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Copper-catalyzed general C–N and C–O bond cross-coupling with arylboronic acid

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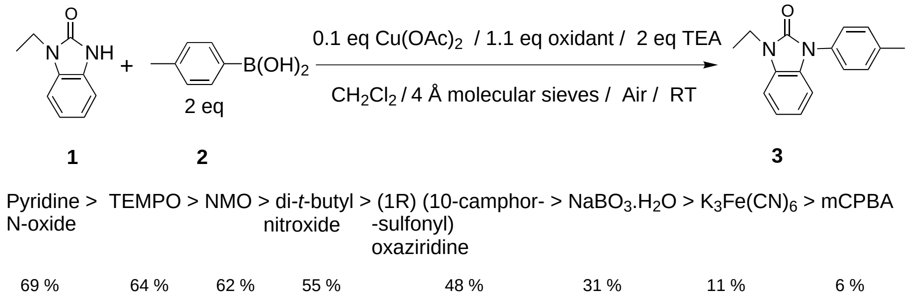
Abstract—General catalytic $Cu(OAc)_2$/TEMPO in air or $Cu(OAc)_2/O_2$ systems for the C–N and C–O cross-coupling reactions with arylboronic acid have been discovered. *N*- and *O*-vinylation have also been demonstrated. © 2001 Published by Elsevier Science Ltd.

Copper-promoted carbon–nitrogen (C–N) and carbon–oxygen (C–O) bond cross-coupling reactions of NH- and OH-containing substrates with arylmetalloids have emerged as powerful synthetic methods since the initial reports by Chan, Evans and Lam.[1,2] This novel methodology is an important addition to the general transition-metal promoted C–N and C–O bond cross-coupling reactions[1–7] useful for the synthesis of arylamines, *N*-arylheterocycles and biarylethers in pharmaceuticals, crop-protection chemicals and material sciences. The advantage of the copper-promoted methodology, as compared to the well-known palladium-catalyzed methodology,[7a,b] is the diverse substrate scope[1,2] and mild reaction conditions—room temperature, weak base and in air. The mild conditions are comparable to the classical amide C–N bond condensation reactions and should be tolerant to many sensitive functional groups. Many extensions and applications of this new methodology have been recently reported.[3–6] In addition to arylboronic acids, the cupric acetate ($Cu(OAc)_2$) methodology has been expanded to include other organometalloids such as hypervalent aryl siloxanes,[2] hypervalent diaryliodonium salts[5] and arylstannanes.[1a] The copper-promoted method employing commercially widely-available arylboronic acids, however, suffers from the drawback that it requires the use of stoichiometric amount of $Cu(OAc)_2$. Herein, we report several *catalytic* $Cu(OAc)_2$ systems that are applicable to a wide range of substrates containing NH and OH functional groups.

Recently, Collman[6] reported an efficient catalytic copper/O_2 system to carry out the *N*-arylation of imidazoles with arylboronic acids.[1b] The copper catalyst employed is $[Cu(OH)\cdot TMEDA]_2Cl_2$, which was previously developed[8] for C–C bond oxidative homo-coupling of naphthols or alkynes. However, the Collman conditions, although catalytic, work only for a limited



Scheme 1. Oxidant screening.

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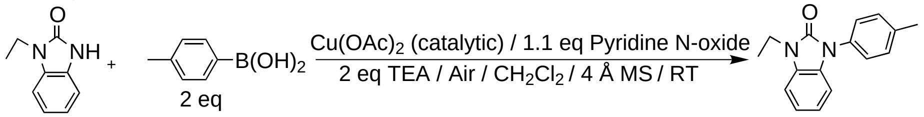
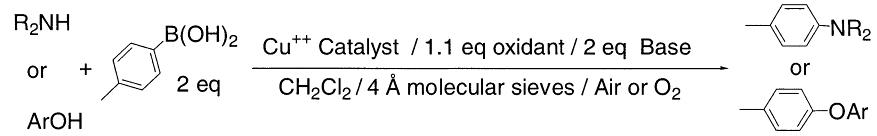
Table 1. Catalyst loading

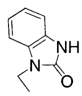
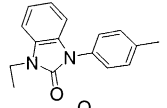
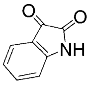
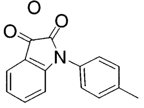
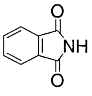
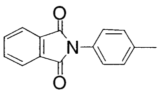
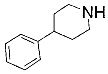
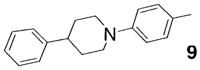
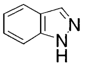
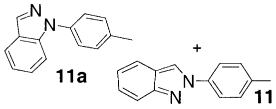
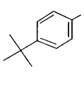
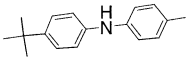
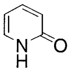
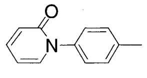
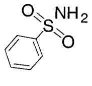
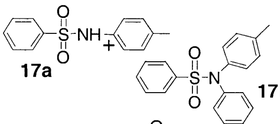
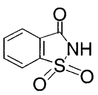
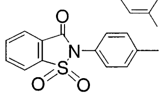
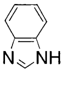
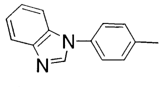
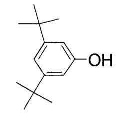
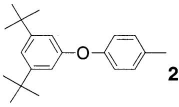


1 **2** **3**

Entry	Equivalent of Cu(OAc)$_2$	Isolated yield (%)
1	0.01	14
2	0.05	41
3	**0.1**	**69**
4	**0.2**	**70**

Table 2. Copper catalyzed cross-coupling of *p*-tolyl boronic acid and NH- or OH-containing substrates



Entry	Substrate	Product	Cu^{++} Catalyst + Oxidant^a	Base, Temperature	Isolated Yield
1	 **1**	 **3**	A	TEA, RT	57%
			B	TEA, RT	**64%**
			C	TEA, RT	**69%**
			D	No base, RT	NR
2	 **4**	 **5**	A*	TEA, RT	36%
			B*	TEA, RT	**68%**
			C*	TEA, RT	**70%**
			D*	no base, RT	55%
3	 **6**	 **7**	A*	TEA, RT	57%
			B*	TEA, RT	**77%**
			C*	TEA, RT	49%
			D*	no base, RT	44%
4	 **8**	 **9**	A*	Pyridine, RT	37%
			B*	Pyridine, RT	**55%**
			C*	Pyridine, RT	36%
			D*	no base, RT	5%
5	 **10**	 **11a** + **11b**	A*	Pyridine, RT	52% (4:3)
			B*	Pyridine, RT	**87% (3:1)**
			C*	Pyridine, RT	14% (3:1)
			D*	no base, RT	63% (3:2)
6	 **12**	 **13**	**A**	TEA, RT	**84%**
			B	TEA, RT	**82%**
			C	TEA, RT	72%
			D	no base, RT	30%
7	 **14**	 **15**	**A***	Pyridine, RT	**100%**
			B*	Pyridine, RT	90%
			C*	Pyridine, RT	93%
			D*	no base, RT	40%
8	 **16**	 **17a** + **17b**	**A***	TEA, RT	**84% (11:3)**
			B*	TEA, RT	77% (21:4)
			C*	TEA, RT	80 % (31:9)
			D*	no base, RT	38% (100:0)
9	 **18**	 **19**	**A***	Pyridine, 50°C^b	**90%**
			B*	Pyridine, 50°C^b	81%
			C*	Pyridine, 50°C^b	27%
			D*	no base, 50°C^b	45%
10	 **20**	 **21**	A	Pyridine, 65°C^b	70%
			B	Pyridine, 65°C^b	80%
			C	Pyridine, 65°C^b	80%
			D	no base, RT	**97%**
11	 **22**	 **23**	**A***	Pyridine, 50°C^b	**79%**
			B*	Pyridine, 50°C^b	16%
			C*	Pyridine, 50°C^b	9%
			D*	no base, 50°C^b	3%

[a] Conditions :
A. 0.1 eq Cu(OAc)$_2$ and O$_2$
B. 0.1 eq Cu(OAc)$_2$, 1.1 eq TEMPO and air.
C. 0.1 eq Cu(OAc)$_2$, 1.1 eq Pyridine N-oxide and air.
D. 0.1 eq [Cu(OH).TMEDA]$_2$Cl$_2$ and O$_2$.
* 0.2 eq of Cu^{++} catalyst instead of 0.1 eq.

[b] DMF as solvent.

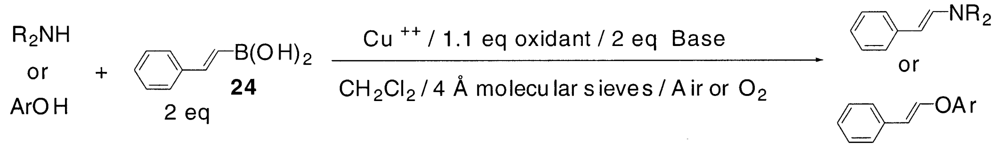
number of substrates. For example, we found that the conditions are not suitable for important NH- and OH-containing substrates such as anilines, amines and phenols (vide infra).

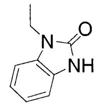
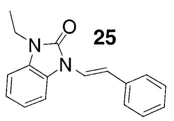
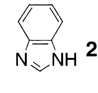
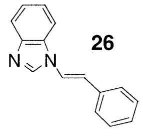
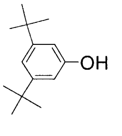
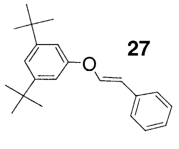
It has been observed that the presence of oxygen is required for the copper-promoted *N*- or *O*-arylation reactions. The molecular oxygen in the copper-promoted C–N or C–O bond cross-coupling has been hypothesized to facilitate the oxidation of the Cu(II) complex to the Cu(III) complex.[1a,c] The Cu(III) complex,[9] being at a higher oxidation state, can undergo more facile reductive-elimination to form C–N or C–O cross-coupled product than the Cu(II) complex. We reasoned that addition of a mild oxidizing agent may be more efficient for the conversion of the Cu(II) complex to the Cu(III) complex than the molecular oxygen and may enable us to use $Cu(OAc)_2$ in a catalytic amount. At the outset we recognized that the optimal oxidizing agent should be able to competitively oxidize the Cu(II) complex to the Cu(III) complex without oxidizing boronic acid to phenol. Indeed, we found that the cross-coupling of *p*-toluylboronic acid with *N*-ethylbenzimidazolinone **1** furnished *N*-arylated **3** in 69% yield in the presence of 1.1 equiv. of pyridine *N*-oxide (PNO) and a catalytic amount (0.1 equiv.) of $Cu(OAc)_2$ (Scheme 1). The success with PNO prompted us to investigate the use of other oxidants such 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), *N*-methylmorpholine *N*-oxide, di-*t*-butylnitroxide, (1*R*)-(10-camphorsulfonyl)oxaziridine, sodium perborate, potassium ferricyanide and *m*-chloroperbenzoic acid (Scheme 1). Oxidants other than PNO and TEMPO appear to be less effective as the competing oxidation of *p*-toluylboronic acid to *p*-toluylphenol becomes significant. The resulting *p*-toluylphenol can undergo further *O*-arylation to give bis-*p*-toluylether as a side product. PNO and TEMPO were further investigated to test the generality of the substrates as well as the catalyst loading (Table 1). We found that 0.1 equiv. is the minimum amount $Cu(OAc)_2$ required for the optimum yield (69%) of **3**.

We investigated *N*-arylation of a diverse set of NH- and OH-containing substrates under four different conditions (Table 2): (A) catalytic $Cu(OAc)_2$/ O_2; (B) catalytic $Cu(OAc)_2$/TEMPO in air; (C) catalytic $Cu(OAc)_2$/PNO in air; (D) catalytic $[Cu(OH)\cdot TMEDA]_2Cl_2/O_2$ (Collman conditions[6]).

For benzimidazolinone **1** (entry 1), catalytic $Cu(OAc)_2$/PNO (69%) and catalytic $Cu(OAc)_2$/TEMPO (64%) are better than catalytic $Cu(OAc)_2/O_2$ (57%). Catalytic $[Cu(OH).TMEDA]_2Cl_2/O_2$, on the other hand, surprisingly gave no product. Similarly for isatine **4** (entry 2), catalytic $Cu(OAc)_2$/PNO (70%) and $Cu(OAc)_2$/TEMPO (68%) work best. For phthalimide **6** (entry 3), piperidine **8** (entry 4) and indazole **10** (entry 5), catalytic $Cu(OAc)_2$/TEMPO is the superior system (77, 55, 87%, respectively). For aniline **12** (entry 6) catalytic $Cu(OAc)_2/O_2$ (84%) emerges to be as efficient as catalytic $Cu(OAc)_2$/TEMPO (82%).[10] Indeed, for pyridone **14** (entry 7), sulfonamide **16** (entry 8) and acylsulfonamide **18** (entry 9), simple catalytic $Cu(OAc)_2/O_2$ (100, 84 and 90%, respectively) is the best system. For benzimidazole **20** (entry 10), we found that the reported catalytic $[Cu(OH)\cdot TMEDA]_2Cl_2/O_2$ (97%) is indeed the best system.[11] It occurs at room temperature, whereas the other three catalytic systems require heating at 65°C. We have also investigated the *O*-arylation of phenol **22** (entry 11) and found that catalytic $Cu(OAc)_2/O_2$ gave the best yield (79%).

Table 3. C–N and C–O bond cross-coupling of vinyl boronic acid and NH- or OH-containing substrates



Entry	Substrate	Product	Cu⁺⁺ + Oxidant[a]	Base, Temperature	Isolated Yield
1	 1	 25	**E**	TEA, RT	**79%**
			A*	TEA, 50°C[b]	**73%**
			B*	TEA, 50°C[b]	55%
			C*	TEA, 50°C[b]	71%
			D*	no base, 50°C[b]	22%
2	 20	 26	**E**	Pyridine, RT	**79%**
			A*	Pyridine, RT	71%
			B*	Pyridine, RT	73%
			C*	Pyridine, RT	**84%**
			D*	no base, RT	68%
3	 22	 27	**E**	TEA, RT	**67%**
			A	TEA, 50°C[b]	22%
			B	TEA, 50°C[b]	23%
			C	TEA, 50°C[b]	13%
			D	no base, 50°C[b]	NR

[a] Same as Table 2 except condition E is stoichiometric in $Cu(OAc)_2$ (1.1 eq) in air.

In the course of our investigation, we became interested in the application of the copper-promoted reaction for vinylation of NH- or OH-containing substrates. The preliminary result shows that, analogous to arylboronic acid **2**, vinylboronic acid **24** is also capable of undergoing a Cu(OAc)$_2$-promoted cross-coupling reaction (Table 3, condition E) with benzimidazolinone **1**, benzimidazole **20** and phenol **22**. While the coupling of vinylboronic acid with benzimidazolinone, and benzimidazole proceeds under the catalytic conditions, the coupling with phenol requires stoichiometric amount of Cu(OAc)$_2$. The scope of these novel and useful *N*- and *O*-vinylations[12] is currently under further investigation.

In summary, we have explored four catalytic copper systems for C–N and C–O bond cross-coupling of arylboronic acid with a diverse set of NH- and OH-containing substrates. This report serves as a practical guide for carrying out copper-catalyzed C–N and C–O cross-coupling reactions. No single general catalytic copper system works for all the substrates. This is perhaps not surprising since the N–H functional group constitute the single most diverse functional group in organic chemistry.[13] Nevertheless, in general catalytic Cu(OAc)$_2$/TEMPO in air and catalytic Cu(OAc)$_2$/O$_2$ systems appear to work for the majority of the substrates. Preliminarily, we have also demonstrated that *N*- and *O*-vinylation is possible with vinylboronic acid. We are continuing our study to understand the scope and mechanism of this synthetically very valuable copper-promoted C-heteroatom cross-coupling reaction.

Acknowledgements

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10. Representative procedure (condition B) for *N*-4′-tolyl-4-*t*-butylaniline **13**: To a 20 mL vial was added in sequence 33 mg 4 Å molecular sieves, *p*-tolyboronic acid (90 mg, 0.667 mmol, 2.0 equiv.), 3 mL of dry dichloromethane, triethylamine (93 μL, 0.667 mmol, 2.0 equiv.), 4 *t*-butyl aniline **1** (53 μL, 0.333 mmol, 1.0 equiv.), cupric acetate (6.1 mg, 0.033 mmol, 0.1 equiv.) and TEMPO (57.3 mg, 0.367 mmol, 1.1 equiv.). The progress of the reaction was monitored by TLC (eluent: 15% ethyl acetate/hexane). After 15 min, 90% of the starting material was consumed. The reaction was allowed to stir under air at room temperature for 4 days (4 days was chosen for all reactions to be consistent). The reaction was quenched by a solution of 50 μL of NH$_3$ in MeOH (2 M). The solvent was evaporated under reduced pressure and the residue was dissolved in 3 mL of dichloromethane and purified by silica gel chromatography (eluent: 15% ethyl acetate/hexane) to give 66 mg (82%) of *N*-4′-tolyl-4-*t*-butylaniline **3**. MS (AP) m/z 240.1 (100%) $(M+H)^+$; ^{1}H NMR (CDCl$_3$) 7.26 (d, $J=8.8$ Hz, 2H), 7.06 (d, $J=8.3$ Hz, 2H), 6.97 (d, $J=8.3$ Hz, 2H), 6.96 (d, $J=8.8$ Hz, 2H), 5.55 (br, 1H), 2.29 (s, 3H), 1.30 (s, 9H) ppm; HRMS calcd for $C_{17}H_{22}N$ $(M+H)^+$ m/e 240.1752, found m/e 240.1758.
11. A 10–15% yield of bis-*p*-toluene was obtained as a side-product in many reactions under condition D. This is probably a result of homo-coupling of *p*-toluylboronic acid in the presence of [Cu(OH)·TMEDA]$_2$Cl$_2$ in view of the fact that this copper catalyst was originally developed to perform C–C homo-coupling of naphthols.[8]
12. Other substrates are currently being explored. *N*-vinlyation has not been reported by Buchwald[7a] or Hartwig.[7b]
13. A search of the Available Chemicals Directory shows that 33% of commercially available compounds contain an NH functional group. This substrate diversity makes the copper methodology ideal for preparing combinatorial libraries.