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Copper-Catalyzed Aerobic Intramolecular Carbo- and Amino-Oxygenation of Alkynes for Synthesis of Azaheterocycles

Kah Kah Toh, Stephen Sanjaya, Sophian Sahnoun, Sin Yee Chong, and Shunsuke Chiba*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

shunsuke@ntu.edu.sg

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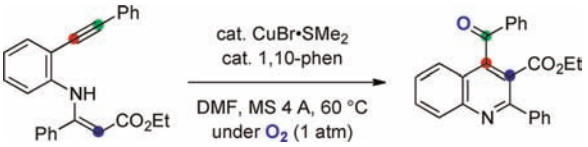
ABSTRACT



A synthetic method of highly substituted quinolines has been developed from *N*-(2-alkynylaryl)enamine carboxylates under Cu-catalyzed aerobic conditions via intramolecular carbo-oxygenation of alkynes. This strategy was further applied for *N*-alkynylamidines for amino-oxygenation of alkynes, leading to imidazole and quinazoline derivatives.

Aromatic azaheterocycles are an omnipresent component of numerous natural alkaloids and potent pharmaceutical drugs.[1] While diverse synthetic approaches toward azaheterocycles have been exploited,[2] there remains a demand of conceptually novel and versatile methodologies for chemical synthesis of aromatic azaheterocycles from readily available building blocks.

We have studied copper-mediated oxidative functionalization of carbon−carbon unsaturated bonds under aerobic conditions using enamine carboxylates,[3] *N*-H imines,[4] and amidines[5] to construct azaheterocyclic frameworks (Scheme 1).[6] In this context, we became interested in oxidative functionalization of carbon−carbon triple bonds (alkyne)[7] under copper-catalyzed aerobic reaction conditions. As shown in Scheme 2, a sequence of intramolecular carbo(or amino)-cupration[8] of alkynes followed by oxygenative carbonylation could be envisioned to occur in an

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(9) As a prelminary result, we have found that the reactions of *N*-propargyl enamine carboxylates provided 4-benzoylpyrroles via carbo-oxygenation of alkynes under copper-catalyzed aerobic conditions; see ref 3h.

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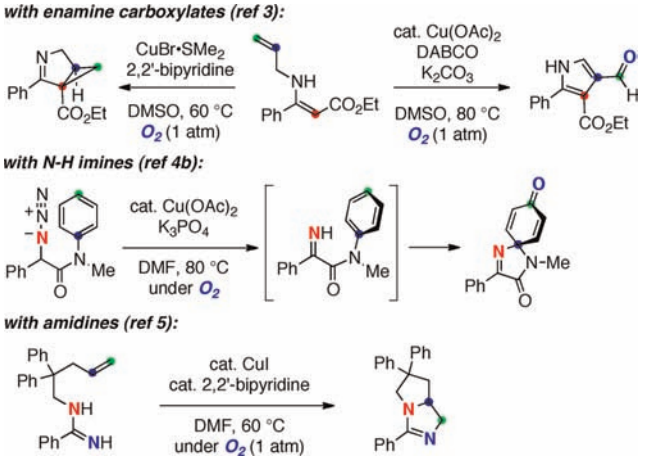
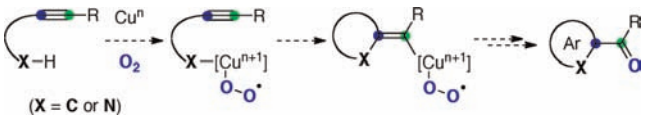
unprecedented mode of oxo functionalization of alkynes, resulting in various acylated cyclic compounds.[9,10] Herein, we report copper-catalyzed aerobic synthesis of aza-aromatic heterocycles such as quinolines, imidazoles, and quinazolines from *N*-(2-alkynylaryl)enamine carboxylates and *N*-alkynylamidines.

Scheme 1. Cu-Catalyzed Aerobic Functionalization of Alkenes and Benzene Rings

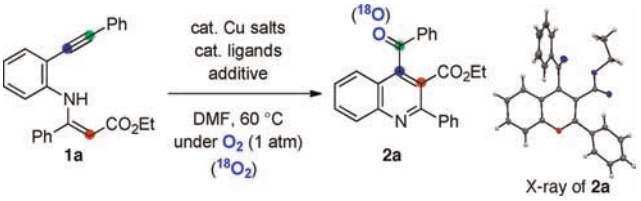


Scheme 2. Cu-Catalyzed Aerobic Oxo Functionalization of Alkynes (This Work)



Our study was commenced with the reactions of *N*-(2-alkynylaryl)enamine carboxylate **1a** under copper-catalyzed aerobic conditions (Table 1). When **1a** was treated with 20 mol % of $CuBr•SMe_2$ in the presence of K_2CO_3 in DMF at 60 °C under an O_2 atmosphere, an intramolecular carbo-oxygenation[11] product, 4-benzoylquinoline **2a** was isolated in 57% yield (entry 1).[12] The yield of product **2a** was improved by the addition of nitrogen bases/ligands to $CuBr•SMe_2$ (entries 2–4). The highest yield of **2a** was achieved using 1,10-phenanthroline (1,10-phen) (entry 4).

Table 1. Optimization of Reaction Conditions[a]



entry	Cu salts [mol %]	ligands [mol %]	additive	time [h]	yield [%][b]
1	$CuBr•SMe_2$ (20)	–	K_2CO_3[c]	0.3	57
2	$CuBr•SMe_2$ (20)	DABCO (20)	–	1	(60)
3	$CuBr•SMe_2$ (20)	DMAP (20)	–	2	(55)
4	$CuBr•SMe_2$ (20)	1,10-phen (20)	–	0.5	(62)
5	$CuBr•SMe_2$ (10)	1,10-phen (20)	–	2	(76)
6	$CuBr•SMe_2$ (10)	1,10-phen (30)	MS 4 A[d]	1.5	83
7[e]	$CuBr•SMe_2$ (10)	1,10-phen (30)	MS 4 A[d]	4.5	83
8	$CuBr_2$ (10)	1,10-phen (30)	MS 4 A[d]	1.5	(70)
9	$Cu(OAc)_2$ (10)	1,10-phen (30)	MS 4 A[d]	24	(60)
10	$FeCl_3$ (10)	1,10-phen (30)	MS 4 A[d]	24	0
11	$CoBr_2$ (10)	1,10-phen (30)	MS 4 A[d]	24	(26)
12	$Pd(OAc)_2$ (5)	1,10-phen (30)	MS 4 A[d]	24	0

[a] The reactions were carried out using 0.3 mmol of enamine **1a** in DMF at 60 °C under an O_2 atmosphere. [b] Isolated yields are recorded. NMR yields were shown in parentheses. [c] 1.1 equiv of K_2CO_3 was added. [d] 100 wt % with **1a**. [e] The reaction was conducted under an air atmosphere. DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = *N*,*N*-dimethyl-4-aminopyridine; 1,10-phen = 1,10-phenanthroline.

The catalytic loading of $CuBr•SMe_2$ could be reduced to 10 mol % (entries 5 and 6), and quinoline **2a** was obtained in 83% yield with 30 mol % of 1,10-phen (entry 6), where addition of molecular sieves 4 A (MS 4 A) made the reaction more reproducible in terms of the reaction rate.[13] Using $^{18}O_2$ as an atmosphere, incorporation of the oxygen atom from O_2 was observed in the resulting carbonyl group of **2a**-^{18}**O** (see Supporting Information for details). Reduction of the oxygen partial pressure under an air atmosphere (0.21 atm of O_2) did not affect the product yield of **2a**, while the reaction rate became slightly longer (entry 7). It is noted that the reaction under a N_2 atmosphere did not give any cyclized product at all, which suggested that the presence of molecular oxygen might be indispensable for initial C–C bond forming cyclization.[14] Copper(II) species also showed the catalytic reactivity toward the present quinoline formation (entries 8 and 9). It is noted that other metals such as Fe(III), Co(II), and Pd(II) were not viable for this transformation (entries 10–12).

(10) Li recently reported copper-catalyzed aerobic carbo-oxygenation of alkynes of 1,6-enynes to synthesize 1,4-naphthoquinones; see: Wang, Z.-Q.; Zhang, W.-W.; Gong, L.-B.; Tang, R.-Y.; Yang, X.-H.; Liu, Y.; Li, J.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8968.

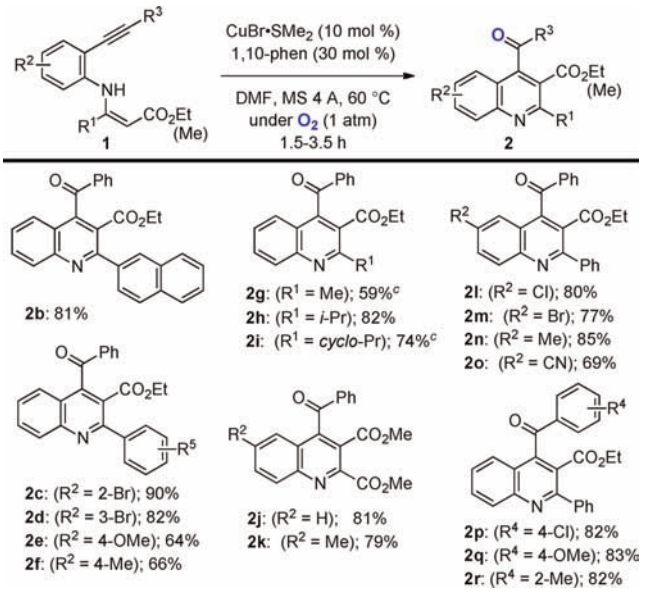
(11) For recent selected reports on carbo-oxygenation of alkynes using other oxygen sources, see: (a) Gronnier, C.; Kramer, S.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2012**, *134*, 828. (b) Qian, D.; Zhang, J. *Chem. Commun.* **2011**, *47*, 11152. (c) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 3076. (d) Li, C.-W.; Pati, K.; Lin, G.-Y.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891. (e) Yeom, H.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J.; Lee, S.; Shin, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611. (f) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (g) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225. (h) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (i) Zhang, D.; Ready, J. M. *Org. Lett.* **2005**, *7*, 5681.

(12) The structure of **2a** was secured by X-ray crystallographic analysis (CCDC-872056); see Supporting Information.

(13) Addition of 2 equiv of H_2O rendered the reaction of **1a** (using 10 mol % $CuBr•SMe_2$ and 30 mol % 1,10-phen) slow, giving quinoline **2a** in 85% yield after 24 h.

(14) A proposed reaction mechanism is discussed in the Supporting Information.

Scheme 3. Substrate Scope for Synthesis of Quinolines[a,b]

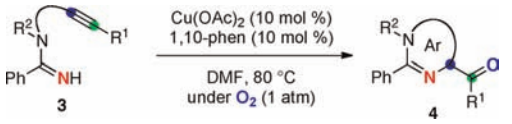


[a] Reactions were carried out using 0.3–0.6 mmol of enamines **1** with CuB•SMe_2 (10 mol %) and 1,10-phenanthroline (30 mol %) in the presence of MS 4 A (100 wt %) at 60 °C under an O_2 atmosphere. [b] Isolated yields are recorded. [c] The yield was obtained from the corresponding aryl iodide via Pd-catalyzed Sonogashira coupling followed by the present Cu-catalyzed aerobic quinoline formation; see Supporting Information for more details.

With the optimized conditions in hand, we next examined the substrate scope for the synthesis of highly substituted quinolines (Scheme 3). By varying substituents R^1 of enamines **1**, it was shown that both electron-rich and -deficient benzene rings could be introduced, and a bromine substituent was tolerated while keeping the C–Br bond intact (for **2b**–**2f**). Several alkyl groups (for **2g**–**2i**) as well as a methoxycarbonyl group (for **2j**, **2k**) were all installed in good yields. At the C(6)-position of quinoline frameworks, halogen atoms as well as a cyano group could be introduced (for **2l**–**2o**). As for R^3 on the alkyne moiety, several substituted benzenes could be used (for **2p**–**2r**), while no cyclization was observed when substituents R^3 were alkyl groups.

Stimulated by the structural analogy of amidines with enamine carboxylates, amino-oxygenation of alkynes[15] could be envisioned to occur by Cu-catalyzed aerobic reactions of *N*-alkynylamidines (Table 2). As expected, the aerobic reactions of *N*-benzyl-*N*-propargylamidine **3a** with 10 mol % of $Cu(OAc)_2$ and 10 mol % of 1,10-phenanthroline in DMF at 80 °C provided 4-benzoylimidazole **4a** in good yield (entry 1).[16] This amino-oxygenation showed an interesting chemoselectivity in the reaction of *N*-allyl-*N*-propargylamidine **3c** (entry 3). The cyclization exclusively selected the alkyne tether to afford *N*-allyl-4-benzoylimidazoles **4c**. Moreover, 4-benzoylquinazoline **4d** could be synthesized in good yield from *N*-(2-alkynylphenyl)amidine **3d** (entry 4).[17]

Table 2. Cu-Catalzyed Aerobic Reactions of *N*-Alkynylamidines[a]



entry	amidines **3**	time	products **4** (yield)
1 2	**3a** (R^1 = 4-Me-C_6H_4) **3b** (R^1 = 4-MeO-C_6H_4)	4 h	**4a** 66% **4b** 42%
3	**3c**	4 h	**4c** 65%
4	**3d**	12 h	**4d** 84%

[a] The reactions were carried out using 0.5–0.6 mmol of amidines **3** with $Cu(OAc)_2$ (10 mol %) and 1,10-phenanthroline (10 mol %) at 80 °C under an O_2 atmosphere. [b] Isolated yields are recorded.

In summary, we have developed Cu-catalyzed aerobic oxofunctionalization of alkynes that could deliver a variety of aza-aromatic heterocycles. Further investigation for the scope, detailed mechanisms, and synthetic applications of the present strategy to other azaheterocycles is currently underway.

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Supporting Information Available. Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) For recent selected reports on amino-oxygenation of alkynes using other oxygen sources, see: (a) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Narayan Karad, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 15372. (b) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (c) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236. (d) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395. (e) Yeom, H.-S.; So, E.; Shin, S. *Chem.—Eur. J.* **2011**, *17*, 1764.

(16) The reaction of **3a** with CuB•SMe_2 (10 mol%) and 1,10-phenanthroline (30 mol %) at 60 °C under an O_2 atmosphere for 4 h provided **4a** in 46% yield.

(17) Zhang and Zhu reported copper-catalyzed aerobic reactions of *N*-allyl amidines, that afforded formylimidazoles via carbo-oxygenation of the alkene; see: Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678.