12 | **1c** |  <br>**7a** | 120 | 24 | 79[c] |
| 13 | **1d** |  <br>**7h** | 120 | 24 | 63 |
| 14 | **1d** |  <br>**7h** | 120 | 24 | 82[c] |
| 15 | **1d** |  <br>**7j** | 120 | 24 | 75[c] |

**Table 3** Iron/Copper-Cocatalyzed Cross-Coupling of Aryl Halides with Phenols[a] (continued)



| Entry | Aryl halide | Product | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 16 | **1e** | <br>**7k** | 120 | 24 | 83[c] |
| 17 | <br>**1i** | <br>**7l** | 120 | 24 | 74[c] |

[a] Reaction conditions: aryl halide (1.0 mmol), phenol (1.2 mmol), ligand (0.2 mmol), $Cs_2CO_3$ (2 mmol), DMF (2 mL) under $N_2$. Amount of catalyst relative to aryl halide.

[b] Isolated yield.

[c] Addition of KI (2.0 mmol).

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(17) **General Procedure A: Coupling of Aryl Halides with Amines**
A flask was charged with $FeCl_3$ (16 mg, 0.1 mmol), CuO (8 mg, 0.1 mmol), $Cs_2CO_3$ (651 mg, 2 mmol), BINOL (57 mg, 0.2 mmol), and any remaining solids (amine and/or aryl halide). The flask was evacuated and backfilled with nitrogen (this procedure was repeated five times). Aryl halide (1 mmol, if liquid), amine (1.2 mmol, if liquid), and DMF (2 mL) were added to the flask under nitrogen atmosphere. The mixture was allowed to stir under nitrogen atmosphere at the shown temperature for the indicated period of time in the text (see Tables 1 and 2). After cooling to r.t., the mixture was diluted with $CH_2Cl_2$ (ca. 20 mL), the solution was filtered, and the filter cake was further washed with $CH_2Cl_2$ (ca. 5 mL). The filtrate was washed with 1 M NaOH (ca. 10 mL). The combined aqueous phase was extracted with $CH_2Cl_2$ ($2 \times 10$ mL). Organic layers were combined and dried over anhyd $Na_2SO_4$. The solvent of the filtrate was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on $SiO_2$ using PE–EtOAc (60:1 to 10:1) as eluent to provide the desired product.
**1-Phenyl-1H-indole (5l)**:[16a] yellow oil, yield 88%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (d, 1 H, $J = 7.56$ Hz), 7.42–7.51 (m, 5 H), 7.25–7.30 (m, 2 H), 7.13 (dd, 2 H, $J = 9.60$, 1.74 Hz), 6.61 (t, 1 H, $J = 3.45$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 139.9$, 135.9, 129.7, 129.4, 128.1, 126.5, 124.5, 122.5, 121.2, 120.5, 110.6, 103.7. MS (EI): m/z = 193.23 [$M^+$].

(18) **General Procedure B: Coupling of Aryl Halides with Phenols**
A flask was charged with $FeCl_3$ (16 mg, 0.1 mmol), CuO (8 mg, 0.1 mmol), $Cs_2CO_3$ (651 mg, 2 mmol), 1,1′-binaphthyl-2,2′-diol (57 mg, 0.2 mmol), and any remaining solids (phenol and/or aryl halide). The flask was evacuated and backfilled with nitrogen (this procedure was repeated five times). Aryl halide (1 mmol, if liquid), phenol (1.2 mmol, if liquid), and DMF (2 mL) were added to the flask under nitrogen atmosphere. The flask mixture was allowed to stir under nitrogen atmosphere at the shown temperature for the indicated period of time in the text (see Table 3). After cooling to r.t., the mixture was diluted with $CH_2Cl_2$ (ca. 20 mL), the solution was filtered, and the filter cake was further washed with $CH_2Cl_2$ (ca. 5 mL). The solvent of the filtrate was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on $SiO_2$ using PE or PE–EtOAc (60:1 to 100:1) as eluent to provide the desired product.
**1-(4-Chlorophenoxy)-3-methylbenzene (7f)**:[6d] colorless oil, yield 79%. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (dd, 2 H, $J = 6.87$, 2.07 Hz), 7.18 (d, 1 H, $J = 7.53$ Hz), 6.91 (dd, 3 H, $J = 6.84$, 2.04 Hz), 6.78 (s, 2 H), 2.31 (s, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 157.0$, 156.2, 140.2, 129.8, 129.7, 128.2, 124.6, 120.1, 119.8, 116.1, 21.5. MS (EI): *m/z* = 218.22 [$M^+$].